

**PUBLIC REPORT:
Microbicide Donors Committee
Quick Working Group
Meeting #9**

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ACRONYMS AND ABBREVIATIONS

AE	adverse event
AMD	Alliance for Microbicide Development
ARP	ARVs for HIV prevention
AVAC	AIDS Vaccine Advocacy Coalition
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CDC	US Centers for Disease Control and Prevention
CROI	Conference on Retroviruses and Opportunistic Infections
FHI	Family Health International
FTC	emtricitabine
GCM	Global Campaign for Microbicides
HPTN	HIV Prevention Trials Network
IMB	information, motivation and behavioural skills (model)
IPM	International Partnership for Microbicides
HBV	hepatitis B virus
MDP	Microbicides Development Programme
MSM	men who have sex with men
MTN	Microbicide Trials Network
NIAID	National Institute of Allergy and Infectious Diseases
PD	pharmacodynamic
PK	pharmacokinetic
PrEP	pre-exposure prophylaxis
QC	quality control
QWG	Quick Working Group
TDF	oral tenofovir
TFV	tenofovir
STI	sexually transmitted infection
USAID	US Agency for International Development

QWG#9 MEETING REPORT

The Quick Working Group (QWG) was established following an April 2004 inaugural consultation among the donors supporting microbicide effectiveness trials. At that meeting, the donors concurred on the need for a mechanism to facilitate exchange of knowledge, experience, data, and ideas among the investigators conducting Phase 2/2B and Phase 3 trials. To address this issue, the QWG convened its first meeting 15-16 November 2004 in Washington, DC. When the donors met again in April 2005, they determined that the QWG was fulfilling its anticipated role and should continue. Pursuant to the agreement that the QWG's meeting venue should circulate among its members, the group has met 7 more times: 10-11 May 2005 at the Population Council headquarters in New York, New York, USA; 16 November 2005, Chapel Hill, North Carolina, USA; 27 April 2006, Cape Town, South Africa; 23-24 January 2007, London, UK; 25-26 May 2007, Cape Town, South Africa; 17 December 2007, Washington, DC, USA; and 18-19 August 2008, Arlington, Virginia, USA.

DAY ONE: 2 February 2009

The meeting was opened by Salim Abdool Karim, QWG co-chair, who presented new QWG co-chair Sheena McCormack, who in turn expressed appreciation for her new role and for her predecessor, Janet Darbyshire. Polly Harrison reminded participants that all QWG meetings are confidential.

Opening Statement, New Co-chair

Sheena McCormack, MRC Clinical Trials Unit

McCormack noted that it was an exciting time for HIV prevention with at least 8 efficacy trials reporting in the next 3 years. Three of these are studying topical microbicides: HPTN 035, to release results in February, followed by MDP 301. Together, these trials end the generation of trials exploring products that could, at least theoretically, be relatively easily rolled out. Should these trials produce sufficient evidence for licensure, they could exert major influence on future trial designs. Also underway are two Phase 2B tenofovir trials and oral prophylaxis trials of tenofovir-based regimens, from which one robust positive result is likely to emerge. Members of the Quick Working Group are well placed to be at the forefront of efforts to capitalize on those findings and ensure efficient exploration of distribution strategies. Thus, McCormack suggested that the Group expand its review of clinical trial reports to consider them in the context of overall product development plans rather than as isolated studies.

1. Issues in Ongoing Trials and Questions Arising from Updates

CAPRISA 004 - Tenofovir

Singe Sibeko and Anneke Grobler, CAPRISA

The primary objective of the CAPRISA 004 Phase 2B trial is to assess the safety and effectiveness of the vaginal microbicide 1% tenofovir gel to prevent HIV infection in women in South Africa. The secondary objectives are to assess the impact, if any, of tenofovir gel on i) tenofovir resistance in HIV seroconverters in the trial; ii) viral load in women who become infected with HIV during the trial; iii) the incidence of deep epithelial disruption; and iv) pregnancy rates and outcomes.

Enrolment at the two South African sites, Vulindlela (rural) and eThekwini (urban), was completed by January 2009. With elimination of co-enrollment, a total of 900 HIV-negative, sexually active women between ages 18 and 40 had been enrolled: 620 at Vulindlela and 280 at eThekwini. The annual retention rate of 90% is exactly where CAPRISA wants it to be. The pregnancy rate is 3.8/100 person-years, and adherence to gel use was measured at 84% of all sex acts (based on used and unused applicators) and 94% of last sex act (self-report). CAPRISA has held 7 Protocol Safety Review Team meetings and there have

been no major safety concerns: of 5 social harms reported, 3 were definitely related to study participation. A total of 2,007 adverse events (AEs) have been reported, of which 90% were deemed mild and 95% categorized as either “probably not related” or “not related” to product. Concerns had arisen about hepatitis B (HBV) so that, while HBV-infected individuals had not been excluded from CAPRISA 004, they will be screened out in the future and HBV-infected individuals already enrolled will be monitored more closely.

Other protocol amendments following the most recent DSMB review in November 2008 include increasing trial power from 80% to 90%, which will increase study endpoints from 68 to 92, and extend study duration by about 6 months. The next DSMB review will take place in Q2 or Q3 2009 and the trial is projected to end in mid-2010, with results available in Q3 2010.

As trial termination approaches, three broad questions are being considered under the TRAPS (Tenofovir gel Research for Advancing Prevention Science) rubric: i) does TDF abort HIV infection and initiate potentially protective host immunity; ii) what TDF drug level correlates with protection and resistance against HIV; and iii) how does TDF alter natural HIV infection (including set point)? Each of those questions subsumes elements being reviewed through TRAPS ancillary studies, including innate immunity and natural killer cells, inflammatory markers, and behavioural patterns determining adherence. In addition, outcome data are being collected on women who become pregnant during the study for analysis at its conclusion, although TDF is not expected to have contraceptive effect.

HPTN 035

Salim Abdool Karim (CAPRISA)

HPTN 035 researchers are gearing up for public release of results at CROI on 9 February 2009. Key developments since the most recent QWG meeting in August 2008 included: i) network lab completion of confirmatory HIV testing for all seroconversions and an equal number of non-conversions; ii) Endpoint Committee review of follow-up HIV testing data on all participants whose HIV status was not fully clear; and iii) labs completion of baseline and follow-up HSV-2 testing and reading of all Gram stain slides.

Anne Coletti (FHI)

The implementation of HPTN 035 accumulated an impressive array of numbers:

- Total number of women enrolled: 3,099
- Final study retention rate: 94%
- Over 64,000 follow-up visits completed, involving over 23,000 pelvic exams
- Nearly 43,000 cartons of study gel dispensed
- Over 400,000 case report forms completed
- Data QC rate: 4.0 per 100 form pages.

Pregnancies are being followed to outcome, with results expected by July.

Prior to public release of results, sites are preparing strategies and written plans for dissemination of results to participants and communities. Key goals in that effort are to ensure accuracy and timeliness of information dissemination and inclusion of participant voices in dissemination plans. Because of CROI and US Securities and Exchange Commission (SEC) restrictions, study findings could not be presented to the QWG.

MDP 301

Sheena McCormack, MRC Clinical Trials Unit

The target minimum enrolment for this trial was set at 9,339 women in 2008 following the discontinuation of the 2% concentration of PRO2000 and the decision to advance the primary endpoint from 40 weeks to 52 weeks. As of 15 August 2008, 9,389 women had been enrolled, with 15 co-

enrolments and, therefore, 9,404 enrolments on the database. Completion date for follow-up is 28 August 2009, and the MRC CTU is aiming to lock the database as quickly as possible in order to be able to present results by end-2009.

HIV seroprevalence at screening by Rapid HIV tests is 25.3% overall, considerably higher at some sites. The pregnancy rate is down to 11.6 per 100 women-years, a level that persists despite efforts (so far unsuccessful) to further reduce it and despite provision of contraceptives at sites, including injectables. Gel was used in 85% of last sex acts at week 52, generally representative of overall use, though lower rates of gel use in unprotected sex acts have been observed in two South African sites.

The Independent Data Monitoring Committee (IDMC) reviews data every 4-6 months and, at its most recent meeting in December 2008, recommended that the trial continue. It also agreed to meet again as soon as requested by the Trial Steering Committee (TSC) after release of HPTN 035 results at CROI. However, the MDP 301 organizers did not anticipate a need for such a meeting, given their assumption—which proved accurate—that no evidence of harm would have been found in HPTN 035, since the overwhelming consensus was that MDP 301 should continue to the end unless HPTN 035 produced evidence of harm. As the MDP 301 closing date of 28 August approaches, the big question for the management of close-out will be whether the trial will or will not be closing for license.

2. Updates from Planned Trials

Invisible Condom[®]

Michel Bergeron, Université Laval, Québec City, Canada

The presentation began with discussion of two different products: a plain polymer, and a polymer + SLS (sodium lauryl sulphate). Both are intended to provide a physical barrier, trap pathogens, and prevent interaction of pathogens with cellular receptors which, together, would respond to interest in microbicides that would offer a broad spectrum of activity. This research has also included development of a vaginal applicator for use with the Invisible Condom[®] or any other microbicide. Unlike standard applicators, this applicator distributes microbicide gel uniformly throughout the vagina rather than exclusively or primarily in the cervical area. There is also no accumulation of product in the cervical area, which should help ensure its safety while providing protection over a 6- to 8-hour period post-application, the assumption being that while many women may apply gel just before sex, this may not always be the case.

More than 500 women (450 in Cameroon, the rest in Québec) have participated in Phase 1/2 clinical trials of different Invisible Condom[®] formulations and have compared gel alone, gel + SLS, and a placebo, all inserted with the custom-built applicator. Results indicate that the product is well tolerated and accepted by women and their male partners. No serious instances of AEs, ulcers, lesions or deep epithelial disruption were recorded; nor were any important changes in vaginal flora or pH identified.

Product developers are now planning trials to evaluate and gauge potential toxicity using sensitive markers like cytokines and chemokines. They are also considering designing a trial for men who are recipient partners in anal sex since animal data suggest that the formulations could be successfully applied in the anus and have little negative effect.

IPM 009 — Dapivirine

Zeda Rosenberg, IPM

A number of trials planned for 2008 were stalled due to delays in ethics and/or regulatory approvals in several African countries. These protocols are now moving through the system, through discussions and protocol amendments, and studies have been initiated in the United States and Europe.

To date, 6 dapivirine studies have been completed. One (IPM 003) was a Phase 1/2 study involving 112 volunteers in Rwanda, South Africa, and Tanzania; the other 5, all Phase 1 trials, took place in Belgium (IPM 001, IPM 005B, IPM 008, and IPM 018) and South Africa (IPM 004) and had between 12 and 36 volunteers. Two trials are ongoing, one in Africa and one in Belgium. IPM 011, a placebo ring safety and acceptability trial, recruited 230 volunteers in Kenya, South Africa, and Tanzania. Data analysis is being conducted on IPM 012, a dapivirine gel study with 36 subjects in Belgium.

Of the planned trials, it is assumed that Phase 3 of IPM 009 (dapivirine efficacy) will start in 2011. Two Phase 1/2 expanded safety trials, IPM 014A and IPM 014B, to begin in 2009 in Kenya, Malawi, Rwanda, South Africa, and Tanzania, will include daily monitoring of adherence and are expected to help determine what can be done in the future to improve adherence measures and evaluation.

IPM has completed or initiated 8 separate clinical trials and is planning 11 more. It is also initiating 3 more HIV incidence studies and at least 1 more market research study in several African countries that will compare different formulations (tablet, soft-cell capsule, and film, in placebo formulations) through focus groups and randomized groups of participants.

MDP Tenofovir

Anatoli Kamali, MRC/UVRI Uganda Research Unit on AIDS

MDP 302 is a multi-centre, randomised, placebo-controlled Phase 3 trial being planned to: i) establish whether vaginal application of 1% tenofovir gel is safe and efficacious in preventing vaginally-acquired HIV infection when applied at the same time daily or pericoitally within 1 hour before sex; ii) assess difference(s) in adherence to gel use between daily and pericoital dosing; and iii) enable licensure should either or both dosing regimens prove efficacious. Participants will be randomised 1:1:1:1 to 1 of 4 arms: daily vaginal administration of 1% tenofovir gel vs. placebo, and pericoital vaginal administration of 1% tenofovir gel vs. placebo. A total of 6,320 HIV-negative, sexually active women are to be enrolled at sites in Mozambique, South Africa, Tanzania, Uganda, and Zambia; the possibility of including a site in Kisumu, Kenya, is being explored.

Further protocol development is subject to confirmation that i) PK data support daily and pre-sex dosing (expected Q2 2009) and ii) women are willing to use gel on a daily basis. Confirmation for issue (i) is expected in Q2 2009, confirmation for issue (ii) will be obtained from the Top Up pilot study expected to report in Q4. If these expectations are satisfied, the Phase 3 trial protocol could be completed and submitted to ethics and regulatory authorities by end-2009, with a first-enrollment target of July 2010.

MDP 302 study designers recognize that findings from the two Phase 2B trials of tenofovir may raise questions about the ethics of doing or continuing a placebo-controlled trial should one of the Phase 2B trials show 50% or better protection; ongoing oral TDF PrEP trials, including those in Botswana and Thailand, could have similar implications.

There were also questions about the timing proposed for MDP 302 start-up and whether it makes sense to initiate enrolment before mid-2010 when CAPRISA 004 results will become available, since those results could answer critical questions about pericoital dosing, motivating and measuring adherence, and counselling participants on pre-sex gel application. The response was that this had been taken into consideration and enrolment in MDP 302 will not start until after the CAPRISA results are released and can inform the dosing regimen in MDP 302.

MIARADIA – Buffer Gel

Frieda Behets, University of North Carolina at Chapel Hill

Miaradia, a Phase 3 trial, focuses specifically on STIs other than HIV and was designed to assess the effectiveness of a diaphragm and candidate microbicide, used in combination, in preventing infection

with gonorrhoea and chlamydia. Planned for implementation at 5 sites in Madagascar, the trial was designed as a partially masked, randomized effectiveness and extended safety trial with 4 arms: i) Ortho All-Flex diaphragm used continuously with Buffer Gel (BG) in the dome of the diaphragm and BG applied intravaginally before coitus; ii) Ortho All-Flex diaphragm used continuously with HEC gel (the placebo) applied in the dome of the diaphragm and HEC applied intravaginally before coitus; iii) BG applied intravaginally before coitus; and iv) HEC applied intravaginally before coitus. (“Used continuously” means that the diaphragm remains inserted except for cleaning once a day.)

For purposes of economy, the study design is asymmetrical: of a total of 1,540 participants, 693 will be assigned to diaphragm + BG or placebo only, 77 each assigned to diaphragm + placebo or BG only. Study participants must be HIV-negative and “at high risk for STIs” (i.e., with laboratory-confirmed gonorrhoea and/or chlamydia at baseline). Based on reviews of other studies, several methods will be used to boost adherence, including continuous diaphragm use, provision of a wristwatch with alarm, and a bag for gel.

In addition to concerns about the implications of political unrest that erupted in Madagascar in early February, QWG#9 participants raised questions about how informed consent would be obtained, given the low educational and economic status of intended study participants. Study designers responded that they had sought to address this concern by developing informed-consent strategies including drawings and pictographs. Questions were also raised about the potential impact of forthcoming results from HPTN 035, which will provide information about the efficacy of Buffer Gel against both HIV and non-HIV STIs of critical relevance for Miaramba. Study organizers agreed that it would be vital to consider those results, but thought their relevance might be limited. Still, participants persisted in asking about the usefulness of the study given declining funding and shifting priorities and asked whether other trials had not already covered the same ground that Miaramba study organizers hope to highlight.¹

MTN-003 (VOICE)

Jeanne Marrazzo, University of Washington/MTN

MTN-003 (VOICE) is a planned Phase 2B trial with 5 arms testing 2 different HIV prevention approaches in women: a once-a-day antiretroviral tablet (tenofovir (TDF)/emtricitabine (FTC) or tenofovir vs. placebo) and a once-a-day application of a vaginal gel (1% tenofovir vs. placebo). A total of 4,200 women aged 18 to 40 will be enrolled at approximately 10 clinical research sites in Africa, and will be randomized into 1 of the 5 arms at enrolment. Both CAPRISA and VOICE are Phase 2B trials involving 1% TFV gel, but VOICE assesses daily dosing while CAPRISA focuses on coitally-related dosing.

The primary study objectives are to: i) estimate the effectiveness of daily tenofovir 1% gel, oral TDF, and oral FTC/TDF in preventing HIV acquisition in women, and ii) evaluate the extended safety of daily tenofovir 1% gel, oral TDF, and oral FTC/TDF in preventing HIV acquisition in women. Secondary objectives focus on assessing issues related to drug resistance among women who acquire HIV while on study, evaluating adherence and acceptability to the daily vaginal and oral regimens, and assessing the vaginal microenvironment in women on study. Evaluation of adherence and acceptability will involve periodic drug level monitoring, face-to-face interview, and administration of audio computer-assisted self-interview (A-CASI).

VOICE researchers are finalizing Case Report Forms (CRFs) and distributing Study Specific Procedures (SSPs) in draft form. A-CASI pretesting was completed in Zambia and Zimbabwe and planned in

¹ Update as of March 2009: The recently completed HPTN 035 study (NIH/NIAID-sponsored) was a Phase 2/2B trial of the safety and effectiveness of BufferGel and PRO2000 in preventing HIV transmission to women. Though shown to be safe, BufferGel did not demonstrate effectiveness against HIV acquisition, nor against the secondary outcomes of gonorrhoea or Chlamydia acquisition. In light of these recent findings, MIARADIA investigators are revising the current study design.

Malawi, South Africa, and Uganda for February 2009. Study product will be delivered to sites by end-February and a central investigators' meeting and training will be held the first week of March in Johannesburg, with individual site trainings to follow Institutional Review Board (IRB) approval. Some delays have been imposed by the time needed for regulatory and ethics committee reviews. In Malawi specifically, regulatory authorities expressed concern that using tenofovir for ARV-specific PrEP could lead to widespread resistance to this drug, potentially compromising its use in the treatment of established HIV infection. Estimated target start dates now range from April 2009 to early summer.

Other obstacles and complexities stem from the presence of a number of PrEP and other prevention studies in similar regions which leads to competition for participants and adds another layer of complication when the male partners of potential participants are themselves enrolled in trials. Recent efforts by many governments and partners to promote and implement male circumcision will also affect the design and implementation of viable HIV prevention studies across the prevention spectrum. As just one example of new variables that have to be taken into account, the benefits of male circumcision as an HIV prevention method will be communicated to VOICE participants as part of the standard educational counselling component at all sites.

3. Quick Working Group Outputs

Polly Harrison, AMD

Currently, QWG-derived recommendations are the only part of reports from QWG meetings available online for general public review. Distribution of full QWG reports and information has been restricted to those directly or semi-directly involved in QWG activities. However, some participants and observers believe this to be unnecessarily limiting and have recommended that learning from QWG meetings be synthesized and entered into the public domain online. Meeting participants agreed but proposed two conditions: i) all participants would be able to review reports in draft in order to flag and/or remove anything they consider objectionable, risky or problematic; and ii) two separate reports would be created, one for the general public (to be placed online), the other to be distributed solely among participants and considered at least semi-confidential. Every effort will be made to ensure that the two versions are as similar as possible so as to maximize learning and awareness beyond the QWG.

4. Looking Back: Adherence—Lessons Learned and Plans for the Future

4a. Adherence--Lessons Learned

Presentation #1

Doug Taylor and Elizabeth Tolley (FHI): Adherence Analysis Task Force

This presentation summarized the final version of a paper prepared by an 8-member task force on "Adherence and Its Measurement in Microbicide Clinical Trials" being readied for journal submission. The paper provides essential background information followed by discussions of i) reasons for collecting adherence-related data; ii) strengths and limitations of currently available measures of adherence; and iii) optimizing adherence. It concludes with recommendations and lessons learned, including:

- The need for clarity in trial design about the purpose(s) of adherence-related data collection with respect to assessing safety, acceptability, and effectiveness, and confirmation/support of trial results;
- How and why to collect adherence-related data to determine effectiveness;
- How and why composite measures of adherence can be developed, identified, and utilized; and
- How and why optimization of adherence can be enhanced and sustained (e.g., recruiting the right people, getting the message right, and intervening if and when necessary).

The authors emphasized that it is lack of biomarkers that imposes dependence on such indirect objective measures as self-reported data on participant adherence to protocol and that designing and applying such measures are therefore essential components of microbicide trial design and implementation.

Presentation #2

Anne Coletti (FHI): Lessons Learned from HPTN 035 that Influenced Integration of Adherence-related Strategies into VOICE

The first key lesson is that it is vital to monitor adherence data from the outset of study implementation, so that any issues or problems can be addressed before they have significant impacts on study quality. For example, early reviews of HPTN 035 data indicated below-target levels of gel use in sex acts during which a condom was not used. As discussed with the QWG in the past, the underlying causes of this were elucidated through discussion with study staff from all sites and adherence counselling messages were modified to address the causes. Thereafter, adherence rates improved over the course of the study.

A second key lesson is the importance of proactive information-sharing and counselling on key product-related issues from the outset of study participation. Even prior to enrolment, potential study participants should be counselled on the importance of adherence and study staff should probe potential barriers to adherence. If such barriers cannot be overcome, consideration should be given to not enrolling the participant in the study. Along similar lines, participants should be encouraged (though not required) to inform their partners and other persons influential in their lives about their study participation. Participants also should be counselled on strategies to avoid mix-ups of their study products with other participants. Lastly, if a trial does not include a run-in phase, participants should be encouraged to complete their first use of study product at the clinic, so that any issues, problems, questions, or concerns related to product can be addressed before the participant needs to use study product on her own.

A third key lesson is the importance of “continuity of care” when providing adherence counselling over time. Study staff are advised to document all counselling sessions and review the documentation of counselling at previous visits as the starting point for client-centred counselling at each subsequent visit.

A final lesson learned is the importance of asking participants to bring their study product supplies with them to each clinic visit. This allows for product counts which can then be used to assess adherence and help counsellors probe adherence issues or problems that a participant might not self-report, and then tailor adherence counselling accordingly.

Presentation #3

Salim Abdool Karim (CAPRISA): Adherence Measurement Strategies in CAPRISA 004

Adherence-related lessons learned from three trials—COL-1492, HPTN 035, and Carraguard—have been of particular interest and usefulness to CAPRISA 004 study designers.

Results from COL-1492 indicated that coital diaries are not easily or consistently interpretable. Moreover, analyzing them adequately is far too time-consuming. Coital diaries are made available to CAPRISA 004 participants if requested, but there is no requirement to return them for analysis as the diaries are for the participant’s own use at her discretion.

HPTN 035 highlighted the importance of separating counselling from measurement. This lesson was factored into the approach taken in CAPRISA 004, where different staff do risk-reduction counselling, adherence counselling, and adherence measurement to try to minimise social desirability in responses.

CAPRISA personnel concluded that while collecting and assessing used and unused applicators is difficult and complicated (a finding reinforced by the Carraguard trials) doing so has proved useful nonetheless from the perspective of adherence measurement. Experience indicates that collecting all applicators is the best way to determine if they have actually been used, since it is usually possible to see

whether or not they have been inserted. Because this was not done in HPTN 035, self-reports are the only adherence measures available.

Other lessons from the 3 trials included the benefits of having a dedicated adherence coordinator; using information-motivation-behavioral skills (IMB)-based approaches²; soliciting input from experts (e.g., Fisher and Fisher); and collecting tissue for biomarkers of gel use.

All that said, based on experience from 8 trials, there is always a small group of individuals who will evade adherence-related monitoring regardless of the procedures put in place. The majority of women want to be in the trial and thus try their best to be adherent and cooperate with study staff. Of greater importance is the fact that in each trial, a sizable number of women genuinely want to use the product as instructed but do not have the wherewithal or ability to do so consistently. Such individuals are not trying to be devious; they just cannot adhere but, to be polite, they often do not admit to not adhering. Efforts to improve adherence should focus on reaching and supporting these women, who constitute a fairly large group (up to 40% or so) in every trial.

Involving the two Fishers in CAPRISA 004 was cited as an extremely useful step. For one thing, their non-judgmental, client-centred approach—based on strategies used by behavioural scientists—do not focus on telling women what to do but, instead, stress the importance of working with participants to identify solutions and addressing problems. One solution identified during such processes was to establish a feedback loop that begins when the client enters the door for a visit. The first thing she does is deliver all applicators, which are then examined promptly for evidence of use. Information obtained from that analysis is then available to the adherence counsellor during his or her talk with the client.

An ancillary behavioural study also led local staff to conduct in-depth interviews with seroconverters (and HIV-negative controls) to identify problems and concerns they might have with adherence and HIV prevention in general. Teams are in place at every site to capture these women on the day they test positive; during that visit, team members take plasma, collect specimens, etc.

CAPRISA is also pilot-testing a system developed by a South African company that relies on electronic sensors and cell phones. When the bag in which a client's products are stored is opened, a signal is sent automatically to a central computer that records the time and date information. The computer also sends a text message to the participant's cell phone to help remind her to use the test product as indicated.

A key take-home message is that although all of these adherence-enhancing measures have potential benefits, they should not be viewed as panaceas, either together or individually. Challenges in adherence and adherence measurement will persist regardless.

4b. Adherence--Plans for the Future

Presentation #1

Zeda Rosenberg (IPM): Different Adherence Approaches Proposed or Under Consideration

As part of its approach to adherence, IPM is looking at longer-acting formulations, including once-a-day gels and once-a-month rings. It is also emphasizing the importance of product acceptability studies, based on the belief that its efforts to better measure and improve adherence can ultimately be successful only if women like the products, consider them useful, and are comfortable utilizing them properly.

² A well-established conceptualization with demonstrated efficacy for changing HIV risk behavior (Fisher JD, Fisher WA. Theoretical approaches to individual level change in HIV-risk behavior. IN Peterson J, DiClemente RJ, eds. HIV Prevention Handbook, pp. 3–55. New York: Kluwer Academic/Plenum Press, 2000.)

IPM has also designed a pilot study (IPM 014A and B) to determine if daily-monitored adherence (DMA) is feasible. The initiative is driven by local input: community liaison officers and other personnel at research centres are developing plans based on what may work in their communities. Understanding what does and does not work is essential before any large-scale trial is contemplated or prepared. An important element of a DMA design is a clear recognition of what is really being measured and whether DMA results in increased adherence with gel; if not, there is little point in pursuing it further.

IPM also hopes to evaluate, in a pilot study, the recently developed “Smart Applicator”. This device records the time and the temperature of the environment in which the gel dose was dispensed; those data are then sent to a central reader. Results from this pilot will help determine the applicator’s feasibility and performance and, given that it is relatively expensive, whether it will be utilized in a Phase 3 trial.

Among the key issues regarding the measuring of adherence to rings is whether there is daily contact—and if so, what that means. Random testing for drug (either systemically or locally) may also hold promise. This is based on the assumption, as yet unproven, that if women do not know when and where they will be tested, they will be more likely to use the product regularly.

The overarching challenge for all of these plans and strategies is to ensure that trials are not compromised. Any and all information regarding adherence must therefore be obtained in ways that are thoroughly vetted and understood by participants, researchers, and community-based personnel alike.

Presentation #2

Angela Crook (MRC Clinical Trials Unit): How will MDP be measuring adherence in its Top Up study?

This presentation focused on adherence-related observations from MDP 301. Key indicators included self-reported gel use during sexual behaviour (SB) interviews, during which participants were asked specifically about usage at last sex act and all sex acts during the past week. Used gel returns were recorded on gel accountability (GA) forms for each participant.

The MDP triangulation process, applied to a subset of the MDP301 trial population who participated in the social science component (~300 women), was found to elicit more consistent data compared with the SB questionnaire data alone. This process involved reconciling (“triangulating”) information and observations from clinic interviews, coital diaries, and applicator returns entered into a “comparison form”, which is then probed for inconsistencies during an in-depth interview, providing insight into the reasons for under- and over-reporting of gel and condom use. The data from this subset of women have influenced the adherence data to be collected in the Top Up study.

The Top Up study is seeking to determine the feasibility of conducting a trial of daily vaginal gel, and to assess 3 different methods of monitoring applicator returns. The name refers to the idea that women are getting “topped up” through daily dosing. Several of the MDP 301 trials sites are working on this study with MDP, which hopes that the study will help streamline the triangulation process for future scale-up. Top Up is designed so that participants are randomised to 1 of 3 methods for monitoring adherence: handing in applicators once a day, once a week, and every 4 weeks (MDP’s current practice). A total of 225 participants from up to 5 sites are involved, with follow-up for 12 weeks. The primary outcome is adherence to daily gel use; the secondary outcomes are consistency of adherence measures across multiple data sources, retention of participants at week 12, and reasons for non-adherence. Assessments will be based on a wide range of sources, including interviews, laboratory tests and examinations, daily gel diaries, and focus group discussions.

Presentation #3

Craig Hendrix (Johns Hopkins University School of Medicine): Drug Pharmacokinetic Biomarkers to Measure Adherence

Discussion centered on how use of drug concentration and knowledge of pharmacokinetics (PK) could be utilized as a biomarker to measure adherence, how such a biomarker might work in practice, what the resulting data might look like, and how to move from theory (the ideal) to actual practice (the real). Also considered were PK-PD relationships and whether intracellular drug sampling is logistically feasible.

Necessary initial steps in using PK to assess adherence include: i) dosing a subject to steady-state; ii) drawing blood at specified times relative to the last dose; iii) assaying for plasma and/or intracellular drug(s); iv) estimating % adherence based on individual drug levels informed by population-based estimates; and v) adjusting estimates based on ancillary data.

Different scenarios were explored using simulations of different dosing regimens, adherence patterns, and variability. The following points were made in the discussion and simulations:

- TFV-DP (tenofovir-diphosphate) half-life is greater than TFV plasma half-life; TFV-DP half-life is greater than FTC-TP (FTC-triphosphate). Accordingly, intracellular tenofovir diphosphate provides a more useful measure of drug exposure over longer periods of time and is less susceptible to “white coat” adherence prior to a study visit.
- With daily dosing and high levels of adherence, TFV plasma concentrations should be detectable for up to 7 days; intracellular TFV-DP concentrations may be detectable for up to 21 days. For this reason, intracellular drug sampling can detect a dose taken more distantly in the past than is the case for plasma concentrations.
- After vaginal dosing of tenofovir, plasma and intracellular concentrations of drug in blood will be detectable for far shorter periods of time. This reduces the ability to detect recent doses of tenofovir after vaginal dosing in comparison to oral dosing. Sampling tissue is more invasive, but would increase the sensitivity to detecting more distant dosing.
- Large differences in adherence are probably discernable, e.g., 90% compared to 50%. A smaller difference, e.g., 90% versus 75% or 50% versus 25%, is likely impossible to detect given inter-individual differences and different patterns of adherence, e.g., holidays versus sporadic dropped doses.
- Duration of holidays (a cluster of days without dosing) significantly reduces the accuracy of PK assessments of adherence. However, MEMS (medication event monitoring systems) should provide very useful information to identify holidays and indicate when PK methods are most accurate (e.g., in research participants who do not take extended drug holidays).
- Individual sparse sampling for drug concentration after an observed dose should increase the accuracy of PK methods to assess adherence by reducing the impact of inter-individual variation.
- The impact of adherence on seroconversion depends on the active drug concentration relative to the EC_{50} , the concentration at which the preventive effect is half-maximal. When concentration is well above the EC_{50} , large differences in adherence may have trivial differences in preventive efficacy. When drug concentration is near the EC_{50} , differences in adherence have a maximal impact on preventive efficacy.
- Collection of blood, tissue, and intracellular samples required for drug analysis is feasible in resource limited settings where only a centrifuge is available, thus extending the scope of sites that can participate in PK directed assessments.

In sum, using drug concentration as a biomarker to assess adherence is theoretically possible for microbicide trials. Success depends largely on the magnitude of inter- and intra-subject variability (not well defined for intracellular tenofovir) and adherence patterns (sporadic dropped doses vs. extended drug holidays). Ancillary data, e.g., individual PK parameters derived from several drug levels or adherence pattern data from a MEMS device, will likely improve the accuracy of PK estimates of adherence. Demonstration of usefulness awaits successful implementation in well-designed clinical studies.

5. Summary of Day One Discussions

Sheena McCormack, MRC Clinical Trials Unit

- **Much of the first day's discussion was directly related to, or influenced by, the pending results of HPTN 035 and their implications. Several trial methodologies and product development plans are likely to be re-examined and re-evaluated after 9 February.**
- **Funders not only urgently request but are increasingly adamant, given the current economic climate, that the field consider more coordinated strategies for product development and trials.**
- **It seems that there is a diminishing window for placebo-controlled trials.**
- **Adherence remains a thorny and complicated issue. New strategies and procedures are regularly considered and developed, but it is still unclear how effective they will be in improving adherence to consistent, satisfactory levels. PK assessment is tantalizing because it is increasingly precise and quantifiable, but it remains impractical from a logistical and cost perspective. Based on the current situation and trends, it seems apparent that multiple methods are needed to measure and ensure adherence. It is also apparent that interviewer skills are critical to accurate data collection.**
- **An "open" report of this and future QWG meetings, including scientific recommendations, will be produced and distributed. It will take into account political and ethical issues and aim to complement, not replace, the more comprehensive, confidential report distributed among QWG members.**

DAY TWO: 3 February 2009

6. Looking Forward: Topics of Special Relevance for ARV Development and Trial Design

Presentation #1

Sharon Hillier (University of Pittsburgh): Daily vs. Coitally-dependent Dosing/adherence

As part of HPTN 059, a safety and acceptability study of the vaginal microbicide 1% tenofovir gel, a total of 200 women were followed for 6 months to compare daily vs. coitally-dependent dosing adherence. All participants were given either tenofovir or placebo gel. Recruitment was launched in August 2006 at sites in India and the United States; follow-up was completed in October 2007. The majority of participants in India were married, which was not the case in either Alabama or the Bronx; all women were relatively low-income, however. Full safety and acceptability assessments were conducted at baseline, 1 month, 3 months, and 6 months. The product was found to be safe throughout. AEs accounted for 24 of the 26 total product holds or discontinuations among the 200 women. Of the 26 product holds, 12 were among women on tenofovir.

For both the coitally-dependent and daily-use arms, adherence assessment was based on self-reported gel use, with assessment performed during visits at weeks 4, 12, and 24. In terms of total number of gel applications overall in the study, gel use was nearly the same for those using tenofovir and placebo. Moreover, although participants in the coital group used much less product overall, about the same share (80%) in each group reported using the gel as requested. There was little difference in self-reported adherence between those on tenofovir and the placebo in either arm. (Menses was a key reason that many in the daily use arm, particularly those in India, skipped a dose—even though they had been specifically instructed not to do so. They said, however, that they did not have sex while having their periods.) Overall, 92% of those on tenofovir and 94% of those on the placebo said they would use the gel if it were found to help prevent people from getting HIV in the future. Another lesson learned, based on self-reported adherence, is that both coitally dependent and daily use gels are highly acceptable.

Tenofovir drug levels were measured in the plasma of women as part of this protocol. Overall, women assigned to the daily-use group were more likely to have drug detected during the scheduled visits, which

was expected since they were instructed to use the products daily. The study confirmed that the level of drug absorbed into the bloodstream from the vaginal gel was quite low (about 1% of what is detected after oral drug use). Importantly, this study provided the first biological measure of gel use and showed that about 80% of women who reported using vaginal gel in the previous 12 hours had detectable drug in their plasma. These data suggest that self-reported product use had a high correlation with an independent biomarker of product use. Based on the acceptability of daily gel use and the increased product exposure achievable with daily dosing, the VOICE trial was designed for daily use of gel and oral tablets.

Presentation #2

Sharon Riddler (University of Pittsburgh): Differences between Oral and Vaginal Preparations and Their Implications

Key issues with respect to topical and oral preparations for prevention are pharmacokinetics; efficacy; potential for resistance; and feasibility, which is best determined by considering acceptability and adherence, toxicity monitoring, and use in pregnancy/breastfeeding. Topical agents have higher concentrations in mucosal tissues; have potential for long-acting formulations and as components of combination products; have little systemic toxicity, thus requiring less monitoring; and can be used during pregnancy and breastfeeding. In contrast, oral agents are characterized by systemic exposure; have potential for greater toxicity, thus requiring extensive monitoring; are likely to engender more resistance and perhaps less likely to lend themselves to combination; and overlap with treatment.

Comparison of study results and published data indicate that tenofovir concentrations are higher when gel is used and that the vaginal tissue is not the only mucosal surface to be protected. However, data from nonhuman primate studies indicate that neither topical tenofovir gel nor tenofovir in oral formulation used alone provided complete protection. In contrast, data from a study of rectal SHIV transmission in macaques have indicated that an oral combination, TFV/FTC, might provide greater protection.

As for HIV drug resistance, much of what is known comes from studies of use of anti-retroviral (ARV) therapies in infected individuals, which have found that rates of viral replication are extremely high, that just a single mutation can result in resistance, and that resistance to ARVs used in monotherapy develops very quickly, often within two weeks.

Available data from ARV use for pre-exposure prophylaxis (PrEP) are few and insufficient. One macaque model identified resistance to emtricitabine (FTC), but data from that single study are not enough to support expectations about the extent to which ARVs used prophylactically might trigger resistance. At present, researchers are limited to hypothesizing, for example that resistant virus will be selected with continued PrEP but unlikely to do so if PrEP is interrupted with appropriate timeliness.

It may be that tolerance will depend on product efficacy and that it might therefore be appropriate to accept a little resistance if a given product works very well; the same might be true for toxicity. While no systemic toxicity to topical tenofovir has been observed to date, there may well be instances, though probably rare, of serious toxicity from current ART oral PrEP (TFV and TFV/FTC).

In sum, questions around the potential of resistance for both oral and topical pre-exposure prophylaxis remain open, continue to raise challenges with respect to their safety for that purpose, and will demand energetic monitoring in connection with clinical trials.

Presentation #3

Sharon Riddler (University of Pittsburgh): Follow-up of Seroconverters to Assess Resistance

MTN is designing a study to follow up seroconverters enrolled in its VOICE and MTN 015 trials. Follow-up of seroconverters is useful for numerous reasons, including to: i) assess for transmitted resistant virus;

ii) monitor for resistance resulting from PrEP; iii) evaluate the effect of PrEP on disease progression, if any; and iv) monitor the long-term impact of any resistance on treatment response to ART.

There is evidence that transmission of drug-resistant virus can occur. One US study of adolescents in the United States found that about 18% had a resistant virus, and newer data on ART resistance from Africa are also indicating high levels of resistance. A study from Malawi, for example, showed a disturbingly high level of tenofovir resistance (23%), though this is not uncommon in the current scale-up of ARV therapy. In contrast to resistance that develops on therapy, transmitted resistance mutations appear to persist for a year or more after infection. This means that if a resistant virus is transmitted, there is no wild-type virus to overgrow it, so that the virus must in effect “mutate back”; since this can take a while, resistance can be identified up to 3 years after treatment.

Overall, at least in resource-limited settings, the following conclusions appear valid:

- Transmission of HIV with NRTI and NNRTI resistance mutations is likely to increase;
- Individuals who are put on oral ARV PrEP with undiagnosed HIV infection will develop resistance;
- Individuals who become infected on ARV PrEP will likely develop resistance unless it is interrupted; and
- Response to ART may (or may not) be impacted by PrEP-selected mutations.

These conclusions indicate a need to stop drug PrEP if resistance develops. Thus, the MTN approach to seroconverters includes early, inclusive evaluation of resistance (in VOICE) and long-term follow-up of the cohort study designated as MTN 015. The overall goal of MTN 015 is to evaluate and monitor the virologic, immunologic, and clinical outcomes of participants who seroconvert during microbicide trials. Its primary objective is to compare plasma HIV-1 RNA levels 12 months after HIV-1 seroconversion in ART-naïve participants assigned to the active study arm, i.e., to a microbicide or chemoprophylactic agent, compared to participants in the control. Among several secondary objectives, the most important is to establish a repository of biological specimens for future analyses.

Presentation #4

Doug Taylor (FHI): Minimum levels of efficacy/effect size

A test product has an unknown, hypothetical efficacy. The underlying effectiveness is also unknown, is less than hypothetical efficacy due to non-adherence, and is study-specific (i.e., the same product tested in different populations will have different underlying effectiveness levels). The study-specific effectiveness level is what is estimated in a microbicide trial, and is reported with a lower confidence bound. Up to this point, most studies have targeted a lower 95% confidence bound on effectiveness greater than a threshold level of 0%, which would be regarded as at least preliminary evidence that the product has a non-zero effect. The assumption about what the underlying effectiveness might be for a given product in a given study population, as well as the threshold level one hopes to rule out with specified confidence, has dramatic consequences on the number of events required to achieve a desired target power. For example:

- MDP 301: ~232 events per pair-wise comparison provides 90% power to rule out a 0% threshold with 95% confidence if the underlying effectiveness is 35%.
- CAPRISA 004: ~92 events provides 90% power to rule out a 0% threshold with 95% confidence if the underlying effectiveness is 50%.
- FEM-PrEP:
 - ~72 events provides 90% power to rule out a 30% threshold with 95% confidence if the underlying effectiveness is 70%.
 - ~72 events provides 90% power to rule out a 10% threshold with 95% confidence if the underlying effectiveness is 60%.
- VOICE:

- ~260 events per pair-wise comparison provides 90% power to rule out a 25% threshold with 99% confidence if the underlying effectiveness is 55%; being a Phase 2b screening trial, however, VOICE will target ~ 94 events per pair-wise comparison and use those results to inform what -- if any -- additional research needs to be performed.³
- Other examples:
 - ~100 events provides 90% power to rule out a 15% threshold with 99% confidence if the underlying effectiveness is 60%.
 - A mere 12 events provides 85% power to rule out a 0% threshold with 95% confidence if the underlying effectiveness is 85%.

Among the questions raised by such calculations is: What do we think the underlying effectiveness *should* actually be? Discussion focused on what is expected by the community in terms of effectiveness. For VOICE, the community appears to want convincing evidence that the underlying effectiveness of a product is clearly and substantially greater than 0% (e.g., 99% confidence in greater than a 25% effect); the IPM will be seeking a 30% threshold at the very minimum.

Presentation #5

Marcus Altfeld (Massachusetts General Hospital): Pathogenesis Studies in ARC Microbicide Trials

It is useful to think about microbicides in terms of success and failure in order to understand how their use influences the development of HIV-1-specific immunity. Success would be exposure to HIV-1 with no establishment of infection, while failure would be HIV-1 infection. Studies of successes would ideally focus on whether the development of HIV-1-specific immunity might enhance the protection by microbicides. Studies of HIV-1 pathogenesis in failures, meanwhile, would provide a unique opportunity to study the impact of a very early intervention on i) manifestations of acute HIV-1 infection, ii) HIV-1 disease progression, and iii) HIV-1-specific immunity (correlates of protective immunity).

Innate immune response is so important because significant HIV-1-specific adaptive immune responses are detectable only weeks to months following acute HIV-1 infection. Moreover, adaptive immunity develops in the context of a strongly activated innate immune system, and innate immunity itself shapes the quality of the adaptive virus-specific immune response in animal models. However, knowledge regarding innate immune responses to HIV-1 is very limited.

Further analysis of natural killer (NK) cells and their receptors might provide some useful data in determining which ARV prophylaxis might have the best and most protective impact, if any. For one thing, specific NK cell genotypes in conjunction with HLA (ligand) genotypes have been associated with slower HIV-1 disease progression. Also, i) there is a massive expansion of NK cells in acute infection prior to seroconversion, ii) specific NK cell populations can strongly inhibit HIV-1 replication in vitro, and iii) NK cells can develop memory and recall responses.

The following conclusions may be drawn from available data and observations:

- Studies of individuals infected with HIV-1 despite the use of microbicides might provide important insights into the correlates of immune protection in HIV-1.
- The use of microbicides might have a significant impact on the *initial* events occurring following infection. Such impacts might include a reduction in initial viremia, a reduction in initial insult on the immune system, the modulation of innate immunity, and the shift in balance toward immune control.
- Studies of HIV-1 pathogenesis should be integrated into clinical trials using microbicides to understand the mechanisms underlying success/failure.

³ Fleming TR and Richardson BA. Some design issues in trials of microbicides for the prevention of HIV infection. *J Infectious Diseases* (2004) 190:666-674.

Presentation #6

Timothy Mastro (FHI): Review of Developments Regarding Use of ARVs for HIV Prevention (ARP)

The possibility of using ARVs for broad-scale HIV prevention has been considered for more than a decade. The rationale behind such efforts is based on data suggesting that ARV prophylaxis may be effective (for example, ARVs are used successfully for PMTCT and as post-exposure prophylaxis). Available ARVs appear to be safe and some available oral ARVs can be used once daily (including TDF, FTC, and a combination pill of those two medicines [Truvada]).

One completed oral ARP (PrEP) trial in West Africa proved inconclusive due to inadequate power to assess efficacy; however, it provided important safety data on African women. Six such trials (both oral and topical) are ongoing, with at least 2 others planned to start in 2009. The ongoing trials include:

- US Extended Tenofovir Safety Trial (CDC): TDF oral, HIV-negative MSM in the USA
- Bangkok Tenofovir Study (CDC): TDF oral, HIV-negative injecting drug users in Thailand
- Botswana TDF-2 (CDC): TDF/FTC oral, heterosexual men and women aged 18 to 29
- iPrEX (NIH): TDF/FTC oral, high-risk MSM in Brazil, Ecuador, Peru, South Africa, Thailand, USA
- CAPRISA 004 (CAPRISA, FHI, CONRAD): tenofovir 1% gel, high-risk women in South Africa
- Partners PrEP (University of Washington): TDF oral and TDF/FTC oral, HIV-1-discordant heterosexual partners in Kenya and Uganda.

The ongoing trials share these common elements:

- Randomized, double-blind, placebo-controlled
- Assess safety and efficacy in preventing HIV infection
- Daily product use (except CAPRISA 004)
- Assess AEs: bone, renal, hepatic, lipids
- Assess pregnancy outcomes
- HBV flares (only iPREX by design)
- Provide optimal HIV prevention
- Evaluate risk behaviour and adherence
- For intercurrent infections, assess ARV resistance and impact on disease progression (VL and CD4).

FHI is sponsoring 1 of the 2 planned Phase 3 studies, FEM-PrEP, which will enrol 3,900 high-risk women in a double-blind, randomized, placebo-controlled effectiveness study of daily oral TDF/FTC (Truvada). First screening is planned for Q1 2009 at sites in Kenya, Malawi, South Africa, and Tanzania. MTN's VOICE study will evaluate whether oral TDF, oral TDF/FTC, and/or topical tenofovir 1% gel prophylaxis provide protection from HIV infection; a randomized trial with 5 study groups at sites in Malawi, South Africa, Uganda, Zambia, and Zimbabwe, its target enrolment is 4,200 women. The total number of participants in all 8 ongoing and planned trials exceeds 20,000. The first set of results, from the ongoing US Extended Tenofovir Safety Trial, will be available in Q3 2009. Results from the planned studies are not expected until 2012.

In terms of next steps for ARP, it is expected that attention will focus on i) intermittent or periodic dosing; ii) new ARVs and combinations; iii) new and different formulations (e.g., oral, injectable, gel and vaginal ring); and iv) issues around program implementation. Studies of ARP in macaques have been used to guide human trials. Recent CDC macaque studies suggest that intermittent dosing has similar efficacy to daily dosing, and data from this model could conceivably inform future human clinical trials.

Presentation #7

Henry Gabelnick (CONRAD): Monthly Tenofovir Teleconference Group

More than 10 organizations participate in a monthly teleconference on tenofovir gel development. A typical agenda focuses on issues and developments related to ongoing or planned trials. Participating entities include Gilead (which serves as chair), FHI (providing the secretariat), CAPRISA, CDC, CONRAD, the Gates Foundation, IPM, MDP, NIAID (including grantees), MTN, and USAID. Representatives from those entities also gather for an annual face-to-face meeting. Representatives from Gilead, CONRAD, FHI, IPM, and NIAID also participate in a monthly regulatory call that focuses on issues specific to regulatory approval, including preparation for filings. A similar call takes place monthly to coordinate UC781 activities. An annual face-to-face meeting is also held.

Presentation #8

Mitchell Warren (AIDS Vaccine Advocacy Coalition): AVAC's Perspective on PrEP

As an advocacy organization, AVAC is understandably excited about and supportive of efforts to identify a safe and effective PrEP product and has been actively engaged in PrEP advocacy since 2004. At the same time, though, it aims to manage expectations based on a thorough review and understanding of key scientific issues, including the need for all relevant PrEP-related questions to be addressed.

AVAC believes that the following is currently needed:

- Ensuring the current clinical trials have the best chance of producing decisive results;
- Identifying and investing in additional research;
- Planning *now* for optimal use of PrEP;
- Preparing for global procurement and delivery of PrEP; and
- Providing adequate financing.

Greater effort is needed to ensure that all of these objectives are achieved. In terms of funding for PrEP, for example, the amount allocated to date (about \$40 million) is extremely low in comparison with funds provided for research into microbicides and other HIV prevention efforts. (A direct comparison is challenging, as PrEP is studying existing drugs, while vaccines and microbicides research must include early-stage product development as well; still, the PrEP investment remains quite low for such a promising approach.) Another liability stems from the fact that the entire PrEP field is currently based on tenofovir. Additional research is needed into other agents, either separately or as follow-on to TDF.

AVAC's PrEP-related activities focus on analysis, monitoring, and advocacy and include publication of *Anticipating the Results of PrEP* in August 2008; convening think tanks on key issues, including intermittent dosing and US financing; and renewed emphasis on the US legislative agenda. In terms of in-country support, AVAC has held national and regional stakeholder consultations in several African countries and provided PrEP-related media training and briefings. Future efforts will include advocacy for considering other products for oral and topical PrEP (e.g., maraviroc); accelerating conversation to determine how to deal with pharmaceutical companies once appropriate PrEP products are identified; and initiating and sustaining more PrEP advocacy, especially in countries where trials are taking place.

Presentation #9

Lori Heise (Global Campaign for Microbicides): GCM's work on PrEP

In 2007, GCM expanded its mission to include work on all non-vaccine prevention methods, especially as they affect women. GCM is re-structuring its programs to focus on ARV-based prevention, including PrEP. The Campaign does not engage directly in product development or testing, but instead focuses on creating an enabling environment for the development, testing, introduction, and use of new prevention methods, and building the capacity of advocates to engage with the scientific process, involve affected communities, and resolve ethical challenges.

GCM is concerned that as the ARV-based prevention field widens, the term “microbicides” could be lost. The organization believes that preserving the term is vital because it helps retain the focus on women, which is not only HIV-related but a political imperative in many parts of the world. Also, while current leads are based on ARV drugs, it is important to sustain the search for non-ARV microbicides, especially those that may provide protection against other STIs.

GCM’s PrEP-related priority outputs include i) restructuring its materials to focus on ARV-based prevention; ii) developing new standardized PowerPoint presentations that provide overviews of ARV-based prevention and highlight key advocacy issues; and iii) developing relevant fact sheets and briefing papers. All of these outputs are geared to non-scientists and will include the production of “low literacy” materials for community members.

GCM’s ethics work focuses on PrEP trials and developments, and building consensus about when it becomes ethically obligatory to provide trial participants with a new prevention method as part of standard prevention packages. Another focus is on ethical design of trials to collect data on evolution of resistance among individuals who use PrEP and ARV-based microbicides after becoming HIV-positive.

GCM’s has also launched a Prevention Research E-Learning Centre that provides self-instructional and distance-learning courses on microbicide science and clinical trials to help raise awareness and basic scientific and treatment literacy among trial participants and community members.

Presentation #10

Monica Ruiz (Forum for Collaborative HIV Research): PrEP Trialists Working Group

Established in 2008, the PrEP Trialists Working Group is modelled after the QWG. Its primary goal is to facilitate synergistic collaboration of researchers engaged in conducting clinical trials examining the efficacy of PrEP in preventing HIV transmission. Toward that end, it aims to create opportunities for meaningful comparisons of data and information across trials and among all PrEP researchers. Participants hope to build and sustain effective communication among researchers, sponsors, and members of advocacy and target user communities.

Members include representatives of planned, ongoing, and completed Phase 2B and Phase 3 PrEP safety, efficacy, and effectiveness trials. Also participating are representatives from the trial funders/sponsors and the PrEP advocacy community. The Forum for Collaborative Research serves as the Secretariat for the PrEP Trialists Working Group, much as the Alliance for Microbicide Development serves as the Secretariat for the QWG.

Concerns were raised during discussions on PrEP as to whether it is wise to even discuss implementation at this stage. Those voicing such concerns argued that it is irresponsible to set expectations that probably cannot be met, at least in the short or medium term. In response, other participants agreed that though it is not appropriate to give specific dates or times in the future for PrEP availability, it is nevertheless important to create an environment available to receive and disseminate eventual research results. Also mentioned was the fact that a gray market already exists, most notably among MSM in the United States and Europe, where individuals are taking ARVs as PrEP before going out at night. Because of this, it is not too soon to consider implementation issues so as to more quickly bring such individuals into evidence-based prevention programs.

FINAL AGENDA
Quick Working Group
Meeting #9
2-3 February 2009

One Dag Hammarskjold Plaza (Population Council)
New York, New York, USA 10017

QWG Meeting #9

Monday, 2 February 2009

- 1:00 Welcome, Introductions, and PrEPARATION for QWG Meeting #9 –
Salim Abdool Karim and Polly Harrison
- 1:15: Introduction of New Co-Chair – Sheena McCormack
- 1:25 Issues in Ongoing Trials and Questions Arising from Updates
- CAPRISA 004 – Singe Sibeko
 - HPTN 035 – Salim Abdool Karim
 - MDP 301 – Sheena McCormack
- 2:15 Updates from Planned Trials
- Invisible Condom – Michel Bergeron
 - IPM 009 – Zeda Rosenberg
 - MDP Tenofovir – Anatoli Kamali
 - MIARADIA – Frieda Behets
 - VOICE – Jeanne Marrazzo
- 3:00 QWG Outputs – Polly Harrison
- Protocol CD
 - QWG Recommendations Summary
 - Site Capacity Catalogue Demonstration
- 3:15 *Coffee Break*
- Looking Back*
- 3:30 *Adherence: Lessons Learned*
- 3:30 Panel discussion on improving and measuring adherence – “Adherence Analysis Task Force:”
Betsy Tolley and Doug Taylor
- 4:00 What lessons from HPTN 035 were integrated into VOICE and approaches proposed or under
consideration? – Anne Coletti and Sharon Hillier
- 4:30 Adherence measurement strategies in CAPRISA 004 – Salim Abdool Karim
- 4:45 *Adherence: Plans for the Future*
- 4:45 Different adherence approaches proposed or under consideration in IPM – Zeda Rosenberg
- 5:15 How will MDP be measuring adherence in Top Up? – Angela Crook

5:45 Drug pharmacokinetics biomarkers to measure adherence – Craig Hendrix

6:15 Summary of Day 1 – Sheena McCormack

7:00 *QWG Dinner – Ristorante DeGrazia (231 East 50th Street)*

Tuesday, 3 February 2009

8:00 *Breakfast*

Looking Forward: Topics of Special Relevance for Antiretroviral Development and Trial Design

8:20 Daily vs. coitally-dependent dosing/adherence – Sharon Hillier

8:40 Differences between oral and vaginal preparations and their implications – Sharon Riddler

9:00 Knowledge about drug resistance relevant for current microbicide compounds – Jonathan Weber

9:20 Follow-up of seroconverters to assess resistance – Sharon Riddler

9:40 Minimum levels of efficacy/effect size – Doug Taylor

10:00 Potential impact of ARV prophylaxis on host immune responses and surrogate markers of disease progression (CD4, VL): What should be studied in ARV microbicide trials – Marcus Altfeld

10:30 *Coffee Break*

10:40 The array of tenofovir trials and their developmental future – Timothy Mastro

11:00 Monthly Tenofovir Teleconference Group – Henry Gabelnick

11:20 AVAC PrEP Activities – Mitchell Warren

11:40 Global Campaign for Microbicides' PrEP Activities – Lori Heise

12:00 PrEP Working Group – Monica Ruiz

12:20 *Lunch*

1:20 EXECUTIVE SESSION: QWG Mandate, Mission, Next Steps – Polly Harrison

3:45 Summary of QWG Meeting #9 – Salim Abdool Karim

4:00 Adjournment (FIRM)