A NEW ERA FOR HIV PREVENTION?

REPORT OF THE FORUM FOR COLLABORATIVE HIV RESEARCH *BIOMEDICAL INTERVENTIONS OF HIV PREVENTION* WORKING GROUP SEPTEMBER 2006 MEETING*

Written on behalf of Working Group Members by Chris Collins and edited by Meagan Lyon and Veronica Miller

*In collaboration with the Bill & Melinda Gates Foundation

February 2007

FORUM FOR COLLABORATIVE HIV RESEARCH

DEPARTMENT OF PREVENTION AND COMMUNITY HEALTH
THE GEORGE WASHINGTON UNIVERSITY
SCHOOL OF PUBLIC HEALTH AND HEALTH SERVICES

TABLE OF CONTENTS

TABLE OF CONTENTS 2
ACKNOWLEDGMENTS 3
EXECUTIVE SUMMARY 4
FIGURE 1 – BIOMEDICAL INTERVENTIONS FOR HIV PREVENTION CLINICAL TRIALS TIMELINE 6
TABLE 1- NOTES ON BIOMEDICAL INTERVENTIONS FOR HIV PREVENTION CLINICAL TRIALS TIMELINE 7
INTRODUCTION 9
STATUS OF RESEARCH ON NEW HIV PREVENTION INTERVENTIONS 10
MALE CIRCUMCISION 10
FEMALE INITIATED BARRIER METHODS 12
HSV-2 TREATMENT 14
MICROBICIDES 15
PRE-EXPOSURE PROPHYLAXIS (PREP) 17
INDEX PARTNER TREATMENT 19
PRIORITIES TO ADVANCE THE FIELD 21
SUPPORT PREVENTION TRIAL SITES 21
FILL GAPS IN SCIENTIFIC KNOWLEDGE 22
PROMOTE COORDINATION WHILE DRIVING INNOVATION 24
BUILD OWNERSHIP IN HOST COMMUNITIES 26
PREPARE FOR GLOBAL DELIVERY 27
CHOICES AHEAD 29
REFERENCES- 31
APPENDIX A – WORKING GROUP MEMBERS 35
APPENDIX B- AGENDA 38

ACKNOWLEDGMENTS

This roundtable was organized by the Forum for Collaborative HIV Research, an independent public/private partnership that receives core operational funding from government agencies and industry. Special support for this workshop was received from the Bill and Melinda Gates Foundation.

The Forum is deeply grateful to the workshop co-chairs Myron Cohen and Ward Cates for their leadership and guidance of the project, and to Nick Hellmann and Renee Ridzon of the Bill and Melinda Gates Foundation for their vision, insightful contributions and support of this workshop.

Very special thanks goes to all Working Group members (see Appendix A) for their thoughtful, considerate as well as critical and engaged contributions to the meeting agenda (see Appendix B).

Special thanks go to the project coordinators, Ipsita Das and Meagan Lyon, without whose expert coordination the project would not have become a reality.

The Forum thanks Debbie Cooke from Meeting Masters, Inc, for managing the hotel and travel arrangements and for supporting the meeting on site.

EXECUTIVE SUMMARY

The HIV prevention research community is increasingly optimistic that one or more interventions now in development or clinical testing will demonstrate their effectiveness as powerful new HIV prevention tools. Yet several challenges need to be addressed for today's prevention research to realize its potentially enormous impact. These include improving coordination of the field, making tough choices about research priorities, expanding clinical research capacity, and overcoming barriers to widespread delivery that hamper current HIV prevention programs.

A meeting hosted by the Forum for Collaborative HIV Research in September 2006 brought together researchers, donors, and community advocates to discuss how to accelerate and better coordinate the HIV prevention research effort. A primary objective of the meeting was to review the status of biomedical prevention research and identify barriers to progress and strategies to address these challenges. Other objectives were to discuss criteria for setting research priorities; identify potential interventions not included in the research agenda; and promote an integrated research effort. Participants heard updates on candidate HIV prevention interventions, including:

- **Male circumcision.** Three randomized trials have demonstrated that male circumcision, provided in the context of a clinical trial, can significantly reduce the risk of HIV infection. Delivery of this intervention requires extensive provider training, Phase IV and operations research, and continued emphasis that condom use and behavioral interventions remain essential HIV prevention tools.
- **Female-initiated barrier methods.** The diaphragm and female condom are both already available commercially, and the female condom has been used for years as a pregnancy and disease prevention tool. The first HIV prevention effectiveness study of the diaphragm is due to produce results in 2007. The feasibility of widespread implementation of the diaphragm and female condoms in HIV prevention has not been established.
- **Herpes Simplex Virus-2 treatment.** Several studies of episodic and suppressive treatment of HSV-2 are ongoing and one trial has provided modestly promising results. Data from several trials is being analyzed and additional trials will report results in 2007 and 2008.
- **Microbicides.** Three products are in effectiveness trials and will report results over the next several years. A new generation of candidate products, including several that incorporate antiretroviral (ARV) drugs, are in preclinical or late stage development or early testing.
- **Pre-exposure prophylaxis.** Results of a study reported in 2006 indicated that the intervention group experienced no increase in adverse events. The data was suggestive, but not conclusive, of some level of protection. Clinical trials of two different ARVs will report results in the next several years.

- **Index partner treatment.** Researchers are seeking to better understand the interaction of ARV treatment and infectiousness, the prevention efficacy of pre- and post-exposure prophylaxis, and the correlation of blood plasma viral load with viral levels in semen and cervical secretions. Retrospective studies suggest HIV treatment substantially reduces infectiousness.

Each of these interventions have potential advantages and disadvantages that involve factors such as ease of use, acceptability, short and long term safety, cost, and ability to be scaled up for wide delivery. The status and details of prevention phase 2B/3 research trials are highlighted in Figure 1 and Table 1 of this report.

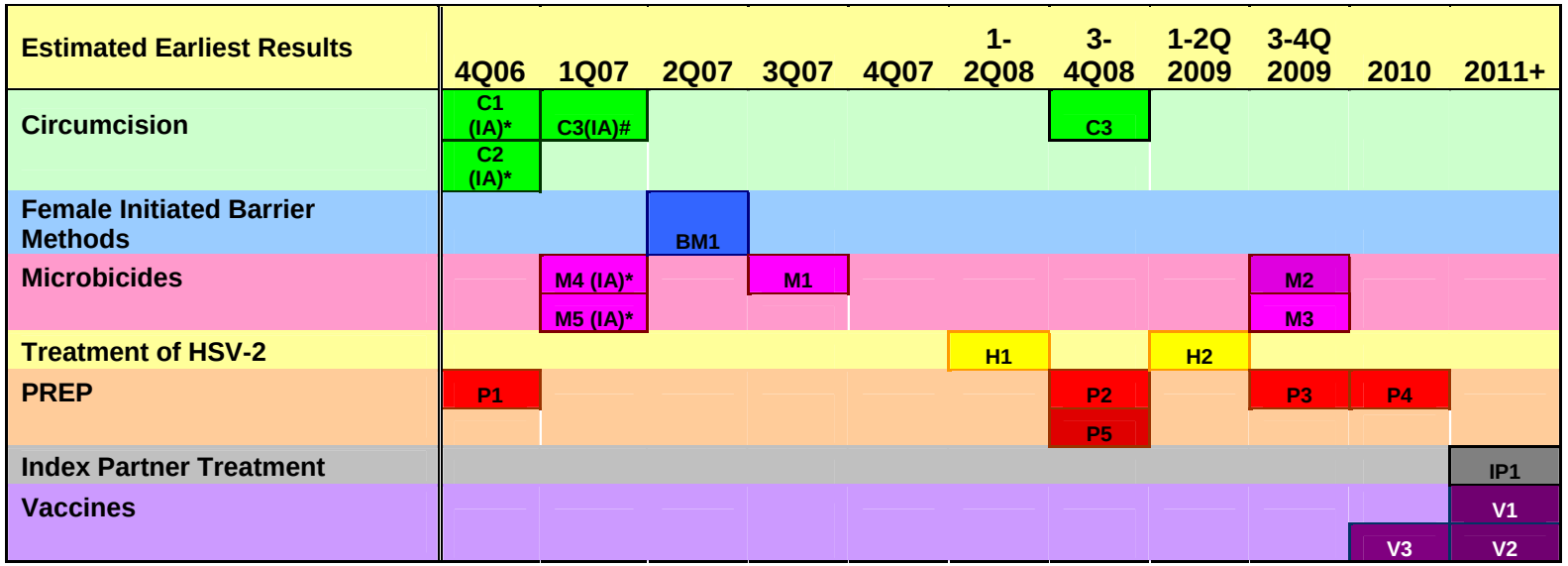
In addition to pursuing research and testing of these interventions, the HIV prevention research field must grapple with a set of overarching challenges that include:

- Supporting the sustainable capacity of clinical trial sites, maintaining staff expertise at these sites, and improving incidence estimates
- Filling gaps in scientific knowledge on issues such as combination products, viral resistance, long term safety, and optimized use of animal models
- Promoting coordination among researchers and donors while also driving innovation and more fully engaging the private sector
- Building ownership in host communities by genuinely involving local researchers and establishing standards for trial participant protections and community engagement
- Preparing for global delivery of male circumcision and other prevention interventions through a coordinated operations research effort, improved marketing, behavioral research, use of AIDS treatment scale up as an opportunity to deliver prevention, and lower prices and adequate purchase capacity for prevention commodities.

All those engaged in HIV prevention research now face several choices in the months and years ahead. Donors, researchers and other stakeholders need to decide how to better coordinate efforts and share information through a “prevention research forum” or other entity; promote sustainable trial site capacity and retain staff expertise; set priorities for use of Phase III clinical sites; most efficiently address priority scientific questions; actively investigate combination and multi-component interventions; more fully engage communities hosting research; and, ensure delivery and widespread use of new interventions. How these and other choices are made over the coming years will help determine the ultimate impact of today’s HIV prevention research on the global AIDS epidemic.

FIGURE 1 – BIOMEDICAL INTERVENTIONS FOR HIV PREVENTION PHASE 2B/3 CLINICAL TRIALS TIMELINE

See Table 1 for explanations



Key

*(IA) = interim analysis; study stopped
#(IA) = interim analysis planned
Phase 2B= stippled color
Phase 3= solid color

An additional resource detailing prevention trial timelines and characteristics is available at the AIDS Vaccine Advocacy Coalition (AVAC)'s website at http://www.avac.org/timeline-website/) .

TABLE 1- NOTES ON BIOMEDICAL INTERVENTIONS FOR HIV PREVENTION CLINICAL TRIALS TIMELINE

(See Figure 1)

Notes	Full Trial Name	Also known as	Phase	Sponsor/ Funder(s)	# of people enrolled/expected enrollment	Country(ies)
C1	Trial of Male Circumcision to Reduce HIV Incidence	Male Circumcision and HIV Rates in Kenya	3	University of Illinois, NIH, Canadian Institute of Health Research	2,784 m	Kenya
C2	Trial of Male Circumcision: HIV, STD and Behavioral Effects in Men, Women and the Community	Male Circumcision HIV Prevention Rakai Trial	3	Johns Hopkins University, NIH	5,000 m	Uganda
C3	Safety of Male Circumcision in HIV Infected Men and Efficacy in Preventing Transmission to Women		3	JHU, Gates Foundation	1361 m, 7,000 w	Uganda
BM1	The Latex Diaphragm to Prevent HIV Acquisition Among Women: A Female-Controlled, Physical Barrier of the Cervix	Diagphram & Replens Gel	3	University of California at San Francisco, Gates Foundation	5,045 w	South Africa and Zimbabwe
M1	Phase 3 Study of Efficacy and Safety of the Microbicide Carraguard in Preventing Seroconversion in Women	Carraguard	3	Population Council, Gates Foundation, USAID	6639 w	South Africa
M2	Phase 2/2B safety and effectiveness study of two vaginal microbicides BufferGel and 0.5% PRO 2000/5 Gel (P) for the prevention of HIV infection in women (HPTN 035)	MTN 035	2/2B	NIH-NIAID, Indevus, ReProtect	3100 w	Malawi, South Africa, USA, Zambia, Zimbabwe, Nigeria
M3	An international, multi-center randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of 0.5% and 2% PRO 2000/5 gels for the prevention of vaginally acquired HIV infection	Pro-2000/5	3	Indevus, MRC, DFID	9673 w	South Africa, Tanzania, Uganda, Zambia
M4	Randomized Controlled Trial of 6% CS Gel and the Effect on Vaginal HIV Transmission	Cellulose sulfate gel	3	CONRAD, USAID, Gates Foundation	2574 w	Uganda, Zimbabwe, India, South Africa, Benin
M5	Randomized Controlled Trial of Cellulose Sulfate Gel and HIV in Nigeria	Cellulose sulfate gel	3	Family Health International, USAID , CONRAD	2160 w	Nigeria
H1	A Phase 3, randomized, double-blind, placebo-controlled trial of acyclovir for the reduction of HIV acquisition among high risk HSV-2 seropositve, HIV-seronegative individuals	HPTN 039	3	University of Washington, NIH	3277 m and w	Peru, South Africa, Zambia, Zimbabwe, USA
H2	Phase III Randomized Placebo-Controlled Trial of HSV-2 Suppression to Prevent HIV Transmission Among HIV-Discordant Couples	Partners in Prevention	3	University of Washington, Gates Foundation	3,000 discordant heterosexual couples	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia
P1	Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial	West Africa TDF	2	Family Health International, Gates Foundation	936 w	Ghana, Cameroon, Nigeria
P2	Study of the Safety and Efficacy of Daily Tenofovir to Prevent HIV Infection Among Injection Drug Users in Bangkok, Thailand	Thailand/TDF	3	CDC	2000 IDU	Thailand
P3	Study of the Safety and Efficacy of Daily Tenofovir Disoproxil Fumarate and Emtricitabine (Truvada®) for the Prevention of HIV Infection in Heterosexually Active Young Adults in Botswana	Andean PREP Trail	3	CDC	1200 m and w	Botswana

P4	Chemoprophylaxis for HIV Prevention in Men	Peru Truvada	3	NIH	1400 MSM (proposal to increase to 2700)	Peru, Ecuador
P5	Phase 2 Extended Safety Study of Tenofovir-Disoproxil Fumarate (TDF) among HIV-1 Negative Men		2	CDC	400 MSM	US A
IP1	A Randomized trial to Evaluate the Effectivness of Antretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 in Serodiscordant Couples	HPTN 052	3	NIH, GSK, Boehringer-Ingelheim	1750 serodiscordant couples	Malawi, India, Zimbabwe, Brazil, Thailand, USA
V1	The purpose of the Merck/HVTN proof of concept trial is to obtain information about the safety of the MRKAd5 HIV-1 gag/pol/nef, or trivalent, vaccine in humans and to learn if it can prevent HIV infection	HVTN 502/ Merck 0123 Step Study	2B	Merck & Co., NIH, HVTN	3000 m and w	Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, USA
V2	A Multicenter Double-Blind Randomized Placebo-Controlled Phase IIB Test-of-Concept Study to Evaluate the Safety and Efficacy of a Three-Dose Regimen of the Clade B-Based Merck Adenovirus Serotype 5 HIV-1 Gag/Pol/Nef Vaccine in HIV-1 Uninfected Adults in South Africa	HVTN503	2B	Merck Research Laboratories, NIH, HVTN, SAAVI	3000 m and w	South Africa
V3	A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX B/E) Boosting in HIV-Uninfected Thai Adults	Alvac + AIDSVAX	3	Thailand Ministry of Public Health, Thai AIDS Vaccine Evaluation Group, Armed Forces Research Institute of Medical Sciences	16,402 m and w	Thailand

INTRODUCTION

No "magic bullets" of prevention are on the horizon and a vaccine against HIV is likely a decade or more in the future. But in the next several years results from clinical trials testing a variety of HIV prevention interventions will become available. Other products are nearing entry into efficacy studies or are in development.

Though the field of HIV prevention research has blossomed in recent years, researchers have few opportunities to network and share their work. Donors are making increasing investments in prevention research, yet efforts remain largely uncoordinated. Much of the scientific knowledge accumulated about HIV over the last two decades points to the potential of combination approaches to prevention and treatment, but a variety of barriers inhibit full exploration of these opportunities. With multiple products approaching Phase III studies and finite clinical research capacity, those interested in the field are increasingly calling for a thoughtful process that can make credible choices about priorities for efficacy studies.

In September 2006, the Forum for HIV Collaborative Research brought together an interdisciplinary group of researchers, product developers, policy makers, and community advocates to discuss the status of HIV prevention research and identify priorities for accelerating research and global delivery of HIV prevention interventions. The meeting, titled "Biomedical Interventions for HIV Prevention Working Group Meeting," was held in Arlington, Virginia and was supported by the Bill & Melinda Gates Foundation.

On the meeting's first day, researchers made presentations on the status of research on several HIV prevention interventions: male circumcision, female-initiated barrier methods, HSV-2 treatment, microbicides, pre-exposure prophylaxis, and treatment of the index partner. Attendees debated the advantages and disadvantages of each intervention. During the meeting's second day attendees discussed priorities for prevention trial sites and unanswered questions about ARV therapy. At the meeting's closing session attendees discussed gaps in information, activities, and coordination.

This report is meant to serve as a summary of the meeting and to present priority issues and needed action steps in the field of HIV prevention research. It summarizes the status of research on the six interventions discussed at the meeting and identifies key next steps in that research. It then explores cross cutting issues in the HIV prevention field and concludes with a list of choices facing stakeholders.

STATUS OF RESEARCH ON NEW HIV PREVENTION INTERVENTIONS

MALE CIRCUMCISION

Compelling data from cohort and randomized clinical trials suggest that male circumcision lowers the risk of HIV infection [1-4]and these findings are supported by a strong biological rationale for the protective effect of male circumcision (reviewed in [5, 6]). In 2005 a Phase III trial of male circumcision, held at Orange Farm in South Africa, was stopped early due to the magnitude of the observed HIV prevention effect [3]. Men in the study who had been circumcised were 60% less likely to acquire HIV than those in the control group. Two additional effectiveness trials, one in Rakai, Uganda, and another in Kisumu, Kenya were stopped early, following the Data Safety Monitoring Board (DSMB) review in December 2006. An interim analysis by the DSMB determined that the intervention reduced the rate of infection by 48% (in Uganda) and 53% (in Kenya) [7].

Men in the study who had been circumcised were 60% less likely to acquire HIV than those in the control group.

Current evidence suggests male circumcision may also have a protective effect against several diseases other than HIV, including urinary tract infections in infants, syphilis, chancroid, HSV-2, human papilloma virus, invasive penile cancer, and cervical cancer in female partners [3, 8, 9]although other studies did not confirm this [1, 10]. Forthcoming Phase III results will provide information on the impact of male circumcision on female partners, but a previous survey suggests male circumcision may provide HIV prevention benefits for women as well as men. Quinn et al [11]found that of 47 couples in which the circumcised male partner was HIV positive and had a viral load under 50,000, no female partners were infected after two years. This compared with 26 infections among the 143 female partners of uncircumcised HIV positive men.

Male circumcision could potentially have a significant public health impact. Williams et al [12] estimated that 100% uptake of male circumcision could avert two million new infections and 300,000 deaths over ten years in sub-Saharan Africa, and 5.7 million new infections over 20 years. Cost effectiveness estimates are highly sensitive to HIV prevalence, the cost of the procedure and the risk reduction associated with this intervention. A study by Kahn et al [13] estimated a cost of $181 per HIV infection averted over 20 years in Gauteng, South Africa, which has a 25.6% prevalence rate. At 8% prevalence, cost per infection averted would be approximately $550, a rate that compares quite favorably with other prevention interventions.

A compilation of 13 studies in sub-Saharan African suggested that major barriers to acceptability of male circumcision are cost, fear of pain, and concern for safety. Major

facilitators of acceptability are improved hygiene, reduced risk for sexually transmitted infections, and attractiveness[14].

Male circumcision has been called an "anatomic vaccine for life," a one time procedure that could offer benefits over a lifetime. Yet many observers urge caution and note that several issues require further exploration. Early indications from the trial in Rakai suggest that the protective effect of this intervention is greatest in the highest risk men; the benefit may not be as evident in populations of low risk men.

Scale up of male circumcision could lead to widespread increases in risky behavior or "risk compensation." The Orange Farm trial found that circumcised men had a higher mean number of sexual contacts [3]. (However, when behavioral differences between study arms were controlled for, the protective effect of male circumcision did not change.) Results from research in one country or one community may not be applicable elsewhere; each country may want to evaluate this intervention, taking into account its own cultural values, including possible stigma against those who have been circumcised.

Safety is a paramount concern. Within research settings the complication rate from male circumcision is relatively low – 3.8% in the Orange Farm trial; 1.7% in the randomized control trial in Kisumu [15]. But in practice, much higher complication rates have been observed. A study in Nigerian and Kenyan hospitals estimated a 12% complication rate from male circumcision. A study in Bungoma, Kenya found a complication rate of 17.5% in medical settings and 35% in traditional settings[16].

The widespread delivery of male circumcision presents several significant challenges. Operations research is needed urgently to develop models for training practitioners in the health sector in safe circumcision techniques. Health care facilities need to be adequately equipped to provide the service. Male circumcision is an opportunity to bring people into clinical settings where other reproductive health care can be provided -- including voluntary counseling and testing, treatment of sexually transmitted infections, behavioral counseling, and other HIV prevention services -- but strategies are needed for integrating male circumcision into these services.

Male circumcision demonstrated efficacy in the context of clinical trials in which high quality medical techniques were available and trial participants were consistently reminded of the importance of condom use. Delivery of male circumcision in the real world will require a determined focus on safety and consistent and ongoing emphasis on condom use. Research is also needed to develop easier circumcision methods that can be used safely in the field.

Some have warned that insufficient medical expertise in many regions could lead to many injuries as male circumcision is scaled up, undermining public support for the intervention. Several meeting attendees called for extensive training of health care

providers. In some areas, it may be appropriate to train traditional male circumcision providers in safe procedures, especially since many men may seek their services.

Public health guidance is needed on a variety of issues, including the best age at which to administer male circumcision, taking into account the greater difficulty of performing male circumcision in adults. UNAIDS has launched a series of stakeholder meetings in east and southern Africa to discuss scale up of male circumcision, and the World Health Organization (WHO) has developed a training manual for practitioners in hospitals and health centers [17].

What's next?

- Urgent need for operational research on delivery, acceptability and community issues, and staff training models
- Develop marketing and communications plans in anticipation of possible effectiveness results
- Develop new surgical and non-surgical techniques for safer and easier use
- Establish clear guidance for practitioners and policy makers on provision of male circumcision, and integration of the procedure into broader health services
- Develop monitoring and evaluation research to assess behavioral disinhibition/risk compensation and adverse events
- Assess the impact of male circumcision services on HIV incidence in communities as circumcision is introduced
- Further investigate the biological mechanisms by which the foreskin increases risk of HIV acquisition

FEMALE INITIATED BARRIER METHODS

Female initiated barrier methods such as diaphragms and female condoms have been used for years as contraceptives. Female condoms are also promoted as disease prevention methods. However, until recently, no studies have tested whether these products can help prevent HIV infection in women.

Several factors support the expectation that barrier methods may prove efficacious in HIV prevention. Cervical barriers, including the female condom are made of materials (polyurethane, latex or silicone) that are impermeable to HIV, bacteria and sperm. All these female initiated barrier methods cover the cervix where many of the cells that are most susceptible to HIV infection are found. Blocking HIV from that area may prevent a significant percentage of infections [18-22]. Pregnancy rates with use of these methods are comparable to those for male condoms.

Cervical barriers are made of materials that are impermeable to HIV, bacteria and sperm.

The first HIV prevention effectiveness study of the diaphragm is now being conducted in South Africa and Zimbabwe and is due to produce results in 2007. Another Phase III study, to examine the effectiveness of diaphragm against sexually transmitted infections in Madagascar, is set to begin in 2007. Three previous effectiveness studies of the female condom found no difference in acquisition of sexually transmitted infections among women who received female and male condoms, as compared to those receiving male condoms only. There was sufficient evidence for most scientists and providers to conclude that female condoms are as effective as male condoms for disease prevention [23].

One presenter reminded the group that, "Not all cervical barriers are created equally." A variety of novel barrier designs have recently been developed and they are being tested with different gel formulations. As is the case for all prevention interventions, promotion of male condoms among trial participants is ethically required, but it confounds researchers' ability to measure the relative impact of the diaphragm and male condoms. This is because, unlike the female condom, women can simultaneously use a diaphragm and a male condom. Measurement of adherence to product use is also difficult as it relies on participant self reports and complicates the ability to assess the efficacy of the product.

Many believe cervical barriers have great promise as HIV prevention interventions. Women can already use barrier protections and they are commercially available worldwide. But a number of concerns about the applicability of female-initiated methods in HIV prevention were raised. One is cost – the female condom is 27 times as expensive as the male condom. In addition, these barriers are only appropriate for women who do not want to become pregnant. Diaphragms are also initially expensive but they can be reused, making their cost per coital act much lower than the female condom.

There is also the concern that many women simply might not want to use these products. Advocates counter that diaphragms, the female condom, and other barrier methods have never been adequately marketed. Past acceptability studies, and acceptability as measured in the current trial, demonstrate that many women do want to use these interventions. Other issues with the diaphragm include fitting and leaving in the device continuously or longer than instructed so that it is completely dissociated from coitus. Much more effort is needed to examine these issues and to design and sell these products so they will be seen as sexy and pleasurable.

What's next?

- Develop effective marketing strategies in anticipation of effectiveness results from clinical trials of the diaphragm
- Conduct studies on continuous diaphragm use and on other cervical barriers that do not require fitting
- Improve marketing for the female condom

- Make products more affordable
- Conduct more research on combination interventions, such as cervical barriers with microbicides.

HSV-2 TREATMENT

Herpes Simplex Virus-2 (HSV-2) has a synergistic relationship with HIV. HSV-2 infection increases susceptibility to HIV infection and infectiousness among people living with HIV. Increased infectiousness among HIV/HSV-2 co-infected persons is likely related to the increased plasma and genital HIV viral loads during HSV-2 reactivations, even when asymptomatic. HIV infection causes longer duration of HSV-2 lesions (among people with CD4+ cell counts below 200 cells/ul) and increases the likelihood of HSV-2 acquisition and transmission. On a population level, these different interactions between HSV-2 and HIV could be significant; in sub-Saharan Africa, approximately 80-90% of HIV-infected persons and 50% of HIV-negative women also are HSV-2 infected [24-29].

In sub-Saharan Africa, approximately 80-90% of HIV-infected persons and 50% of HIV-negative women also are HSV-2 infected

Several studies are now testing the efficacy of HSV-2 treatment as an HIV prevention strategy, with most studies using acyclovir as the intervention. Three studies are testing the potential of episodic treatment of HSV-2 to reduce shedding of HIV. Because only a minority of people with HSV-2 are symptomatic and only a portion of those seek care, episodic treatment may have limited public health impact even if it is efficacious. A study of episodic HSV-2 treatment in Ghana reported no reduction in HIV shedding [30]; data from a study in Malawi is being analyzed; a study in South Africa is due to report results in 2007.

Suppressive therapy, in which treatment is provided on an ongoing basis, has more promise as an effective public health intervention. Nine trials have been run or are ongoing in sub-Saharan Africa; data are available on two. One of these, the study in Burkina Faso among HIV/HSV-2 coinfected women demonstrated a reduction in HIV viral load in blood plasma and the genital tract of the intervention group[30]. A recent trial among HIV/HSV-2 coinfected men who have sex with men in Peru showed similar findings with reduced HIV levels in plasma and rectal secretions in the intervention group [31]. Results from three other trials are being analyzed. Three additional early stage trials are due to report results in 2007, and two phase 3 trials are ongoing (see Figure 1).

Several factors support the expectation that HSV-2 treatment can significantly impact the HIV epidemic. There is a clear biologic and epidemiologic link between the two viruses, and mathematical modeling suggests HSV-2 suppression could have a major impact on HIV incidence.

However, the skeptics will argue that the effect of HSV-2 to enhance HIV susceptibility or infectiousness may in part be mediated by other behavioral and/or biologic factors. And even if HSV-2 treatment is shown to be efficacious in preventing HIV acquisition, implementation will be expensive and complex, requiring widespread HSV-2 testing and increased availability and lower costs of acyclovir. Currently the lowest cost for generic acyclovir is $40 per person per year, meaning considerable resource demands if the intervention is delivered broadly to HIV-negative individuals.

Adherence could be a challenge as well, particularly because HSV-2 is often asymptomatic, and people may be reluctant to take a treatment for a mild or asymptomatic infection. Nevertheless, the rationale for counseling HIV-infected and at-risk HIV-uninfected persons about HSV-2, as well as for more operations research to facilitate delivery of HSV-2 treatment remains strong.

What's next?

- Prepare for trial results due in 2008 and 2009
- Use modeling for 'roll-out' and prioritization of how best to target HSV-2 interventions
- Conduct operations research to develop adherence and scale up strategies
- Determine best formulation of therapy
- Work to reduce cost of primary intervention
- Improve diagnostic test for HSV-2

MICROBICIDES

Microbicides are substances designed to reduce the transmission of HIV during sexual intercourse, and could potentially be made in many forms, including gels, creams, sponges, films, lubricants, suppositories, tablets, vaginal rings or diaphragms.

A variety of microbicide products are now in development and testing. Three non-specific entry inhibitors are in Phase III trials that are expected to report results over the next several years.(In January 2007 two trials of cellulose sulfate gel were stopped early because a higher number of HIV infections were found in the active compared with the placebo group in one of the trials[32, 33]). The next generation of microbicide candidates is also in pre-clinical development and safety studies. These microbicide candidates include several that incorporate ARVs or combinations of these drugs [34-36]. A limited number of concepts are currently in clinical safety trials; several others are still in preclinical development [37].

An important challenge for the field is to develop products that are easy to use and which do not require application immediately before sex, for example gels that could be applied once a day or less often and maintain their protective capacity. At least one of the new ARV-based candidates is now being tested in both a daily use gel as well as a sustained-use intra-vaginal ring [38, 39]. Researchers are also looking for more reliable compliance measures that can accurately assess how often trial participants use the study product. Coitally dependent microbicides present particular challenges to researchers attempting to measure product usage.

Developing and testing combination products (such as two or more microbicides, or microbicides with pre-exposure prophylaxis – PrEP - or vaccines) is now an important priority for the field. Key challenges to accelerated microbicide research include lack of validated animal models, lack of regulatory agency experience in microbicide product review, inadequate industry engagement in the field, and the need for better estimates of incidence in clinical trial settings.

The next generation of microbicide candidates is in pre-clinical development and safety studies. These microbicide candidates include several that incorporate ARVs or combinations of these drugs.

Several concerns were raised about the ultimate impact of microbicides. Not all women will want to use a vaginal product, and male partners might object. Microbicides might not have sufficient bioavailability in the vagina to be effective. Rectal transmission may represent a significant share of HIV transmission risk, yet none of the current studies assess the efficacy of rectal use of microbicide candidates, although there are some rectal safety studies ongoing. Women may also use other products during sex that could theoretically compromise the effectiveness of a microbicide.

Several people said the case for microbicides remains strong, driven by the clear need for female-initiated HIV prevention interventions. Protection using microbicides has been demonstrated in monkeys [40-43]. Highly potent ARVs that act early in the HIV lifecycle are now being tested as microbicide candidates, as are combination approaches. Furthermore, advances have been made in developing formulations for "coitaly-independent" products that would allow women to insert or apply the microbicide hours, days or even months before sexual activity, hopefully avoiding compliance issues and the need to negotiate with sexual partners.

"We need to bring business schools together with scientists," to design marketing campaigns for microbicides, one person said. "We need to make it sexy if we expect people to use these products."

What's next?

- Prepare for effectiveness results from products now in clinical trials

- Accelerate development and testing of next-generation products and new delivery technologies
- Work on marketing techniques (e.g. making products fun and sexy)
- Identify animal models that more accurately predict human outcomes
- Plan for operational research (e.g. adherence, risk stratification, male partner concerns)
- Expand research on rectal use of microbicides

PRE-EXPOSURE PROPHYLAXIS (PREP)

PrEP would allow people to take one pill a day and receive significant protection against HIV, much like a daily birth control pill is used to prevent pregnancy. Studies in primates have demonstrated the effectiveness of PrEP, at least for a period of time [44-46]. It is not yet known now whether PrEP will be effective in people. Two ARV products are being tested in PrEP clinical trials: the single agent tenofovir was tested in West Africa,[1] [47] and is currently being tested in clinical trials the USA and Thailand; the combination of tenofovir and emtricitabine in one tablet (truvada) is being tested in Botswana and Latin America.

In August 2006, findings from the West Africa study of tenofovir (in a cohort of high risk women) were reported at the International AIDS Conference in Toronto[47]. The study was a two-arm, placebo-controlled, double-blind randomized trial, in which the primary endpoints were safety and preliminary effectiveness (HIV seroconversion) of oral tenofovir. Of the 936 HIV-negative women enrolled in the trial, eight seroconversions occurred — two in the tenofovir group and six in the placebo group. These results were not statistically significant. Tenofovir was shown to be safe, with no significant differences identified between treatment groups in clinical or laboratory outcomes. Adherence to the daily regimen was estimated at approximately 70%. There was no evidence of self-reported risk compensation (disinihibition) among study participants.

In August 2006, findings from the West Africa study of tenofovir showed those in the intervention group experienced no increase in adverse events.

The Thai study (injection drug users) is expected to report efficacy results early 2008, and the US study (men who have sex with men) will produce safety results in the third quarter of 2009. Of the truvada studies, Botswana (heterosexual men and women) is scheduled to report efficacy results in early 2009 and the Latin American study (MSM) in late 2009. PrEP trials in Cameroon and Cambodia closed early when community members raised concern about trial participant protections and community involvement.

[1] The West Africa study was done at sites in Cameroon, Ghana, and Nigeria. For a variety of reasons, data collection in Nigeria and Cameroon was stopped prematurely.

Additional clinical trials may be needed to answer a range of significant questions in PrEP research. Current trials are not powered to establish efficacy below 60%. One researcher suggested this may not be a bad thing as PrEP might be impractical and prohibitively expensive at lower efficacy rates. PrEP is expected to be cost effective at high efficacy rates similar to those observed with malaria and TB chemoprophylaxis. Current trials are not evaluating the safety of PrEP in people with Hepatitis B infection, for use in combination with acyclovir, or among adolescents or pregnant women.

A meta-analysis of current studies is possible, but will not fill holes in data for specific populations. The most notable data gap is adequate evaluation of safety and efficacy among women. Other questions that will go unanswered by current trials are optimal dosing regimens and whether "weekend dosing" (or episodic use) is effective. There are also no head-to-head comparisons of the two drugs being used in PrEP, and no current studies of other promising PrEP candidates [48] including 3TC (lamivudine), FTC (emtricitabine) alone, integrase inhibitors, or entry inhibitors.

A host of relevant questions remain regarding wide use of PrEP in the field. Primate data raises questions about long term efficacy of PrEP and data on safety and toxicity is limited to 18 months. As one person said, "we have massive amounts of no information." There is also the potential for PrEP to lead to development of drug resistance, though transmitted tenofovir resistance is extremely rare. What if people who do not know they are infected with HIV and take PrEP? Will they be more likely to transmit drug resistant virus? How will their treatment options be affected once they learn their HIV status?

Adherence to PrEP may be sporadic, with people taking the drug just before a risky evening rather than daily. The very long term intracellular half life of tenofovir and emtricitabine suggest that protective effects may persist even if some doses are missed. Hopefully, the current studies will allow us to know what levels of drug are needed for protection. It is quite possible that risk taking will increase among people who are taking PrEP and believe themselves to be protected. If this occurs, will the protection effects be cancelled out? And then there is a question of access. PrEP drugs are ARVs that would normally require a prescription. If that is the case, it would make it more difficult for community health workers to distribute the drug.

Still, there are many reasons to believe that PrEP holds real promise as a new HIV prevention tool. The concept of once-daily dosing using drugs with long half-lives that act prior to the integration of HIV into cells has scientific merit. PrEP drugs tested thus far appear safe and well tolerated. Infections did occur in primate studies, but protection was achieved in a significant percentage of cases, and drug resistance was not observed in the majority of animals that became infected despite ongoing PrEP use. Much of the primate testing was done under conditions in which viral challenge involved extremely high doses of viruses and routes of transmission that are far

more likely to establish infection than heterosexual intercourse [49]. Use of two ARVs in combination would help guard against the selection of resistant variants.

What's next?

- Prepare for results from clinical trials in 2008
- Address gaps in current research, including safety and efficacy in women and research on additional candidate drugs
- Expand clinical trial capacity for PrEP
- Develop standards for community involvement and prevention programming in PrEP clinical trials
- Develop regulatory strategies to allow more efficient testing of combination products
- Develop policies for compensation to trial participants in the event of physical harm and liability protections for manufacturers
- Clarify distribution strategies (e.g. need for a prescription, targeting of delivery)

INDEX PARTNER TREATMENT

Evidence strongly suggests that reduction of viral load through ARV treatment reduces the likelihood of HIV transmission [50-52]. It is therefore possible that treatment of HIV infected individuals earlier in disease course than recommended by current treatment guidelines may reduce infectiousness. Treatment should be provided for the good of the person with HIV disease, and currently conclusive evidence that earlier therapy will benefit the patient is lacking, although available data do indicate that earlier treatment may be clinically beneficial [53]. Researchers are seeking to better understand the interaction of ARV treatment and HIV infectiousness and there are a variety of areas that require further exploration. For example, it will be important to understand the prevention efficacy of both Pre- and Post Exposure Prophylaxis. Measurement of blood plasma viral load may not correlate with virus levels in semen or cervical secretions, and further research is needed on drugs that concentrate in semen and cervical mucosa. Little is known about genotypic and phenotypic viral correlates of infectiousness, hereditary resistance, innate resistance and acquired immune resistance. Increasing levels of transmission of drug resistant virus pose additional challenges for both treatment and prevention.

Researchers are seeking to better understand the interaction of ARV treatment and HIV infectiousness and there are a variety of areas that require further exploration.

Two encouraging observational studies presented at the International AIDS Conference in August 2006 documented significant reduction in the HIV transmission rates following initiation of effective antiretroviral therapy[52, 54]. An ongoing study, HPTN 052, is testing whether early initiation of therapy is effective in reducing HIV transmission. In

one study arm volunteers are provided ART when their CD4 count reaches 350-550 cells/ul. In another arm, volunteers receive ART at CD4 counts or 200 or less, or when they have an AIDS-defining illness. The pilot phase has been completed and the study is ongoing. If the full study is moved forward, it will seek to enroll 1750 serodiscordant couples at nine sites in six countries.

What's next?

- Additional research on drugs that concentrate in semen and cervical mucosa
- Study the impact of treatment on development of viral resistance
- Study the impact on risk behavior, including condom use

PRIORITIES TO ADVANCE THE FIELD

SUPPORT PREVENTION TRIAL SITES

Clinical research sites and the people who work at them should be seen as long term assets in the prevention field. "You lose incredible knowledge if you close a site after one trial," one person said. "We need to use valuable skills that are developed during a study." Local members of the research team often need training and other supports, particularly in the area of laboratory skills. Experienced staff from nearby sites can provide mentoring, and networking among study staff can be highly beneficial.

In order to avoid "brain drain" of trained staff, career paths and links to local universities need to be better established. Local study staff, including researchers and other site personnel, could be paid to help establish other sites, and do training and site maintenance during breaks in research studies.

"You lose incredible knowledge if you close a site after one trial. We need to use valuable skills that are developed during a study."

Maintenance of trial sites should figure prominently as researchers and donors plan clinical research. It may be appropriate to layer studies to minimize gaps between studies at sites. Donors, in particular, should establish the imperative of using site resources well, but also maintain enough flexibility to be able to close sites when necessary.

Sustained capacity at trial sites may help researchers better understand dynamics of local epidemic. Lower than expected incidence rates have emerged as a critical challenge to HIV prevention research. Lower rates speak to the efficacy of prevention interventions provided in the context of research, but they also reflect the need to develop more accurate predictions of incidence as a trial is planned. Sites based in communities with mature HIV epidemics may have lower incidence rates, and may be most appropriate for safety studies. Sites in communities with younger epidemics may be better suited for efficacy trials.

"We need to have a longer view of where we are going. There's a need for more coordination, but also more flexibility and adaptability to changing conditions."

Broad knowledge of the host community is important to a full interpretation of study data. Ideally, investigators will know the host community well enough to have a sense of who is not enrolling in studies as well as who is, and use this understanding to help them assess generalizability of findings. Interventions that might work in mature epidemics might fail in those with newer epidemics. Interventions that show efficacy in a trial might be less effective in the real

world. For example, researchers ask women in clinical trials to use condoms and may remove them from the trial if they become pregnant. Yet in real life many women will want to become pregnant and may be far less likely to follow safer sex guidelines that made sense in the trial.

Different perspectives on the usefulness of establishing networks of research sites were discussed. Several people noted that greater coordination and sharing of knowledge among prevention sites would be useful, and more rational planning of site usage is needed. Others noted that networks can create inflexibility and unnecessary bureaucracy. "We need to have a longer view of where we are going," one person said. "There's a need for more coordination, but also more flexibility and adaptability to changing conditions." Effective sites can be developed and be quite successful outside of a network structure, as demonstrated by sites funded through individual grant mechanisms rather than network mechanisms. A word of caution was expressed regarding the building of big networks: funders must ensure these structures remain flexible and do not create needless delays.

New opportunities to improve linkages in HIV prevention research are provided by bi- and multi-lateral HIV care and treatment programs. Information technology capacity is being developed as part of the President's Emergency Plan for AIDS Relief (PEPFAR) and other service delivery efforts as providers seek to track consumers over time. "There is a tremendous infrastructure being built for PEPFAR," one person said, "and it's an opportunity to layer research onto that…it's a moment in time we should not lose." A representative from the U.S. Office of the Global AIDS Coordinator noted that PEPFAR is also introducing a Public Health Evaluation (PHE) system that is designed to promote operational research and optimize introduction of current and new interventions and PEPFAR programs can help coordinate prevention research at the country level. A new commodity procurement mechanism called Supply Chain Management System (SCMS) has been set up to create economies of scale in purchasing and supply chain management. An African Clinical Trial Portal (www.africaclinicaltrials.org) now maps 91 trial sites on the continent.

"There is a tremendous infrastructure being built for PEPFAR and it's an opportunity to layer research onto that…it's a moment in time we should not lose."

FILL GAPS IN SCIENTIFIC KNOWLEDGE

A variety of scientific questions, if answered, would significantly advance development of new biomedical prevention interventions. One question researchers are asking is what constitutes the ideal ARV for prevention? Is it potency? The characteristic of a high barrier to drug resistance? Better understanding of the benefits and risks of combination versus single agent interventions is needed. Combination approaches may have better

tissue and organ coverage, block a wider variety of viruses, and more effectively prevent development of viral resistance.

Combination products may also add complexities to the regimen and increase costs. The benefit/cost ratio of adding a second drug may depend on the efficacy of the first drug when administered alone. One challenge is that regulators require the efficacy and safety of each agent be demonstrated separately in order to show the contribution of each agent to the efficacy of the combination. But testing each component of a combination intervention may not always be feasible. For example, it would require a 20,000 subject trial to demonstrate the superiority of tenofovir/FTC verses tenofovir alone in PrEP.

"the bar has to be higher, but where is the bar?"

By using drugs developed for treatment in order to prevent infection are we potentially breeding the "Andromeda strain" of HIV? There are some concerns about the use of R5 coreceptor antagonists which might favor the transmission of X4-tropic viruses. Few documented cases of people being infected with CXCR4 tropic virus exist. Attendees asked what the consequences of transmission in the presence of a CCR5 antagonist might be. Major questions remain about the potential for drug resistance development both in HIV negative individuals who receive PrEP and are later infected and among those who take PrEP not knowing they have HIV.

On the issue of long term safety of ARV use in HIV negative individuals one person said that, "the bar has to be higher, but where is the bar?" Use of animal models needs to be standardized so animal research can better address long term safety questions. Recently, efforts to standardize animal use have been initiated, but no ideal animal model exists and animals will never be a surrogate for proof of concept or efficacy trials. Animal models also need to be used more effectively to help set clinical research priorities.

Another question is how PrEP differs from Post-Exposure Prophylaxis (PEP) in terms of prevention efficacy. In a monkey challenge model, when a CCR5 antagonist (CMPD167) was given for four days pre-challenge, there was no protection [40].When the drug was given for 10 days post challenge there was 50% protection. What are the implications for HIV prevention research?

The demands of regulatory authorities are central to framing the research agenda. Ongoing discussion is needed on how to use systemic ARV therapies in PrEP and other interventions, as pointed out by an FDA representative. It is important to conduct proof of concept studies with different doses and different combinations before starting Phase III studies. Any approved product for PrEP will not likely be available over the counter and will require a prescription, according to the FDA.

It is important to study viral resistance potentially caused by use of prevention drugs to ensure biomedical prevention interventions do not jeopardize an individual's treatment options if he or she becomes infected.

Sexually transmitted infections should be a secondary endpoint in ARV prevention trials, and the agency believes that an increase in STIs among trial participants would raise concerns about the overall public health impact of such interventions.

According to the FDA, PrEP studies should be powered at a level similar to microbicide studies, which are generally designed to detect a 30% - 50% reduction in transmission. Adequate measurement of toxicity from a chronically dosed oral product will need to be factored into power calculations for PrEP studies. The amount of data required will be different depending on whether the product is already approved for use in another indication. FDA is considering holding an advisory committee hearing on PrEP soon.

Criteria for selecting optimal PrEP candidates include safety profile, ease of use, mode of action and pharmacology, antiviral profile, and cost-effectiveness [48]. Based on these criteria, lamivudine was suggested as an interesting candidate for use in PrEP, though issues including development of resistance and safety for individuals with hepatitis B infection would need to be carefully evaluated.

Other potential areas for research on new HIV prevention interventions include the effect of HPV vaccines on HIV acquisition, approaches to providing reproductive health services to pregnant HIV infected women, and safety of hormonal contraception methods in HIV positive women.

Cost effectiveness questions about the resources necessary for prevention drugs versus funds required to treat the disease being prevented need to be considered. Attendees noted that prevention expenditures should not impact the budget for treatment of HIV infection. It is also important to study viral resistance potentially caused by use of prevention drugs to ensure biomedical prevention interventions do not jeopardize an individual's treatment options if he or she becomes infected.

PROMOTE COORDINATION WHILE DRIVING INNOVATION

The Working Group members agreed that the field of HIV prevention research would benefit from some level of improved coordination. There are gaps in research that need to be filled; there are overlapping efforts that result in inefficient use of resources; and there is fierce competition for financial support.

"NGO wars..inter- and intra-foundation politics…and battles for funding," in the prevention field. "Everyone knows the stories; its time to stop!"

One person at the meeting referred to "NGO wars..inter- and intra-foundation politics…and battles for funding," in the prevention field. "Everyone knows the stories; its time to stop!" Investigators seeking funding are sometimes reluctant to be entirely forthcoming about the timeline of their prevention research, worried that scarce funds will be

redirected to interventions that seem closer to implementation. Committees that review research proposals are often risk averse and do not support innovative ideas.

Many people spoke to the need for some kind of forum or planning body where research can be coordinated and tough decisions made. "The treatment field has lots of mechanisms to have discussions," one person said, "prevention does not." Combination approaches are an example. The increasing interest in combination interventions is not matched by opportunities to review and plan the most promising research. "We need to look for additive and synergistic effects of multiple approaches to prevention," a researcher said.

Resources available for prevention research have expanded, but funding is not organized and coordinated – a particular concern since funding often drives the interests of investigators. Multiple funders interested in one particular intervention can distort research priorities. "Funders need to talk to each other and streamline research in the field," one person said.

"There are hard choices, but we have to think about the public health impact."

Several working group members called for a more "systematic, quantitative" and pragmatic approach to assessing a range of potential interventions: "we need a plan, not an investigator driven agenda," one said. "How would the private sector prioritize research?" one person asked. "They'd look at what is the potential market, the chance of success, the cost and potential profit. We need more of that thinking." Another said that, "There are hard choices, but we have to think about the public health impact." Some called for an "enterprise model" that would provide a strategic plan for research and establish a mechanism to set priorities.

Coordination will be all the more important in the future if the clinical trial infrastructure is able to accommodate fewer studies. If forthcoming trial results identify additional prevention interventions, these interventions will need to be provided to clinical trial participants, likely driving up sample sizes and potentially limiting the number of Phase III trials that can be run. In this scenario, "we can't escape making choices." "We need an investigator driven effort," another said, "but then when we get to Phase III we need a body to decide what goes ahead for testing."

"You can't run science by committee, but you can coordinate. There is already coordination within fields but not across fields."

While few argued the points above, many people felt that fostering innovation and diversity in pre-clinical research is critical, and that such an effort cannot be managed from above. "The top down approach is only good if you know exactly what you want," said a researcher. Others said that the debate between coordination and investigator-initiated research is a "false dichotomy." It is possible to identify research priorities, set aside funding, and then invite proposals in those areas. "You can't

run science by committee," one person said, "but you can coordinate. There is already coordination within fields but not across fields."

Several people also called for efforts to more fully engage industry in HIV prevention research. Scientific agendas are waiting to be pursued, and greater industry involvement would broaden the research effort. One person called for more transparency in the way donors make prevention research funding decisions.

BUILD OWNERSHIP IN HOST COMMUNITIES

Community and national government support is crucial to success of prevention research. Several people highlighted the need to include more people from countries that are hosting research, including researchers and community members, in future meetings on HIV prevention research. "It's important that people own the research," one person said. "We need more people like me, an African woman researcher, at the table."

Involving more researchers from less developed countries may require a reassessment of how research is funded. In many research budgets the overhead allocation for African institutions is quite low when compared with US and UK institutions. Increasing overhead is key to building sustainable institutional capacity. Investments in site maintenance between trials and capacity building (including among national regulatory authorities) are also important.

"We need more people like me, an African woman researcher, at the table."

A variety of issues affecting trial participants, including participant protections and standard of care in trials, cut across the field of HIV prevention research. Concerns about participant rights and community involvement in research have lead to the cancellation of two PrEP trials in recent years [55, 56]. In many cases, international ethical guidelines do not sufficiently address core issues of importance to participants and host communities. Resolution of these issues to the satisfaction of researchers, donors, and participating communities would be a significant step forward for the prevention research field. Areas where policies need to be clarified and standardized include:

- Compensation for physical harm caused as a result of trial participation (including development of viral resistance in seroconverters who participate in clinical trials of PrEP or ARV-containing microbicides)
- Long term access to ARV therapy if a participant becomes infected with HIV during the trial
- Care and referral for individuals who "screen out" at trial enrollment due to HIV infection or another condition that makes them ineligible

- Long term access to products that are proven efficacious and licensed for use as a result of the trial
- Standards for informed consent
- Strategies to reduce stigma against trial participants and consumers of HIV prevention products when products are licensed for use

Standards are also needed for community engagement in research. "It's important to consult with the community from the beginning of the research concept," "not once the protocol is done and you are just seeking sign off." Researchers should include community and resolve community issues up front in order to avoid problems after trials have been launched.

"Its important to consult with the community from the beginning of the research concept, not once the protocol is done and you are just seeking sign off."

Researchers also need to do more to promote scientific research literacy in communities, as better understanding of research will improve the informed consent process, community engagement in research, and, hopefully, public acceptance of products when ready for use. Good communications are essential too. Researchers need to build relationships with the local media and advocacy groups, and be candid about the time it may take to test interventions and have new interventions ready for delivery to the community at large.

UNAIDS is holding several meetings relevant to these issues. Upcoming consultations will address subjects such as standard of care in prevention clinical research, services for those who "screen out," models for community engagement, and revision of the UNAIDS/WHO HIV vaccine research ethical guidelines.

PREPARE FOR GLOBAL DELIVERY

HIV prevention interventions can only be effective against the epidemic if they are widely accessible and used in populations at elevated risk of infection. The need to do more to promote delivery and use of prevention technology was a recurrent theme at the meeting. Several people called for a well funded and coordinated operational research strategy for delivery of male circumcision. Though results from two circumcision trials are not due until 2007, operational research can begin now in places where male circumcision is already being delivered.

"One assumption we make is that people at highest risk want these products the most, but that's not true."

None of the new interventions will be 100% effective. Operations research should be used to develop models for integrating partially effective interventions into the overall prevention package. Against a backdrop of AIDS treatment scale up, operations research should help identify approaches for

integrating delivery of new prevention tools into broader health services that include treatment, voluntary counseling and testing, and STI screening.

Both the World Bank and the Global Fund will provide support for operational research through their grants, but this funding needs to be set aside in the original grant proposal. WHO is sponsoring operational research for scale up of AIDS services in several countries, but no one is coordinating a comprehensive operational research effort to accelerate wide delivery of current and future prevention and treatment interventions.

"All biomedical interventions need to include a behavioral intervention research component."

Better marketing of products was another recurrent theme. Donors, product developers, and researchers need to give more attention to designing prevention interventions with consumer tastes in mind. Developers should define who should use a product, and then design it for them. "One assumption we make is that people at highest risk want these products the most, but that's not true," one person said. Another summed the situation up: "We do a bad job of marketing sex."

Behavioral interventions and the behavioral dynamics involved in the use of new prevention interventions was not a major focus at the meeting, but several people emphasized that behavioral research should be a key component in prevention intervention design, testing and delivery. "All biomedical interventions need to include a behavioral intervention research component," one person said. Among the many behavioral issues that should be studied are the potential for risk compensation when new interventions are introduced.

Finally, product pricing was raised several times as a significant barrier to widespread access to new and existing interventions. If technologies such as HSV-2 treatment, PrEP or other interventions are to have a major impact on the epidemic, public health officials, donors and manufacturers need to work together to bring prices down and establish adequate purchase capacity.

CHOICES AHEAD

This is a pivotal time in the HIV prevention effort, with new opportunities to deliver proven prevention interventions as other health services are scaled up, and results of trials of a variety of new prevention interventions expected in the coming months and years. Donors, researchers, and communities now face several choices as they seek to maximize the impact of today's HIV prevention research:

* **What should a prevention research forum look like?** Greater collaboration is needed to facilitate design and testing of combination products, share information, connect donors and stakeholders, fill gaps and reduce duplication in the research agenda, and make choices about use of scarce resources. Several Working Group members proposed the creation of a forum for HIV prevention research that could set priorities and promote collaboration without undermining flexibility. Vaccine researchers should be included.

* **What measures will be implemented to promote sustainable trial site capacity?** Site capacity is limited, and there will be increasing demands on clinical sites in less developed countries in the coming years. What will donors, researchers, and national governments do to promote sustainable site capacity and human resource development, and maximize retention of staff expertise?

* **Will the field set priorities for use of Phase III clinical sites?** There may be hard choices to make about which candidate prevention interventions are advanced to Phase III study. Would the forum noted above, or another entity, be appropriate for recommending efficacy trial priorities?

* **How will the priority scientific and research challenges be addressed?** How will the field ensure that the most critical scientific questions – including optimized use of animal models, better understanding of resistance, ideal qualities of ARVs for prevention, and the relative benefits of combination verses single drug interventions – be addressed? What is the plan to more fully engage industry in research and development of new tools? Who will test additional ARVs for use in prevention?

* **Will the field develop new approaches for investigating combination and multi-component interventions?** These interventions have been called the future of HIV prevention, but a variety of funding, development and regulatory hurdles stand in the way of combination interventions. A systematic review of combination possibilities is needed. The field needs to work with regulators to promote testing of combination interventions.

* **What will researchers and donors do to enhance local ownership?** Greater efforts are needed to meaningfully involve researchers from host countries in research. A variety of standard of care and community engagement policies need to be established to ensure protection of trial participants and encourage sustained local support for research.

* **What will the field do to ensure delivery and widespread use of new HIV prevention interventions?** A well funded and coordinated operational research agenda is needed for male circumcision and other potential new interventions. Researchers and product developers need to pay increased attention to consumer preferences and to effective marketing. The advent of new prevention interventions is a major opportunity to increase linkages to broader health services. How will the field take advantage of this opportunity? And what can be done to make prevention commodities more affordable?

How these and other choices are made over the coming years will help determine the ultimate impact of HIV prevention research. This first Biomedical Interventions for HIV Prevention Working Group meeting provided a valuable forum for reviewing the status of research on new prevention interventions, bridging the information gap between the various prevention programs, and identifying the key opportunities and challenges that face the field.

REFERENCES-

1. Gray R, Azire J, Serwadda D, Kiwanuka N, Kigozi G, Kiddugavu M. **Male circumcision and the risk of sexually transmitted infections and HIV in Rakai, Uganda.** *AIDS* 2004,18:2428-2430.
2. Siegfried N, Muller M, Deeks J, Volmink J, Egger M, Low N, *et al.* **HIV and male circumcision--a systematic review with assessment of the quality of studies.** *Lancet Infect Dis* 2005,5:165-173.
3. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. **Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial**. *PLoS Medicine* 2005,2:e298.
4. **Male Circumcision: Current Status and Next Steps**. In. Washington, DC: Gates Foundation; 2006:http://www.hivforum.org/projects/Biomedical%20Prevention.htm.
5. Atashili J. **Adult male circumcision to prevent HIV?** *Int J Infect Dis* 2006,10:202-205.
6. McCoombe S, Short R. **Potential HIV-1 target cells in the human penis.** *AIDS* 2006,20:1491-1495.
7. **Adult Male Circumcision Significantly Reduces Risk of Acquiring HIV**. In: *http://www3.niaid.nih.gov/news/newsreleases/2006/AMC12_06.htm*. National Institutes of Health: National Institute of Allergy and Infectious Diseases; 2006.
8. Lavreys L, Rakwar J, Thompson M, Jackson D, Mandailya K, BH C. **Effect of circumcision on incidence of human immunodeficiency virus type 1 and other sexually transmitted diseases: a prospective cohort study of trucking company employees in Kenya** *J Infect Dis* 1999,180:330-336.
9. Castellsague X, Bosch F, Muniz N, Meijer C, Shah K, de Sanjose S. **Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners**. *NEJM* 2002,346:1104-1112.
10. Reynolds S, Shepherd M, Risbud A, Gangakhedkar R, Brookmeyer R, Divekar A. **Male circumcision and risk of HIV-1 and other sexually transmitted infections in India.** *Lancet* 2004,363:1039—1040.
11. Quinn T, Wawer M, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, *et al.* **Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group**. *NEJM* 2000,342:921-929.
12. Williams B, Lloyd-Smith J, Gouws E, Hankins C, Getz W, Hargrove J, *et al.* **The Potential Impact of Male Circumcision on HIV in Sub-Saharan Africa**. *PLoS Medicine* 2006,7:262.
13. Kahn J, Marseille E, Auvert B. **Cost Effectiveness of male circumcision in sub-Saharan Africa**. *XVI International AIDS Conference, TUAC0204*. Toronto, Canada, August 15, 2006.
14. Westercamp N, Bailey R. **Acceptability of Male Circumcision for Prevention of HIV/AIDS in Sub-Saharan Africa: A Review.** *AIDS and Behavior* 2006.
15. Bailey R, Moses S, Agot K, Parker C, Maclean I, Ndinya-Achola J. **A randomized controlled trial of male circumcision to reduce HIV incidence in**

Kisumu, Kenya: progress to date. *XVI International AIDS Conference, TUAC0201*. Toronto, Canada, August 15, 2006.

16. Bailey R. **Studies of the Association Between Circumcision and HIV Acquisition in Men**. *Biomedical Interventions for HIV Prevention Working Group*. Arlington, VA, http://www.hivforum.org/projects/Biomedical%20Prevention.htm, September 18 2006.
17. **Manual for Male Circumcision Under Local Anaesthesia, Version 2.1**. In: World Health Organization, UNAIDS, JHPIEGO; 2006.
18. Hussain L, Lehner T. **Comparative investigation of Langerhans' cells and potential receptors for HIV in oral, genitourinary and rectal epithelia**. *Immunology* 1995,85:475-484.
19. Gipson I, Ho S, Spurr-Michaud S, Tisdale A, Zhan Q, Torlakovic E, *et al.* **Mucin genes expressed by human female reproductive tract epithelia**. *Bio Reprod* 1997,56:999-1011.
20. Zhang Y, Dragic T, Cao Y, Kostrikis L, Kwon D, Littman D, *et al.* **Use of coreceptors other than CCR5 by non-syncytium-inducing adult and pediatric isolates of human immunodeficiency virus type 1 is rare in vitro**. *J Virol* 1998,72:9337-9344.
21. Prakah M, Kapembwa M, Gotch F, Patterson S. **Chemokine receptor expression of mucosal dendritic cells from the endocervix of healthy women**. *J Infect Dis* 2004,190:246-250.
22. Wira C. **Physiology and Immunology of Female Reproductive Tract**. *Women's HIV Interdisciplinary Network Symposium*. UCSF, May 24, 2004.
23. van der Straten A, Padian N. **Female-controlled physical barrier methods**. *Biomedical Interventions for HIV Prevention Working Group*. Arlington, VA, http://www.hivforum.org/projects/Biomedical%20Prevention.htm, September 18, 2006.
24. Gray R, Wawer M, Brookmeyer R, Sewankambo N, Serwadda D, Wabwire-Mangen F. **Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda**. *Lancet* 2001,357:1149-1153.
25. Serwadda D, Gray R, Sewankambo N, Wabwire-Mangen F, Chen M, Quinn T, *et al.* **Human immunodeficiency virus acquisition associated with genital ulcer disease and herpes simplex virus type 2 infection: a nested case-control study in Rakai, Uganda.** *J Infect Dis* 2003,188:1492-1497.
26. Sacks S, Griffiths P, Corey L, Cohen C, Cunningham A, Dusheiko G, *et al.* **HSV-2 transmission**. *Antiviral Res* 2004,63:S27-35.
27. Wald A. **Testing for genital herpes: how, who, and why**. *Curr Clin Top Infect Dis* 2002,22:166-180.
28. Freeman E, Glynn J. **Factors affecting HIV concordancy in married couples in four African cities**. *AIDS* 2004,18:1715-1721.
29. Freeman E, Weiss H, Glynn J, Cross P, Whitworth J, Hayes R. **Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies**. *AIDS* 2006,20:73-83.

30. Mayaud P, Quedraogo A, Nagot N, Konate I, Vergne L, Weiss H, *et al.* **Herpes Simplex virus type 2(HSV-2) suppressive therapy to reduce genital and plasma HIV-1 RNA: Overview of ANRS 1285 trials, potential mechanisms and future interventions** *XVI International AIDS Conference, TUAC0501* Toronto, Canada, August 15, 2006.
31. Celum C, Mayaud P. **Interactions: HSV-2 and HIV**. *Biomedical Interventions for HIV Prevention*. Arlington, VA, http://www.hivforum.org/projects/Biomedical%20Prevention.htm, September 18, 2006.
32. **Press Release: Phase III Trial of Cellulose Sulfate Microbicide for HIV Prevention Closed**. *http://www.fhi.org/en/AboutFHI/Media/Releases/res_CS_Nigeria.htm*: Family Health International; 2007.
33. **Phase III Trials of Cellulose Sulfate Microbicide for HIV Prevention Closed**. *http://www.conrad.org/press/phaseIIItrials.htm*: CONRAD; 2007.
34. Mayer K, Maslankowski L, Gai F, El-Sadr W, Justman J, Kwiecien A, *et al.* **Safety and tolerability of tenofovir vaginal gel in abstinent and sexually active HIV-infected and uninfected women**. *AIDS* 2006,20:543-551.
35. El-Sadr W, Mayer K, Maslankowski L, Hoesley C, Justman J, Gai F, *et al.* **Safety and acceptability of cellulose sulfate as a vaginal microbicide in HIV-infected women**. *AIDS* 2006,20:1009-1116.
36. Jespers V, Van Roey J, Beets G, Buve A. **Dose-Ranging Phase 1 Study of TMC120, a Promising Vaginal Microbicide, in HIV-Negative and HIV-Positive Female Volunteers.** *JAIDS* 2006,Epub ahead of print.
37. Klasse P, Shattock R, Moore J. **Which Topical Microbicides for Blocking HIV-1 Transmission Will Work in the Real World?** *PLoS Medicine* 2006,3:e351
38. Malcom R, Woolfson A, Toner C, Morrow R, McCullagh S. **Long-term controlled release of the HIV microbicide TMC120 from silicone elastomer vaginal rings**. *J Antimicrob Chemother* 2005,56:954-956.
39. Woolfson A, Malcolm R, Morrow R, Toner C, McCullagh S. **Intravaginal ring delivery of the reverse transcriptase inhibitor TMC 120 as an HIV microbicide**. *Int J Pharm* 2006,325:82-89.
40. Veazey R, Klasse P, Schader S, Hu Q, Ketas T, Lu M, *et al.* **Protection of macaques from vaginal SHIV challenge by vaginally delivered inhibitors of virus-cell fusion**. *Nature* 2005,438:99-102.
41. Veazey R, Springer M, Marx P, Dufour J, Klasse P, Moore J. **Protection of mcaques from vaginal SHIV challenge by an orally delivered CCR5 inhibitor**. *Nature Medicine* 2005,11:1293-1294.
42. Lederman M, Veazey R, Offord R, Mosier D, Dufour J, Mefford M, *et al.* **Prevention of Vaginal SHIV Transmission in Rhesus Macaques Through Inhibition of CCR5**. *Science* 2004,306:485-487.
43. Lederman M, Offord R, Hartley O. **Microbicides and other topical strategies to prevent vaginal transmission of HIV**. *Nature* 2006,6:371-382.
44. Subbarao S, Otten R, Ramos A, Kim C, Jackson E, Monsour M, *et al.* **Chemoprophylaxis with Tenofovir Disoproxil Fumarate Provided Partial**

Protection against Infection with Simian Human Immunodeficiency Virus in Macaques Given Multiple Virus Challenges. *J Infect Dis* 2006,194:904-911.

45. Van Rompay K, Kearney B, Sexton J, Colo´n R, Lawson J, Blackwood E, *et al.* **Evaluation of Oral Tenofovir Disoproxil Fumarate and Topical Tenofovir GS-7340 to Protect Infant Macaques Against Repeated Oral Challenges With Virulent Simian Immunodeficiency Virus**. *Acquir Immune Defic Syndr* 2006,43:6-14.
46. Garcia-Lerma J, Otten R, Qari S, Jackson E, Luo W, Monsour M, *et al.* **Prevention of Rectal SHIV Transmission in Macaques by Tenofovir/FTC Combination**. *13th Conference on Retroviruses and Opportunistic Infections, 32LB, Oral Session 8*. Denver, Colorado 2006.
47. Peterson L, Taylor D, Clarke E, Doh A, Phillips P, Belai G, *et al.* **Findings from a double-blind, randomized, placebo-controlled trial of tenofovir disoproxil fumarate (TDF) for prevention of HIV infection in women** *XVI International AIDS Conference, THLB0103*. Toronto, Canada 2006.
48. Derdelinckx I, Wainberg M, Lange J, Hill A, Halima Y, Boucher C. **Criteria for Drugs Used in Pre-Exposure Prophylaxis Trials against HIV Infection**. *PLoS Medicine* 2006,3:2545.
49. Regoes R, Longini I, Feinberg M, Staprans S. **Preclinical Assessment of HIV Vaccines and Microbicides by Repeated Low-Dose Virus Challenges**. *PLoS Medicine* 2005,2:e249
50. Cohen M, Gay C, Kashuba A, Blower S, Paxton L. **Antiretroviral Therapy for Prevention of the Sexual Transmission of HIV-1**. 2007:Sect. In press at Annals of Internal Medicine.
51. Were W, Mermin J, Wamai N, Awor A, Bechange S, Moss S, *et al.* **Undiagnosed HIV infection and couple HIV discordance among household members of HIV-infected people receiving antiretroviral therapy in Uganda**. *XVI International AIDS Conference, THPE0281*. Toronto, Canada, August 17, 2006.
52. Kayitenkore K, Bekan B, Rufagari J, Marion-Landais S, Karita E, Allen S. **The impact of ART on HIV transmission among HIV serodiscordant couples**. *XVI International AIDS Conference, MOKC101*. Toronto, Canada, August 14, 2006.
53. Phillips A. **When should antiretroviral therapy for HIV be started?** . *BMJ* 2007,334:76-78.
54. Bunnell R, Wamai N, Ekwaru J, Moore D, Were W, Bechange S, *et al.* **Changes in sexual behavior and risk of HIV transmission after two years of antiretroviral therapy and prevention interventions in rural Uganda**. *XVI International AIDS Conference, MOAC0204*. Toronto, Canada 2006.
55. Grant R, Buchbinder S, Cates W, Clarke E, Coates T, Cohen M, *et al.* **Promote HIV Chemoprophylaxis Research, Don't Prevent It**. *Science* 2005,309:2170-2171.
56. Page-Shafer K, Saphonn V, Sun L, Vun M, Cooper D, Kaldor J. **HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia**. *Lancet* 2005,366:1499-1503.

APPENDIX A – WORKING GROUP MEMBERS

Bertran Auvert, M.D., Ph.D.
INSERM U687

Robert Bailey
University of Illinois at Chicago

Linda Barnes, M.H.A.
Partners in Prevention

Matthew Barnhart, M.D., M.P.H.
USAID, Office of HIV/AIDS

Brigitte Bazin, M.D.
National Agency for Research on AIDS and Viral Hepatitis

Michelle Berrey, M.D., M.P.H.
GlaxoSmithKline

Dani Bolgonesi, Ph.D.
Trimeris, Inc

Charles Boucher, M.D., Ph.D.
University Medical Centre Utrecht

Elizabeth Anne Bukusi, Ph.D., M.P.H.
Kenya Medical Research Institute

David Burns, M.D.
DAIDS/NIAID/NIH

Willard Cates, Jr., M.D., M.P.H.,
Family Health International

Connie Celum, M.D., M.P.H.
University of Washington

Ben Cheng, M.Sc.
Forum for Collaborative HIV Research

Philippe Chilliade, M.D., M.H.A.

Edith Essie Clarke, M.D
Ghana Health Service, Ministry of Health

Lee Claypool, Ph.D.
USAID

Thomas Coates, Ph.D.
University of California, Los Angeles

Jon Cohen
American Association for the Advancement of Science

Myron Cohen, M.D.
University of NC at Chapel Hill

Chris Collins, M.P.P.
HIV Policy Consultant

Marie-Pierre de Bethune, Ph.D.
Tibotec Bvba

Karen Douville
International Partnership for Microbicides

Ayman El-Mohandes, M.D., M.P.H.
The George Washington University

Wafaa El-Sadr, M.D., M.P.H.
Columbia University

Thomas Folks, Ph.D.
CDC

Nomi Fuchs-Montgomery, M.P.H.
US Department of State-Office of the Global AIDS Coordinator

Azra Ghani, Ph.D., M.A.
London School of Hygiene & Tropical Medicine

Dave Glidden, Ph.D.
University of California, San Francisco

Robert Grant, M.D., M.P.H.
University of California, San Francisco

Ronald Gray, M.D., M.Sc.
Johns Hopkins University

Alan Greenberg, M.D., M.P.H.
The George Washington University

Michael Greenberg, Ph.D.
Trimeris, Inc

Yasmin Halima
International AIDS Society

Catherine Hankins, M.D.
Joint United Nations Programme on HIV/AIDS

Polly Harrison, Ph.D.
Alliance for Microbicide Development

Nick Hellmann, M.D.
Bill & Melinda Gates Foundation

Craig Hendrix, M.D.
Johns Hopkins University

Sharon Hillier, Ph.D.
University of Pittsburg

Sally Hodder, M.D.
UMDNJ

King Holmes, M.D., Ph.D.
Harborview Medical Center

Pamela Johnson, Ph.D.
Voxiva, Inc.

Rowena Johnston, Ph.D.
AmfAR-The Foundation for AIDS Research

Stefano Bertozzi Kenefick, Ph.D.
National Institute of Public Health

Joep Lange, M.D., Ph.D.
Academic Medical center Amsterdam

Michael Lederman, M.D.
Case Western Reserve University

Sandra Lehrman, M.D.
DAIDS/NIAID/NIH

Christine Lubinksi
HIV Medical Association

Meagan Lyon, M.P.H.
Forum for Collaborative HIV Research

Louise Martin-Carpenter
GlaxoSmithKline

Philippe Mayaud, M.D., M.S.C.
London School of Hygiene & Tropical Medicine

Howard Mayer, M.D.
Pfizer

Kenneth Mayer, M.D.
Brown University/The Miriam Hospital/Fenway Community Health

Veronica Miller, Ph.D.
Forum for Collaborative HIV Research

John P. Moore, Ph.D.
Weill Medical College of Cornell University

Kevin O'Reilly, M.D.
World Health Organization

Lynn Paxton, M.D., M.P.H.
CDC

Frank Plummer, M.D.
National Microbiology Laboratory

Thomas Quinn, M.D.
Johns Hopkins University

Renee Ridzon, M.D.
Bill & Melinda Gates Foundation

Joseph Romano, Ph.D.
International Partnership for Microbicides

James Rooney, M.D.
Gilead Sciences, Inc.

Zeda Rosenberg, M.D.
International Partnership for Microbicides

Monica Ruiz, Ph.D., M.P.H.
AmfAR- The Foundation for AIDS Research

Caroline Ryan, M.D.
US Department of State-Office of the Global AIDS

Jorge Sanchez, M.D., M.P.H.
Assococion Civil IMPACTA Salud y Educacion

Robin Shattock
St. Georges University of London

David Stanton, M.D., M.P.H.
USAID, Office of HIV/AIDS

Kimberly Struble, Pharm.D.
FDA

Melanie Thompson, M.D.
AIDS Research Consortium of Atlanta

Lut Van Damme, M.D., Ph.D., M.Sc.
CONRAD

Ariane van der Straten, Ph.D, M.P.H.
University of California San Francisco

Mark Wainberg, Ph.D.
Jewish General Hospital

Mitchell Warren
AIDS Vaccine Advocacy Coalition (AVAC)

Maria Wawer, M.D., M.H.Sc.
Johns Hopkins University

Carolyn Williams, Ph.D.
Division of AIDS/NIAID

APPENDIX B-AGENDA

Biomedical Interventions for HIV Prevention Working Group Meeting

18-Sep	What	Who
11:30-12:30	**Lunch; Registration**	**All**
12:30-12:45	Welcome & Overview; party rules	V Miller
12:45-1:00	Working Group Chairs & Sponsor Perspective	W Cates, M Cohen, N Hellmann
1:00-3:00	**Session I: Checking the time on the intervention clock:** *Where are we today and why are we still here?*	**Moderators: W Cates, T Quinn**
		Rapporteur: C Lubinski; L Barnes
	Session I objectives: 1. Review the current status of research within each program: what do we know; when will we know more? 2. What are the key research questions not being addressed currently? 3. Identify barriers, constraints (choke points) that prevent us from moving forward more rapidly	
1:00-1:10	Female-Controlled Barrier Methods	A Van der Straten
1:10-1:20	Male Circumcision	R Bailey
1:20-1:30	HSV-2 Treatment	P Mayaud
1:30-1:40	Microbicides 1 (basic science)	J Moore
1:40-1:50	Microbicides 2 (clinical science)	R Shattock
1:50-2:00	PREP	R Grant
2:00-2:10	Index Partner Treatment	M Cohen
2:10-3:15	Discussion	All
3:15-3:40	*Coffee Break*	
3:40-6:30	**Session II: Feasibility & Realism**	**Moderators: M Cohen, T Coates**
		Rapporteur: M Ruiz; D Glidden
	Session II objectives: Review why an intervention would or wouldn't work in specific populations based on assumptions made when modeling or projecting effectiveness, from the biologic, behavioral, individual and population coverage perspective (going beyond the good science)	

3:40 - 4:00	Female Barrier Methods -- why they will be effective	M Warren
	Female Barrier Methods -- why they may not be effective	C Hankins
4:00 - 4:20	Male Circumcision -- why it will be effective	R Gray
	Male Circumcision -- why it may not be effective	M Waver
4:20 - 4:40	HSV-2 Treatment -- why it will be effective	C Celum
	HSV-2 Treatment -- why it may not be effective	S Hillier
4:40 - 5:00	Microbicides -- why they will be effective	Z Rosenberg
	Microbicides -- why they may not be effective	C Hendrix
5:00 - 5:20	PREP -- why it will be effective	M Wainberg
	PREP -- why it may not be effective	
5:20 - 5:40	Index Partner Treatment -- why it will be effective	W El-Sadr
	Index Partner Treatment -- why it may not be effective	A Ghani
5:40 - 6:30	Discussion	
7:00-9:00	**Reception**	

19-Sep	**What**	**Who**
7:00-8:00	Breakfast	
8:00 - 9:00	**Session IIIA: Prevention Trial Sites**	**Moderators: A Greenberg, L Paxton**
		Rapporteur: N Fuchs-Montgomery, K Douville

Session IIIA objectives: 1. Develop recommendations to address issues regarding prevention trial sites, including a) number of available sites; b) identifying appropriate sites; c) building site capacity; d) more efficient use of sites. 2. How do sponsors/programs contribute to site development? 3. Is an ongoing discussion/exchange necessary?

		Discussants: C Ryan, J Sanchez, L Claypool, L V Damme, C Williams, B Auvert, P Johnson
8:00-9:00	**Session IIIB: ARV Issues**	**Moderators: T Folks, K Mayer**
		Rapporteur: B Cheng; M-P de Bethune

Session IIIB objectives: 1. Discuss criteria for recommending ARVs or combinations of ARVs for prevention interventions. 2. What are the minimal efficacy/maximum toxicity limits? 3. Do prevention ARVs need to be distinct from therapeutic ARVs? 4. Is an ongoing discussion/exchange necessary?

		Discussants: C Boucher, H Mayer, K Struble, Y Halima, J Rooney
9:00 - 9:15	**Joint Session III: Summary feedback to all participants**	**L Paxton, K Mayer**
9:15-11:45	**Session IV: Priorities for Research: Can we rewind the intervention clock?**	**Moderators: S Bertozzi, J Lange**
		Rapporteur: R Johnston; D Stanton

Session V objectives: 1. To recap biomedical prevention working group discussions on criteria for research priorities and constraints keeping research from happening; 2. How do we fill these gaps?

	Recap of biomedical prevention working group discussion thus far	S Bertozzi; J Lange D Bolognesi; S Hodder
	1. Gaps in information: what information do we need to know to answer the question	P Harrison; B Bazin
	2. Gaps in activity: Mismatch between priorities and what is currently happening	M Lederman; M Berrey
	3. Gaps in facilitation: finding the mechanism to make it happen	E Clarke; E Bukusi
	4.Reality check: on-the-ground perspective	K Holmes
	5. Way forward?	
11:45-12:00	**Wrap up & Next Steps**	**W Cates, M Cohen, V Miller**
12:00-1:00	Box lunch available	