Next steps 1% Tenofovir Gel

Meeting report

Johannesburg, South Africa
25–26 August 2010
Next Steps with 1% Tenofovir Gel

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23 November 2010
Executive Summary

The results of the CAPRISA 004 trial, released in July 2010, showed that 1% tenofovir gel reduced the risk of HIV infection in women by 39% compared with placebo, and by 54% in the women who reported more consistent gel use. These results were historic. After nearly two decades of research, this was the first clinical trial to show that a vaginal microbicide could provide a safe and effective way to prevent sexual transmission of HIV. The gel also provided a 51% protective effect against herpes simplex virus type 2 infection (HSV-2). The announcement raised questions about the most appropriate next steps: making the gel available to women at risk based on this single trial; planning and implementing additional trials to confirm the results; or waiting for the results of the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial, another trial of 1% tenofovir gel using a different dosing strategy. To identify priority next steps, WHO and UNAIDS convened a meeting on 25-26 August 2010 that drew together more than 80 diverse stakeholders from a range of countries. The meeting, hosted by the South African Department of Science and Technology and supported by USAID, aimed to:

- Identify gaps and develop consensus on priority research to confirm safety, effectiveness and acceptability of 1% tenofovir gel;
- Develop the most efficient pathways for licensure and guideline development, including regulatory dossier development and submission;
- Delineate priorities, next steps and lead responsibilities in clinical research, programmatic research, and regulatory submission, and other issues as identified; and
- Agree on mechanisms for coordination and execution, and identify funding sources and gaps.

Over an intense two days of discussion and debate, the meeting participants identified a number of priority actions to support the ongoing development of tenofovir gel, summarized below. Although some felt that the VOICE trial would likely be considered as confirmatory, overall the meeting concluded that additional research on effectiveness was needed. While the VOICE trial and other Microbicides Trial Network (MTN) studies will provide a wealth of evidence on safety and effectiveness of 1% tenofovir gel, it was not clear whether the different dosing strategies studied in the CAPRISA 004 trial and the ongoing VOICE trial would be considered comparable by regulators, policymakers, programme managers, or product users. This uncertainty was underscored by regulators at the meeting who offered somewhat inconsistent views. Most meeting participants therefore felt that it would be important to implement further study of the BAT 24 regimen used in the CAPRISA 004 trial (one dose Before sex, one dose After sex, but no more than Two doses in 24 hrs) to confirm that coital-dependent dosing with 1% tenofovir gel reduces the risk of HIV and HSV-2 infection. Given the different dosing and several years before results will be available, it seemed too risky to rely on the VOICE trial alone to confirm the safety and effectiveness of the gel. Therefore, new research to confirm safety and effectiveness of coital dosing of tenofovir gel should move forward rapidly.

Tenofovir gel is being developed by a consortium of public health agencies, with CONRAD and the International Partnership for Microbicides (IPM) holding a co-exclusive license to develop the gel for use in resource-limited countries. The terms of a sublicense from CONRAD to the Technology Innovation Agency (TIA) have been agreed. These arrangements are aimed at ensuring the product is affordable, and TIA will identify a pharmaceutical partner in South Africa to produce and market the gel in Africa. Meetings for regulatory advice are scheduled with the
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US Food and Drug Administration (FDA) and the South Africa Medicines Control Council (MCC). IPM will submit information on tenofovir gel to the European Medicines Agency (EMA) for scientific advice under the Article 58 mechanism. EMA and WHO will convene an expert group, to include representatives of national regulatory authorities, to provide a scientific opinion on the proposed product development pathway.

Meeting participants generally agreed on a number of priority follow-up actions described below, although there was not consensus that all of the ideas put forward needed to be implemented. These proposed actions would add to the overall body of knowledge about tenofovir gel, including confirming safety and effectiveness against HIV and HSV-2, providing data from other countries in Africa, and answering questions critical to implementation, while continuing to provide gel and other services to the former CAPRISA 004 communities and participants.

- **Additional safety studies.** Tenofovir gel has been tested for safety in a number of different populations. Several priority gaps for safety were identified, primarily among groups that had been excluded from previous trials but would be likely to use the gel once it is on the market regardless of the labelling. These include young women aged 16-17 years, women with hepatitis B infection and women with impaired kidney function. In addition, it is necessary to confirm that existing studies of safety in pregnancy and the pregnancy registry will meet regulatory requirements.

- **Effectiveness trial in South Africa to confirm the CAPRISA 004 BAT 24 dosing regimen.** A consortium of South African researchers proposed a six-centre trial in that country to replicate the CAPRISA 004 trial with two key modifications: including younger women (aged 16-30 years); and adding prevention of HSV-2 as a primary endpoint. Because the CAPRISA 004 protocol had been approved by South Africa’s Medicines Control Council and Institutional Review Boards and the proposed study sites have high HIV incidence, this trial was viewed as the fastest way to licensure and eventual product availability and use. The trial team was moving rapidly with the aim of beginning the trial in the second quarter of 2011 with results expected by the end of 2013. Together with the safety studies outlined above, this trial was considered a priority.

- **Effectiveness and safety trial of simplified dosing and HIV testing schedules.** The Microbicides Development Programme (MDP) proposed a clinical trial, MDP 302, in five African countries to assess the effectiveness of a simplified regimen of one dose of tenofovir gel compared to placebo gel (before or, failing that, as soon as possible after

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2 This group has since been named “FACTS - Follow-on African Consortium for Tenofovir Studies”
sex) as well as to confirm the effectiveness of the BAT 24 regimen. The trial would relate the effectiveness of the single dose and BAT 24 dosing regimens in preventing HIV and HSV-2 infection, and directly compare adherence to the two regimens. The trial would enrol women aged 16-30 years, with HIV testing performed quarterly rather than monthly. It would start enrolment in mid 2011 and would anticipate having results by mid 2014. This trial, seen as a priority to provide critical information for program implementation, would also contribute to licensure.

- **Implementation study in South Africa.** This study (CAPRISA 008) would assess the feasibility and effectiveness of providing tenofovir gel in a clinic setting. Former CAPRISA 004 trial participants and women from these communities could continue to have access to tenofovir gel following either the monthly protocol of resupply, monitoring and testing used in the trial, or a new quarterly protocol at family planning clinics that mirrors service provision for DMPA injectable hormonal contraception. This three-year study would begin to provide information about implementation, demonstrating how tenofovir gel can be provided and monitored in service delivery settings.

- **Treatment outcome and resistance study.** This study (CAPRISA 009) was being planned to provide care, treatment and monitoring for former CAPRISA 004 trial participants who had become infected with HIV while in that trial. The study would compare treatment outcomes for those who receive combined antiretroviral treatment that includes tenofovir with those who receive combined antiretroviral treatment without tenofovir. This would help inform use of tenofovir for prevention and treatment, as well as treatment options for women who acquire HIV while using tenofovir gel.

The trial proposed by the consortium of South African researchers to confirm BAT 24 dosing, now called FACTS 001, would lower the age of eligibility from 18 to 16 years so that tenofovir gel could be labelled for use in younger women. There was some concern that another trial in South Africa alone would limit generalisability to other settings. In general, meeting participants felt that data from a range of settings would be preferable, but recognised that it would be more complex and take longer to launch a trial in multiple countries. The MDP 302 trial in five countries assessing effectiveness of the single dose and the BAT 24 regimens would address concerns that data from South Africa may not be generalisable to populations in other settings. The single dose regimen, if shown to be effective, would be less expensive, easier to translate into programs, and more convenient for women to use.

Some participants saw the merits of studying the single dose strategy and less frequent testing, as proposed by the MDP team, as a crucial bridge toward implementation. Other participants questioned introducing a third dosing strategy into an already uncertain regulatory environment and suggested that the dosing could be worked out using pharmacokinetic (PK) and pharmacodynamic (PD) data. Although PK/PD data were already available to support the potential effectiveness of a single dose applied prior to sex, confirmation of protection against placebo in a clinical trial is considered an essential standard. Nevertheless, some argued that further PK/PD studies could answer remaining questions, obviating the need for a clinical effectiveness trial. However there was no consensus on this point.

The meeting identified other important areas for work, including: receiving feedback from the regulatory agencies about what other studies and data would be needed for the regulatory
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package and ensuring that the many studies completed and underway would meet those requirements; implementing pharmacokinetic and pharmacodynamic studies of dosing; targeted discussions around resistance, HIV testing, and preparing for implementation; and ensuring that product development plans are transparent.

There was a keen sense of urgency to develop and implement additional research to follow up on the promise of the CAPRISA 004 trial by confirming whether 1% tenofovir gel is safe and effective for prevention of HIV and by testing implementation models, so that an effective gel can be made available to women at risk as soon as possible. The meeting concluded that there is a public health imperative to rapidly implement additional research and clarify the regulatory pathways.

Immediately following the meeting, a smaller group of researchers and donors met to further discuss priorities, as well as initial funding needs and possibilities. Cost estimates for the proposed studies amounted to approximately US$ 100 million – US$ 40 million for the FACTS trial, US$ 40 million for the MDP trial, and US$ 20 million for the two follow-on trials in the CAPRISA 004 sites; the safety studies, while critical, were comparatively less expensive. Donors indicated their support, but available funds were not sufficient to support all the prioritized research. Unless additional funds could be found, further prioritization would be necessary. Discussions at this meeting centred on the relative priority of the proposed FACTS and MDP trials, and continued subsequent to the meeting.
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<th>Acronym</th>
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<tr>
<td>ARV</td>
<td>Antiretroviral</td>
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<td>BAT 24</td>
<td>Acronym to describe and help participants remember gel dosing in CAPRISA 004 trial (Before, After and no more than Two in 24 hrs)</td>
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<tr>
<td>CAPRISA</td>
<td>Centre for the AIDS Programme of Research in South Africa</td>
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<td>DMPA</td>
<td>Depot medroxyprogesterone acetate</td>
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<td>DST</td>
<td>Department of Science and Technology</td>
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<td>EMA</td>
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<td>FACTS</td>
<td>Follow-on African Consortium for Tenofovir Studies</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HPTN</td>
<td>HIV Prevention Trials Network</td>
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<td>HPV</td>
<td>Human papilloma virus</td>
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<td>HSV-2</td>
<td>Herpes simplex virus type 2</td>
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<td>IND</td>
<td>Investigational new drug application</td>
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<td>IPM</td>
<td>International Partnership for Microbicides</td>
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<td>MCC</td>
<td>Medicines Control Council</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<td>Microbicides Development Programme</td>
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<td>NDA</td>
<td>New drug application</td>
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<td>NIH</td>
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<td>PD</td>
<td>Pharmacodynamic</td>
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<td>PEPFAR</td>
<td>President’s Emergency Plan for AIDS Relief</td>
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<td>PK</td>
<td>Pharmacokinetic</td>
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<td>SADC</td>
<td>Southern African Development Community</td>
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<td>STI</td>
<td>Sexually transmitted infection</td>
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<td>TIA</td>
<td>Technology Innovations Agency</td>
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<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>VOICE</td>
<td>Vaginal and Oral Interventions to Control the Epidemic</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Background

The results of the CAPRISA 004 trial of 1% tenofovir gel were greeted with cheers, applause and a standing ovation when announced at the Vienna AIDS conference in July 2010. After nearly 20 years of research, CAPRISA 004 provided the first evidence that the use of a vaginal microbicide could provide a safe and effective way to prevent HIV infection in women. The trial demonstrated that 1% tenofovir gel reduced women’s risk of acquiring HIV by 39% compared with the placebo. The reduction in risk reached 54% among women in the subgroup that reported using the gel most consistently. The results were robust and consistent across a range of different analyses. The trial marked the first time that a vaginal microbicide has shown effectiveness against HIV in a clinical trial. As such this represents a major breakthrough in identifying a new method of HIV prevention and a potential new option for women to protect themselves.

The trial results were groundbreaking, and a range of views quickly emerged on the most appropriate and urgent next steps. The CAPRISA 004 trial was not designed – on its own – to provide sufficient evidence to support licensure of the product. Given the urgent need for new prevention options, especially for women, some had called for immediate roll out of tenofovir gel. Others had noted that VOICE (Vaginal and Oral Interventions to Control the Epidemic), another effectiveness trial studying 1% tenofovir gel, is already underway, with results expected in 2013 so it would be best to wait for those results. However, this trial uses a different daily dosing strategy so it is uncertain whether it would be considered comparable or “confirmatory” should the results be positive. Furthermore, others had argued that additional research to confirm and expand on the results was needed to better understand the level of protection that 1% tenofovir gel could provide, and that the quickest way to get the gel to women at risk would be to get priority research to support licensure and implementation underway as rapidly as possible. Some debate had also emerged about the implications of the CAPRISA 004 results for other ongoing and planned HIV prevention trials.

In this context, WHO and UNAIDS convened a meeting in August 2010, just a month following the Vienna announcement, to review the implications of the CAPRISA 004 results and determine the appropriate next steps. The meeting, hosted by the South African Department of Science and Technology (DST) and supported by the US Agency for International Development (USAID), WHO and UNAIDS, brought together a total of 82 stakeholders from eleven countries (see Appendix 4). These included representatives of government agencies, microbicide research teams, microbicide product developers, women’s health and HIV prevention advocates, people living with HIV, key clinical and social science researchers, statisticians, civil society groups, public health experts, ethicists, regulators, and funders. The meeting objectives were to:

1. Identify gaps and develop consensus on priority research to confirm safety, effectiveness and acceptability of 1% tenofovir gel;
2. Develop the most efficient pathways for licensure and guideline development, including regulatory dossier development and submission;
3. Delineate priorities, next steps and lead responsibilities in clinical research, programmatic research, regulatory submission, and other issues as identified; and
4. Agree on mechanisms for coordination and execution, and identify funding sources and gaps.
This report summarizes the discussions and main outcomes of the meeting. The priority actions are listed in Appendix 1.

Summary of the CAPRISA 004 trial results
The CAPRISA team summarized key findings and ongoing additional analyses of the CAPRISA 004 trial data. The trial was carried out in two sites (one rural and one urban) in the province of KwaZulu Natal, South Africa. A randomised, placebo controlled, double blind trial, CAPRISA 004 enrolled 889 sexually active women aged 18-40 years. Trial participants were instructed to insert the gel up to 12 hours before sex, and as soon as possible up to 12 hours after sex, with no more than two doses in a 24 hour period, a dosing strategy called “BAT 24”. This regimen was based on animal data and experience with anti-retroviral drugs for prevention of mother to child transmission using doses before and after delivery. At monthly follow-up visits trial participants were supported and encouraged to adhere to gel use through motivational interviewing. The trial was not designed as a single pivotal study for product licensure.

The trial showed 1% tenofovir gel to be overall 39% effective against HIV-1 ($p = 0.017$, 95% CI $= 6\%-60\%)$. Among women reporting consistent gel use (using both doses as indicated in more than 80% of sex acts), those using the tenofovir gel had a 54% lower risk of HIV-1 acquisition compared with placebo. The gel’s effectiveness appeared to decrease over time. After one year of use, women in the tenofovir gel arm had 50% fewer HIV infections compared to women in the placebo gel arm ($p = 0.007$). After 30 months in the trial, women in the tenofovir gel arm had 39% fewer HIV infections compared to women in the placebo arm. There were declines in the frequency of sex, gel use, and effectiveness in the second year of use. No significant safety concerns were detected in the trial, with mild diarrhoea being the only significant difference between the placebo and tenofovir gel groups.

Results from the CAPRISA 004 trial also showed that 1% tenofovir gel provided a 51% protective effect against the acquisition of herpes simplex virus type 2 (HSV-2), an encouraging result for the prevention of genital herpes. Effect on HSV-2 acquisition was not a primary trial objective and only about half the women were HSV-2 negative at the start of the trial so there are fewer data on this endpoint. If this protective effect is confirmed by other studies, tenofovir gel could be licensed for prevention of genital herpes. Because people infected with HSV-2 are more likely to acquire and transmit HIV, broader use of 1% tenofovir gel, if it is confirmed to reduce HSV-2 risk, could then have an indirect effect on HIV incidence. The study showed that tenofovir gel reduces HIV risk both in women with HSV-2 infection and in women without HSV-2 infection. The effects of 1% tenofovir gel on HIV and HSV-2 infections were independent of each other.

The trial’s main findings were supported by a range of laboratory analyses. Separate studies on cervico-vaginal lavage samples from women in the trial showed that protection against HIV correlated with drug levels found in these samples, although the numbers were small and the samples taken at varying times in relation to HIV infection. While vaginal tissue concentrations of tenofovir were high, blood levels of tenofovir were very low, suggesting that systemic

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3 For more in depth discussion of the trial and results see: Abdool Karim Q et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 2010 Jul 19. (http://www.sciencemag.org/cgi/content/full/329/5996/1168 or http://dx.doi.org/10.1126/science.1193748)
absorption of the drug through vaginal tissue was very limited. Finally, there was no detectable drug resistance among participants who acquired HIV infection while using the tenofovir gel. While this result is encouraging, the evidence on lack of drug resistance is limited – participants who became infected with HIV were taken off the drug immediately after infection was detected, and only 38 participants in the tenofovir gel group became infected.

The CAPRISA team and collaborators described a number of further analyses to better understand some of the key findings. For example, additional analyses are underway in collaboration with a team at Los Alamos to examine resistance using more sensitive assays, and analysing virus in samples from the genital tract as well as in blood collected at earlier time points following sero-conversion.

The CAPRISA team is also planning two follow up studies in the trial communities. These studies would answer key questions while also providing continued access to the active gel for former trial participants and other community members, along with access to care for former trial participants who acquired HIV while in the trial. These two studies would address questions critical to moving what may be the first antiretroviral-based vaginal microbicide from research to implementation:

**CAPRISA 008** would assess the feasibility and effectiveness of providing tenofovir gel in a clinic setting. Trial participants from CAPRISA 004 would be eligible to continue to have access to tenofovir gel following either the monthly protocol of resupply, monitoring and testing used in the trial, or a new quarterly protocol at family planning clinics that mirrors service provision for DMPA hormonal contraception. This three-year study would measure product use, adherence, HIV incidence, and viral load in women who become infected. It would begin to provide information about implementation, suggesting how tenofovir gel can be provided and monitored in service delivery settings.

**CAPRISA 009** would provide care, treatment and monitoring for CAPRISA 004 trial participants who acquired HIV infection while in the trial. The study would compare treatment outcomes for those who receive antiretroviral treatment regimens that include tenofovir with those whose regimens exclude tenofovir. It would assess any effects of using tenofovir gel on the safety and effectiveness of these treatment regimens, and assess viral load, CD4 counts, resistance and disease progression.

**Implications for other research**

The CAPRISA 004 results prompted a lively debate about the implications of the results for other biomedical HIV prevention trials. Meeting participants briefly considered the implications for the standard of prevention provided to all participants (active and control arms) in other biomedical HIV-prevention trials and the timeline for results from other antiretroviral-based prevention studies and their relevance to studies on the effectiveness of topical use.

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4 The CAPRISA team had explored with the South African Medicines Control Council (MCC) whether tenofovir gel could continue to be provided to former CAPRISA 004 trial participants under a compassionate use designation. The MCC indicated that this provision is intended to allow critically ill patients access to experimental treatment drugs that may be of benefit, and as such would not apply to providing tenofovir gel to CAPRISA 004 trial participants for HIV prevention.
The 2007 UNAIDS/WHO Guidance Document: *Ethical Considerations in Biomedical HIV Prevention Trials* states that “… new HIV-risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities.” Tenofovir gel has not yet been “scientifically validated” or “approved by relevant authorities,” so it does not at present meet the criteria for inclusion in other HIV prevention research as a comparator or as part of a standard prevention package. However, as more evidence on safe and effective HIV prevention interventions accumulates, HIV prevention trial design and implementation will become increasingly complex and difficult. Results from the first trial of pre-exposure prophylaxis (PrEP) with oral tenofovir/emtricitabine for HIV prevention are expected in late 2010 or early 2011. Similar trials testing this oral combination or oral tenofovir alone will report in 2012 and beyond.

The implications of the new results for future trial size and complexity were presented. Adding a product such as tenofovir gel to the standard prevention package would likely reduce the background incidence in an HIV prevention trial, thereby increasing the trial’s size and duration. Use of the gel may not be compatible with other study products or may prevent masking in a double blind study. Using tenofovir gel as an active control, where the trial would compare the effectiveness of two products head to head, would still require large trials which may only be feasible if done with a less-intensive follow-up and monitoring schedule. It may be difficult to ensure blinding and achieve comparable adherence in such trials. Non-inferiority studies require even larger sample sizes and may be difficult to implement and interpret. Trial designs with an active control may be better suited to providing supportive, rather than definitive, evidence of effectiveness. New product development and testing may therefore need to rely more heavily on indirect measures of effectiveness: animal models, explant models, pharmacokinetic and pharmacodynamic studies, and surrogate endpoints. There was a sense that the window of opportunity for new placebo-controlled antiretroviral-based microbicide trials may be closing. While this was welcome news as it would reflect consensus that a new method of HIV prevention for women was established as a standard of prevention, it was not clear when this research window would close.

**Civil society perspectives**

Two brief presentations outlined issues from a series of civil society consultations. They underscored the sense of possibility and ownership engendered by the CAPRISA 004 results, while also highlighting a number of ongoing questions, concerns and areas for further work. While it is not possible to reflect fully this rich set of perspectives here, some of the key issues include: understanding the next steps and timeframe for additional research; the implications

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6 Although there was little disagreement on this at the meeting, there was lively debate during and after the meeting in other fora, including on internet listservs, on whether the CAPRISA results mean that there is still equipoise with respect to tenofovir gel. Some commentators held that placebo controlled trials were already “unethical” and that tenofovir gel should be offered to all participants in other HIV prevention trials, and rolled out in the community.
for HIV-positive women and their partners; concerns about balancing resources for prevention and treatment; and affordability and access. The enthusiasm for the result was also tempered with concern that it may open the door to marketing of fake vaginal products. Another concern is how people will understand and apply concepts of partial effectiveness, especially across multiple prevention modalities. Some of these issues can be addressed with tailored, clear messages based on current knowledge, while others will require collaborative research and action. A number of the questions and issues raised by community based workers and advocates echo those raised by researchers and policymakers and reflect the nuance and complexity – as well as the excitement and possibility – surrounding the issues the field now faces.

**Completed and ongoing studies with 1% tenofovir gel**

Work on tenofovir gel stretches back more than a decade and includes a comprehensive assessment of safety, acceptability and pharmacokinetics (PK) and pharmacodynamics (PD) among different populations and with different patterns of use (see Appendix 2 for more detailed summaries of these studies). Diverse clinical studies have assessed: safety and acceptability of different doses and frequencies of vaginal use among abstinent and sexually active women; pharmacokinetics and pharmacodynamics to assess local and systemic absorption and activity; and tolerance of topical application in men.

Ongoing and planned studies are assessing: safety in pregnancy and during lactation; adherence and pharmacokinetics comparing the safety of oral tenofovir pills to vaginal tenofovir; safety, acceptability and pharmacokinetics with rectal use by women and men (including a separate study in young men); and resistance screening. VOICE, with daily gel use, will also generate a wealth of additional data on safety of 1% tenofovir gel.

VOICE, or MTN-003, is examining the safety and effectiveness of daily antiretroviral tablets and 1% tenofovir gel to reduce the risk of HIV acquisition in women. VOICE is implemented by the Microbicide Trials Network (MTN) and supported by the United States of America (USA) National Institutes of Health (NIH). It is a five group randomised phase 2B trial, with two vaginal groups (1% tenofovir gel and placebo gel) and three oral arms (tenofovir, emtricitabine/tenofovir and placebo). The trial is not powered for a head-to-head comparison of oral versus topical pre-exposure prophylaxis. It aims to enrol approximately 5,000 women (1,000 in each study group) in 16 sites in Uganda, Malawi, Zimbabwe and South Africa, of whom about 25% had already been enrolled. Women in the study are instructed to use the products (tablet or gel) daily, whether or not they have sex that day. The trial offers a chance to study the effectiveness of tenofovir gel for preventing HIV infection via daily dosing. In addition to HIV endpoints, it will also examine adherence, behaviour, drug resistance, and pharmacokinetics. The trial will also investigate HSV-2 incidence by study arm through stored plasma samples, and will provide adherence and safety data in multiple sub-Saharan African countries.

The VOICE trial is expected to report effectiveness results in early 2013, as well as a wealth of safety information. As described above, regulators are considering whether VOICE together with CAPRISA 004 would provide sufficient evidence to approve tenofovir gel, despite the two different dosing regimens in the trials. If VOICE shows the gel to have greater than 58% effectiveness, the p-value would be <0.001. This would be considered sufficient evidence for
licensure based on a single pivotal trial, subject to review of the trial results, the quality of data, and the absence of any safety concerns.

**Priority safety studies**

Despite the solid and growing body of information on the safety of tenofovir gel, several priority gaps for safety testing were identified. The most critical issue is safety among young women as previous and ongoing trials have all been done with women aged 18 years and older. Meeting participants felt it would be important to conduct a safety study in younger women aged 16-17 years. Some felt that such a study should be completed before conducting a larger safety and effectiveness trial that includes this age group while others felt that both could be implemented simultaneously. The safety of tenofovir gel use by women with hepatitis B infection and impaired kidney function has not been assessed, so safety data on tenofovir gel use among women with these conditions should be obtained if the product is to be labelled for a wider range of users. As a practical matter, screening for these conditions is unlikely to be available in most service delivery settings and therefore women with hepatitis B infection or impaired kidney function are likely use tenofovir gel regardless of the labelling. It is necessary to confirm that existing studies of safety in pregnancy and the pregnancy registry will meet regulatory requirements. Finally, additional pharmacokinetic and pharmacodynamic studies may be needed to identify an optimal dosing strategy (see also page 12).

**Tenofovir gel development**

Tenofovir gel has had a somewhat atypical drug development process. Unlike most drug candidates that are developed by a single pharmaceutical company, product development has been undertaken by a group of academic investigators, government and private funders, contract pharmaceutical companies, government research agencies, and not-for-profit organizations. Tenofovir was developed for treatment of HIV infection by Gilead Sciences, a pharmaceutical company in California, and in its oral form is a key component of many HIV treatment regimens. An oral tablet, taken daily, is also being testing for effectiveness in preventing HIV infection in a series of pre-exposure prophylaxis trials. Tenofovir was first formulated as a gel (then called PMPA) in the 1990s. Gilead agreed to provide the active pharmaceutical ingredient for development as a vaginal gel for HIV prevention but stipulated that further development and testing of the product would have to be led by and funded through public and/or philanthropic sources. A group of interested organizations has pushed forward product development of tenofovir gel.

Gilead granted CONRAD and the International Partnership for Microbicides (IPM) a co-exclusive license to manufacture and distribute tenofovir gel in resource-poor countries. Gilead continues to provide medical and scientific advice as well as supportive data. The agreement requires

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7 The group consists of: National Institutes of Health, CONRAD, FHI, International Partnership for Microbicides (IPM), USAID, Gilead, Microbicide Trials Network, Centre for AIDS Programme of Research in South Africa (CAPRISA), UK Medical Research Council (MRC), and USA Centers for Disease Control and Prevention (CDC).

8 Gilead is engaged in internal discussions regarding follow-up on the unexpected result of protection against HSV-2 infection. Gilead indicated that it would likely pursue a similar partnership arrangement for the developing world for this indication.
that the active pharmaceutical ingredient is purchased from a Gilead-approved manufacturer and the final product is sold on a non-profit or minimal profit basis. CONRAD has negotiated the terms of a license with South Africa’s Technology Innovations Agency\(^9\) (TIA) to manufacture and distribute tenofovir gel at an affordable price in the African region. TIA in turn is in discussions with several South African biotech and pharmaceutical companies to form a joint venture to produce tenofovir gel. Establishing manufacturing capacity will require substantial investment and time, and while this process is underway tenofovir gel can continue to be produced for research purposes by CONRAD using a contract manufacturer in the USA. Pending availability of funding, this manufacturer could scale up its manufacturing capacity to provide product on a larger scale, but it would likely be relatively expensive to produce and transport gel for widespread use.

In keeping with the original license agreement these negotiations centre on ensuring the gel is distributed at an affordable price to meet public health needs. However, at this time, neither cost nor price is known and they are difficult to predict. Affordability is central to the “cost-plus” agreement being negotiated between TIA and its potential partners. Currently, most of the cost of the finished tenofovir gel product is in the applicator, and so it will be important to identify different applicators or delivery systems to reduce the cost per dose. One approach is a low-cost user-filled paper applicator developed by PATH that will be tested with 1% tenofovir gel in the coming year. In addition, delivery systems that do not require an applicator, e.g. films and suppositories, could also reduce the cost.

Given the numerous sponsors and collaborators, it is critical that the development team take a transparent and collaborative approach to developing and sharing plans in preparing the regulatory dossier, including Gantt charts and timelines for data, and a clear division of labour among the key players. This is important both for moving product development forward as efficiently as possible, as well as for conveying a clear sense of priorities and timelines to donors, policymakers and other key stakeholders.

**Regulatory environments**

Regulatory questions and strategy were a main backdrop to the meeting deliberations. At this stage, the discussion about regulatory strategy was necessarily somewhat circular. Regulators’ requirements must shape the research agenda, but at the same time regulators are not able to provide any clear decision or formal request for information without seeing the trial data and all the supporting evidence. It is important to note that the CAPRISA 004 trial data, while reported in Vienna and published in *Science*, are still being processed for regulatory submission, so at the time of this meeting in Johannesburg in August 2010 no regulatory agency had yet reviewed the

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\(^9\) Technology Innovations Agency (TIA) was established in 2008-2009 through an amalgamation of previous efforts and is sponsored by the South African Department of Science and Technology. Its portfolio includes many different technologies (such as energy, biotechnology and agriculture) and its mission is to stimulate and intensify innovation and inventions to improve economic growth and enhance the quality of life of all South Africans through developing technological innovations, and creating an enabling environment where these innovations can be commercialized.
data or made a formal determination. The CAPRISA team is moving quickly, aiming to finish preparing the regulatory report by October.

The CAPRISA 004 trial was conducted with approval of the South Africa Medicines Control Council (MCC), but not under an FDA investigational new drug application (IND). Discussions are underway with these two key regulatory agencies on the most suitable and efficient pathways to licensure. Other regulatory agencies in the African region represented at the meeting expressed interest in being involved in the initial regulatory review of the new product, but this usually is not undertaken without prior review by well-resourced regulatory authorities. Typically, regulatory authorities in resource-limited settings rely on such prior reviews before making their own assessment of risks and benefits for the populations under their responsibility. The European Medicines Agency’s Article 58 process (discussed below) under which the agency, in collaboration with WHO, can convene an expert panel to provide scientific advice for a drug intended for licensure outside Europe was one mechanism that could permit involvement of developing country regulatory authorities. The situation at the time of the meeting with respect to regulatory agencies is summarised below, although these issues continue to evolve rapidly.

USA Food and Drug Administration (FDA)
CONRAD is leading the discussions with the FDA and, just prior to the Johannesburg meeting, submitted an initial briefing document summarising currently available information on tenofovir gel. A meeting is scheduled in October to review existing information and identify what additional work is needed. Initial indications from the FDA suggest that there are already sufficient preclinical data. The FDA has agreed to review the tenofovir gel file under a “fast track” designation, which also allows for a rolling submission of portions of the new drug application (NDA) package so that data can be reviewed as they become available rather than waiting for the complete file. In collaboration with CONRAD, IPM has contracted with an external project manager to prepare documentation for the FDA and begin a standard regulatory dossier that could be submitted to other national regulatory authorities.

While it was not possible for the FDA to send a representative to the WHO/UNAIDS consultation, several FDA representatives participated in portions of the meeting via telephone. In the discussion, FDA staff suggested that they may consider VOICE a confirmatory trial for CAPRISA 004, pending the outcome of the trials and review of the data. This will be discussed further during the FDA meeting in October (see update in Epilogue).

South Africa Medicines Control Council (MCC)
TIA is taking the lead in contacts with the MCC and has requested a meeting to present the same information sent to the FDA and discuss their regulatory strategy in South Africa. TIA anticipates the meeting will take place sometime in October, and will possibly include local investigators planning a confirmatory study and the local manufacturing partner (pending conclusion of negotiations). During the WHO/UNAIDS meeting, MCC staff indicated they would need to see confirmatory findings before approving tenofovir gel, but did not elaborate on what form this should take.

European Medicines Agency (EMA)
The EMA noted that it is very open to facilitating review of tenofovir gel but was somewhat hampered in making specific suggestions because it had not received any data nor been formally
approached by any of the sponsors. The EMA staff present at the meeting were not sure whether the agency would view VOICE as a confirmatory trial for CAPRISA given the different dosing strategies (daily as opposed to episodic in relation to intercourse). The EMA representatives offered to provide a scientific opinion on tenofovir gel by convening an expert panel that would include representatives from developing country regulatory authorities. This would be under Article 58 which is a mechanism, in collaboration with WHO, to provide a scientific opinion on products intended for markets outside the European Union.

To start this process, IPM agreed to take the lead and submit to EMA the same information and questions submitted to the FDA. Then the EMA’s Scientific Advice Working Party could initiate the scientific advice process involving WHO and developing country experts. FDA would be invited to participate either formally or informally in this process. IPM has recently submitted its dossier on and plans for a Phase 3 trial on a vaginal ring containing the antiretroviral drug dapivirine to FDA and EMA under Article 58 and at the time of the Johannesburg meeting was waiting for the formal response and advice. This experience could inform the best way of proceeding with 1% tenofovir gel.

Regional regulatory efforts

Regarding the regulatory process in other countries in Africa, TIA’s potential pharmaceutical partners have some experience working with other regulatory authorities in the region. This means that, in theory, a regulatory process in other countries would not necessarily need to wait for MCC or FDA approval. In practice, however, few countries are experienced with or have the capacity to review and approve a new product, and most require prior approval in the country of origin or manufacture (in this case the USA).

Many of the African regulators present expressed strong support for sharing information among national regulatory authorities, and several options were explored for facilitating regional collaboration on regulatory review. Countries in East Africa (Kenya, Tanzania, Rwanda, Burundi, Uganda) are moving toward regulatory harmonisation and as such meet regularly and could jointly review a submission. Several efforts have been made toward a similar process within the Southern African Development Community (SADC) region in southern Africa, and the agencies collaborate frequently. However, no joint review process has yet been formalised. Overall, the national regulatory agencies from other countries in Africa noted that they would welcome the EMA’s Article 58 process and WHO expertise as described above. Finally, while the national regulatory authority representatives present did not provide any formal indication about information needed or confirmatory trials, in general they favoured a cautious approach, and argued that both professionals and lay people need to have more comprehensive information about the product. Some areas of concern included risk compensation and safety in pregnancy.

Additional effectiveness trials

There has been some speculation and public pressure that 1% tenofovir gel should be licensed based on the CAPRISA 004 data, but there has been no indication that any national regulatory

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agency would consider approval on the basis of the CAPRISA 004 data alone. While no regulatory agency has formally declared that it would not accept the CAPRISA data alone for licensure, most meeting participants thought it very unlikely. Two independent, well-conducted Phase 3 studies are usually required for regulatory approval, using the same drug formulation and dosing schedule submitted for registration. In exceptional circumstances, one well-conducted, highly significant Phase 3 study can serve as the basis for regulatory approval together with supporting data. CAPRISA 004 was not designed on its own to justify licensure. In addition, the wide confidence interval around the estimated 39% effectiveness means that the effect of 1% tenofovir gel as measured in the CAPRISA 004 trial could range from 6%-60%. Many experts at the meeting felt that it was critical to provide a more precise estimate of tenofovir gel’s effectiveness before considering widespread use.

Meeting participants discussed and debated whether the VOICE study could and should be considered as “confirmatory” of the CAPRISA 004 results. VOICE will provide a wealth of information about safety and effectiveness of 1% tenofovir gel. However, it remained unclear whether the VOICE trial would be considered confirmatory by the MCC, FDA or other regulatory authorities, particularly given its different dosing schedule. As noted above, the FDA suggested it may consider VOICE confirmatory, while the EMA expressed some scepticism given the different dosing regimens. The FDA and MCC may provide some indication about whether another placebo-controlled effectiveness trial is likely to be necessary following the meetings formally requesting advice that are planned in October. However, they may defer such a recommendation until the data from CAPRISA 004 and/or VOICE have been submitted for their review. Furthermore, MTN is conducting a number of the key ancillary and safety studies that will also be central to the regulatory package (see Appendix 2).

Most meeting participants felt that it is important to repeat the CAPRISA trial BAT 24 regimen to confirm that coitally-dependent dosing reduces the risk of HIV and HSV-2 infection. CAPRISA 004 was only done in two sites, both in KwaZulu Natal where HIV incidence and prevalence are very high, and effectiveness in other settings may be different. Results from one trial are not always reproduced by other studies, as had happened in the microbicide field with PRO 2000 when a borderline significant result in a Phase 2B trial was not confirmed in a large Phase 3 trial.\(^\text{11,12}\) With respect to VOICE, even if the safety and effectiveness of tenofovir gel are confirmed, uncertainty may remain about the relative effectiveness and acceptability of coital vs. daily dosing. There was also concern about what would happen if VOICE showed an indeterminate or lower level of effectiveness than CAPRISA, possibly as a result of poor adherence, or if the study raised serious safety concerns. Such an outcome could leave uncertainty about whether it was due to any adverse effects, differences in adherence associated with more frequent use, chance, or any of a range of background factors. Uncertainty based on contradictory or indeterminate results from CAPRISA 004 and VOICE could


stop further development of tenofovir gel, or add several years to the process while another trial was planned and implemented. The general sense was that the VOICE trial is critical to 1% tenofovir gel development, but it would be too risky to wait for the results of the VOICE trial alone. Therefore plans should be implemented now for at least one additional confirmatory trial of coital dosing in parallel with seeking regulatory advice.

In sum, most experts at the meeting felt that it was unlikely the CAPRISA 004 data would be sufficient for licensure. It is possible that a national regulatory authority will provide a firm indication that VOICE has the potential to be confirmatory, or even decide to approve the product based on the CAPRISA 004 results alone. Given the uncertainty around regulators’ perspectives, and the very different dosing schedules involved in VOICE (daily) and CAPRISA 004 (before and after sex), most meeting participants felt it prudent to move ahead with planning additional trials that could confirm whether coitally dependent dosing works to reduce the risk of HIV and HSV-2 infection.

**Proposed Trials**

Two different placebo-controlled trials were proposed to provide confirmatory evidence for licensure of 1% tenofovir gel. They had complementary approaches and each could provide data to help determine whether and how tenofovir gel can be licensed for use, labelled and rolled out to women in high HIV incidence settings.

**South African consortium**

A newly formed consortium of leading South African HIV prevention researchers came together to determine how best to follow up on the CAPRISA 004 results. This group, subsequently named FACTS (Follow-on African Consortium for Tenofovir Studies), is planning rapid implementation of a placebo-controlled safety and effectiveness study testing the BAT 24 dosing regimen of tenofovir gel in women aged 16-30 years. The FACTS 001 study would examine effectiveness of 1% tenofovir gel in preventing HIV and HSV-2 infections. This study would use a protocol very similar to the CAPRISA 004 trial, and would include six trial sites across South Africa to expand the data beyond the settings in KwaZulu Natal where CAPRISA 004 took place. Importantly, it would also expand the age range of participants to test safety and effectiveness in younger women (16-17 years), a group at very high risk of HIV exposure. The trial would aim to accumulate 2,000 woman-years of gel use in a 24-month trial (projecting a 12-month enrolment period, and mean follow up of 18 months). The study would encourage product adherence through the same motivational interviewing techniques used in the CAPRISA 004 trial, and would also include behavioural components focusing on adherence and sexual practices. The consortium is moving quickly to develop a protocol and pending funding and approvals, anticipates starting enrolment during the first or second quarter of 2011.

**Microbicides Development Programme**

The Microbicides Development Programme (MDP) is planning MDP 302, a large-scale study to assess the effectiveness of a single dose of tenofovir gel applied prior to sex compared to placebo gel, and relate this to the effectiveness of the BAT 24 regimen. Adherence to the single dose would be directly compared to adherence to the BAT 24 regimen. Women assigned to the single dose regimen would be instructed to apply the gel before sex, but failing that, immediately after. The study has been under development for some time, has already undergone peer review and received approval, but met challenges raising the necessary funds
for the study before the CAPRISA 004 study results were known. The study would be implemented in five African countries (Uganda, Tanzania, Mozambique, South Africa and Zambia) and aims to enrol 3,750 women aged 16-30 years. The groups would be randomized 1:1 to the single or BAT 24 dosing strategies, and then in a ratio of 2:1 to an active or placebo gel within each dosing regimen.

This trial is designed to provide additional evidence of safety and effectiveness of 1% tenofovir gel in preventing HIV and HSV-2. It would determine whether one dose is sufficient, as some PK/PD and animal data suggest, assisting with validating these indirect measures of product effectiveness. By using a more flexible single dosing strategy and assessing the acceptability and safety of less frequent testing for HIV, it is also designed to more closely reflect the way tenofovir gel may be used. If a single dose provides comparable protection to the BAT 24 regimen, it would be less expensive and more convenient for women to use. Similarly, the proposed quarterly testing and monitoring would be more feasible to implement in service delivery settings than the monthly regimen followed in CAPRISA 004 and the planned FACTS 001 trial. The MDP team aims to begin enrolment during the second quarter of 2011 and complete the trial by mid 2014.

Discussion

Debating the merits of these trial designs and their relative priority was a main focus of the meeting. Some participants thought it likely that the VOICE trial would be sufficient to confirm effectiveness. There was general agreement that the proposed FACTS 001 confirmatory trial of the BAT 24 regimen is more likely to lead to rapid registration of the gel. This is because MCC and South African Institutional Review Boards (IRBs) had already examined and approved a similar protocol, HIV incidence in the South African trial sites remains high, and the trial is studying the same dosing strategy as CAPRISA 004 so the trial results may be directly comparable. There was concern that a trial only in South Africa may be not be easily generalisable. It was suggested that the trial should be expanded to include sites in other African countries and that doing so may facilitate licensure and introduction in a wider range of countries. At the same time, many participants also saw the merits of studying the single dose strategy and less frequent testing, as proposed by the MDP team, as a crucial bridge toward implementation. Although PK/PD data are already available to support the potential effectiveness of a single dose applied prior to sex, confirmation of protection against placebo in a clinical trial is considered an essential standard. Some stated that assessing different dosing approaches could be addressed with further PK/PD studies and would not require a clinical effectiveness trial. This perspective has merit, but needs further, more specific exploration to determine if PK/PD approaches could indeed answer questions about dosing, or if clinical data would be preferred or required for registration, policy recommendations, and programme planning and implementation.

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13 Based on discussions at the meeting and concerns about generalisability, FACTS 001 is exploring the possibility of adding sites in other countries, though it is not clear whether such sites will ultimately be included in the trial.
Some consideration was given to combining the two approaches into a single trial. While such a combination approach may seem to be both economic and efficient (addressing, for example, the need for trial sites in different countries), the trial teams considered a joint trial to be too cumbersome and time consuming. The FACTS team in particular felt that because its protocol would be very similar to the CAPRISA 004 trial which the MCC and IRBs in South Africa had already reviewed and approved, it would be possible to move forward quickly. Members were reluctant to add layers of potentially cumbersome approvals across countries and risk delays in moving rapidly to implementation. Based on discussions at the meeting, the team did propose to explore the feasibility with potential collaborators of starting in South Africa and possibly adding sites in other countries as they are ready and approvals are granted, provided that doing so would not slow down the trial. At the same time, the MDP investigators remained committed to assessing whether a single dose of tenofovir gel would be effective in reducing the risk of HIV infection as women may drift towards a single dose for convenience or cost. They maintained that studying a single dosing strategy, and the proposed quarterly testing and follow-up, is a more realistic approach to providing the gel in service delivery settings and these aspects need to be studied in a placebo-controlled trial.

While combining the trials was not deemed feasible during the meeting, if both trials did proceed, the teams did agree to develop common elements and compatible protocols, so that the trials would be complementary and key data could be analysed jointly. There are good examples of such collaboration, and several people cited the HPTN 035 and MDP 301 trials of PRO 2000, and collaboration between FEM-PrEP and other pre-exposure prophylaxis studies as recent successful examples.

There is now a narrow window for launching a new placebo-controlled microbicide trial; once there are data to confirm the effectiveness of 1% tenofovir gel, it may not be ethical or practical to use a placebo. Indeed some advocates already argue that using placebo is unethical based on the findings from the CAPRISA study. This underscored the urgency of moving planned trials forward to get them reviewed and underway as soon as possible. The FACTS consortium is aiming for the shortest possible timeframe, beginning participant enrolment in mid 2011, aiming to complete enrolment in mid 2012 and follow up in mid 2013, and having results available in late 2013. The MDP team is also moving rapidly and could begin enrolment in the second quarter of 2011, complete enrolment by the end of 2012, finish follow-up by the end of 2013, and report results in mid-2014.

Overall there was a strong sense of urgency – both to focus on determining the most expedient approach to licensure and thereby getting a product to women at risk, and to move forward with additional trials as rapidly as possible. While there were many questions about tenofovir gel that needed to be answered, it was considered important to keep the protocols relatively simple and focused on answering the key question of effectiveness.

**Resistance, HIV testing, implementation**

The meeting also touched on resistance, HIV testing and implementation science – among the key areas where more information will be needed to inform eventual product implementation and use. Some of the most salient issues, such as resistance, are already being addressed both in ongoing and planned trials. Others, like implementation research, would benefit from more
focused planning and targeted research going forward. Overall, the meeting reinforced continuing ongoing work on these topics, and suggested an in-depth examination with experts in each area to review ongoing work, identify gaps and ensure that these implementation issues are being explored as comprehensively and strategically as possible. These review efforts were seen as important in the near to medium term, but not a top priority relative to confirming safety and effectiveness and implementing the follow up studies (which will include work on resistance and some implementation models) in the CAPRISA 004 communities.

**Resistance**

The selection and transmission of resistant virus has been a central concern around the use of antiretroviral drugs for prevention. This concern centres on the possibility that using antiretroviral drugs for prevention will compromise the effectiveness of antiretroviral treatment for individuals and select for drug resistance at the population level. Because of the much higher systemic drug levels achieved with a pill than with the vaginal gel, this may be a more serious concern with oral PrEP. Resistance monitoring will be an important component of any antiretroviral-based prevention approach. However, at the moment regular resistance testing in a service delivery context is not practical as it requires expensive and sophisticated laboratory tests. A number of inexpensive rapid tests more suitable for resistance surveillance are being developed and may be available in the coming few years.

Available data on drug resistance with tenofovir gel use are encouraging but the data are very limited. The field is a long way from having definitive answers about a number of important issues including: whether resistance with gel use is a concern for individuals and the population; whether it would vary by intensity of exposure; whether women who acquire HIV infection while using tenofovir gel require different treatment options; whether it is safe for women who already have HIV infection to use tenofovir gel; and whether use of tenofovir gel or other antiretroviral-containing microbicides would lead to drug resistance at the community level. Current thinking is that women who are already infected with HIV would not be prescribed or offered tenofovir gel, but it is likely that some women with established infection, especially those who are unaware of their status, may use the product. Hence it is important to study the implications of such use. Modelling studies suggest that resistance in a community would be driven much more by treatment than antiretroviral-based prevention programmes.

It will be important to continue to monitor resistance in the proposed CAPRISA 009 treatment study, the VOICE study (MTN-003), the ongoing MTN-009 and MTN-015 studies, Fem-PrEP, Partners PrEP, and future studies of women using oral and topical tenofovir for HIV prevention. Data on treatment with tenofovir for HIV-positive individuals show that the K65R mutation is not common. The field can also draw on considerable data from treatment programs, including a PharmAccess programme monitoring resistance in six different settings. Participants recognized the growing body of work and knowledge on resistance, and also the need to synthesise what is known to inform thinking and possible research to fill any gaps, especially about how and whether to monitor resistance in a service delivery context.

**HIV testing**

Determining programmatic approaches to the nature and frequency of HIV testing is critical for antiretroviral-based prevention. Frequent testing would allow programmes to identify users who seroconvert to HIV and take them off antiretroviral-based products, thereby reducing the
potential for developing antiretroviral resistance. They would also be referred for support, HIV clinical care, and prevention counselling, minimising the risk they will infect their partners. Regular testing linked to resupply can also provide the opportunity for risk reduction counselling and adherence support. The challenge is to balance frequent testing with cost considerations and burden to both clients and programmes. Determining how frequently to test in relation to tenofovir gel provision will be driven by a better understanding of resistance with gel use in women with incident and already established HIV infections, program cost and capacity, and acceptability to clients. The microbicide field can draw on lessons from CAPRISA 008 and MDP 302, as well as work in eventual pilot sites for PrEP programs. Additional work or collaborations may be required to determine how best to implement testing in the context of service delivery to support more widespread use of tenofovir gel.

**Implementation**

Even the best new drug or intervention will not benefit individuals or have an impact on the epidemic if it does not reach people at risk or they do not use it. Models consistently show that public health impact of a given intervention is driven more by coverage and use than by the absolute level of effectiveness. “Implementation science” is a dynamic and growing area of work, and it is important that as the microbicide field moves closer to having an effective product it draws in new expertise to determine how best to provide and market the product to women at risk. Experts in service delivery, social marketing and product introduction will all be needed to help develop innovative models and appropriate ways of introducing these products and measuring their impact. Relatively few participants at the consultation were experts in operations research, or other fields related to implementation, so this area will be explored in a separate, smaller brainstorming session to identify and prioritize next steps. These efforts can build on the access models developed by the microbicide field for a number of years that have been lent more urgency and relevance by the positive results from the CAPRISA 004 trial that have underscored the possibility of an effective microbicide. This was viewed as an important area of work over the near term, but not a top priority relative to the additional trials to confirm effectiveness of 1% tenofovir gel.

**Priority next steps**

The priority next steps identified during the consultation and highlighted throughout this report are summarized in the matrix contained in Appendix 1, with the following actions identified as priorities:

**Additional safety studies**

Several priority gaps for safety were identified, primarily among groups that had been excluded from previous trials but would be likely to use the gel once it is on the market regardless of the labelling. These include: young women aged 16-17 years; women with hepatitis B infection; and women with impaired kidney function. In addition, it is necessary to confirm that existing studies of safety in pregnancy and the pregnancy registry will meet regulatory requirements.

**Effectiveness trials**

**Effectiveness trial in South Africa to confirm the BAT 24 dosing regimen**

A consortium of South African researchers proposed a six-centre trial in South Africa to replicate the CAPRISA 004 trial with two key modifications: including younger women (proposed age
range 16-30 years); and prevention of both HIV and HSV-2 as endpoints. This was viewed as the fastest way to licence and eventual product availability and use. The trial team is moving forward rapidly and, pending the availability of funding, could start enrolling in the first half of 2011 with results expected by the end of 2013.

**Effectiveness and safety trial of simplified dosing and HIV testing schedules**
The Microbicides Development Programme proposed a clinical trial in five African countries to assess the effectiveness of a simplified regimen of one dose of tenofovir gel compared with placebo gel. The trial would relate the effectiveness of the single dose and BAT 24 dosing regimens in preventing HIV and HSV-2 infection and directly compare adherence to the two regimens. The trial would enrol women aged 16-30 years, with HIV testing performed quarterly rather than monthly. While not everyone at the meeting agreed that two confirmatory trials are needed or that a third dosing regimen should be tested, this trial was seen as important for informing implementation. While contributing to approval and licensing, it would address concerns that data from South Africa may not be generalisable to populations in other settings. The simpler regimen, if effective, would be less expensive, easier to translate into programmes, more acceptable, and more convenient for women to use. The trial team is currently completing a placebo gel study and, pending availability of funding, could start enrolling by mid-2011 with results expected in mid-2014.

**Implementation studies in CAPRISA 004 communities**

**Implementation study**
CAPRISA 008 would assess the feasibility and effectiveness of providing tenofovir gel through family planning clinic settings. Former CAPRISA 004 trial participants from the these communities would be eligible to continue to have access to tenofovir gel following either the monthly protocol of resupply, monitoring and testing used in the trial, or a new quarterly protocol at family planning clinics that mirrors service provision for hormonal contraception. This three-year study would measure product use, adherence, HIV incidence, and viral load in women who became infected. It would begin to provide information about implementation, demonstrating how tenofovir gel can be provided and monitored in service delivery settings.

**Treatment outcome and resistance study**
This study (CAPRISA 009) would provide care, treatment and monitoring for former CAPRISA 004 trial participants who became infected with HIV while in the trial. The study would compare treatment outcomes for those who receive an antiretroviral regimen that includes tenofovir with those who receive one without tenofovir. It would assess any effects of using tenofovir gel on the safety and effectiveness of these treatment regimens, and document viral load, CD4 counts, resistance, and disease progression. This would provide critical information on use of treatment regimens containing tenofovir for women who acquire HIV while using tenofovir gel.

**Looking ahead**
The historic CAPRISA 004 results infused the microbicide field – and many working on HIV prevention – with a renewed sense of energy and optimism. This was coupled with a sense of urgency to move forward as efficiently as possible to confirm the effectiveness of 1% tenofovir gel in reducing the risk of HIV infection in women, while looking ahead and planning for potential product introduction and use. Participants at the consultation grappled with a range
of complex issues, including uncertainty about the regulatory environment and how regulators would view the different ongoing and proposed trials, given differing dosing strategies, countries and epidemiologic contexts. Despite these uncertainties, and some participants questioning whether both proposed confirmatory trials were needed, the meeting reached general agreement about the most urgent next steps and also identified other priority actions. These recommendations have been met with some encouraging commitments from donors but unfortunately not enough funding to implement all the top priority actions, nor the other activities also identified as critical. Many actors in the field continue to work together with a keen sense of urgency, moving forward rapidly to develop protocols and seek funds. It was noted that there is an ethical imperative to work on these actions concurrently rather than sequentially in order to get products to women at risk as quickly as possible.

**Epilogue**

Debate and discussion about the most appropriate next steps with 1% tenofovir gel have continued in a range of formal and informal fora since the WHO/UNAIDS meeting in August. These debates have taken place against a backdrop of constrained resources and competing priorities for funds for microbicide research and for HIV prevention more generally.

Immediately following the meeting, a smaller group of researchers and donors met to further discuss priorities, as well as initial funding needs and possibilities. An initial rough estimate of the costs of the proposed trials totalled approximately US$ 100 million (US$ 40 million for the FACTS trial, US$ 40 million for the MDP trial, and US$ 20 million total for the two follow-on trials in the CAPRISA 004 sites. The safety studies, while critical, are considerably less expensive.) While this total figure is significant, especially in the current economic climate, it is relatively small when contrasted with investments in other HIV prevention research. Given the excitement and potential around tenofovir gel, some participants felt that it would be reasonable to advocate for this level of funding to support all of the identified trials as a coordinated and complementary programme of research leading to licensure and introduction.

Donors, notably USAID and the Department of Science and Technology, have committed to supporting the FACTS trial, with the Gates Foundation indicating that it would fund the cost of gel with funds from an existing grant to CONRAD. The UK Medical Research Council committed to providing some funding for the MDP 302 trial. NIH underscored its significant commitment to tenofovir gel development including support for some of the initial basic research, as well as the current suite of studies within the MTN network. NIH indicated that it may consider additional support for some portion of the proposed research, for example laboratory work through one of its facilities. NIH did indicate that any support would require scientific peer review and echoed concerns about generalisability, preferring a study done in more than one country.

The proposed trials for the CAPRISA 004 sites did not have specific funding support, but the investigators were confident that given that those studies would be more geared toward implementation they would be able to raise the funds from local and international sources. These discussions have continued and appear to be on course.

Other donors expressed their support and interest, but were unable to make specific commitments citing funding constraints, a shift in priorities away from research, or ongoing commitments to other microbicide research including IPM and the dapivirine ring.
The overall shortfall was sobering and raised questions about whether it would be possible to support all the proposed trials. A number of the meeting participants resolved to try to raise funds to support the full research agenda, and resource mobilisation activities are continuing as this report is being finalised. Some people in the field have questioned the necessity of conducting two additional effectiveness trials or assessing a third dosing strategy (single dose). Yet others have said that assessing simplified dosing is important for cost-effective implementation. Some have said that it was important to wait for feedback from regulators to determine what further research, if any, is on the regulatory pathway. The feedback from regulators will be critical but is only one of several perspectives that need to be addressed. Finally, many people, both meeting participants and others, have argued that there is a public health imperative to rapidly implement additional research and clarify the regulatory pathways to confirm whether tenofovir gel is safe and effective and so that women at risk could have access to a new product as rapidly as possible.

In late October, as this report was being finalised, sponsors held separate meetings with South African (MCC) and USA (FDA) regulators. TIA and researchers from the CAPRISA and the FACTS teams met informally with the MCC which suggested that additional confirmatory data on the BAT 24 regimen would be useful and encouraged submission of the FACTS 001 trial protocol. MCC would also like to see data on safety in pregnancy and adolescence. CONRAD and a number of other agencies met with the FDA to determine the next steps required for licensure of 1% tenofovir gel. Importantly, the FDA indicated that it would consider both CAPRISA 004 and VOICE as pivotal trials despite the different dosing strategies. The FDA also indicated that it would want to see additional safety data, including in younger women and post-menopausal women.
Appendix 1: Matrix of priority activities

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<thead>
<tr>
<th>Activity</th>
<th>Organization Lead</th>
<th>Timing</th>
<th>Funding</th>
<th>Comments</th>
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<td><strong>Confirmatory Trial(s)</strong></td>
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<tr>
<td>Develop strategy, plan, protocol, funding for South Africa confirmatory trial of BAT 24 regimen for HIV and HSV-2 prevention</td>
<td>South African consortium, later named FACTS (Follow-on African Consortium for Tenofovir Studies)</td>
<td>Immediate</td>
<td>DST, USAID, others TBD</td>
<td>Potential for protocol to allow for pooled data and analysis across trials (SA Consortium and MDP 302)? FACTS 001 Study would enrol 16 &amp; 17 year old women Study would examine tenofovir gel for HIV and HSV-2 prevention Possibility for including sites in other African countries to improve generalisability</td>
</tr>
<tr>
<td>Develop strategy, plan, protocol, funding for confirmatory trial using multiple regimens (coitally dependent single dose/BAT 24) in multiple southern African countries</td>
<td>MDP and collaborating sites</td>
<td>Immediate</td>
<td>MRC, others TBD</td>
<td>Protocol to allow for pooled data and analysis across trials (SA Consortium and MDP)? Dosing strategy Contingent on additional funding</td>
</tr>
<tr>
<td>Develop clear strategy for joint work on above</td>
<td>SA Consortium/MDP</td>
<td>Immediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Develop approach to PK/PD research to address questions around dosing and effectiveness</td>
<td>TBD CONRAD, MTN, CAPRISA Product developers</td>
<td>Immediate</td>
<td>TBD</td>
<td>Consult with product developers, Angela Kashuba, others on best approach to PK/PD studies to address dosing and effectiveness to complement trial result evidence Explore small substudy using biopsies from VOICE, CAP 004, other approaches</td>
</tr>
<tr>
<td>Develop research agenda/plan for HSV-2</td>
<td>Gilead, CONRAD, others TBD</td>
<td>Q4 2010</td>
<td></td>
<td>Some info will be generated by VOICE and FACTS Most efficient to study separately and in other settings (potentially in USA or Europe) Discussions ongoing between Gilead and licensees</td>
</tr>
<tr>
<td>Activity</td>
<td>Organization Lead</td>
<td>Timing</td>
<td>Funding</td>
<td>Comments</td>
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<tr>
<td><strong>Additional Clinical (safety) Studies</strong></td>
<td></td>
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</tr>
<tr>
<td>Clarify other studies/data needed for regulatory process</td>
<td>CONRAD, IPM, TIA, regulatory agencies</td>
<td>Q4 2010</td>
<td></td>
<td>(see also regulatory section)</td>
</tr>
<tr>
<td>Safety in adolescents</td>
<td>Small initial safety trial TBD</td>
<td>Immediate</td>
<td>TBD, USAID</td>
<td>Small separate trial</td>
</tr>
<tr>
<td></td>
<td>Also addressed SA</td>
<td>Q2 2011</td>
<td></td>
<td>Determine whether enrolment of this age group in FACTS 001</td>
</tr>
<tr>
<td></td>
<td>Consortium trial Other data/bridging studies needed?</td>
<td></td>
<td></td>
<td>effectiveness trial will be sufficient for regulators</td>
</tr>
<tr>
<td>Safety in pregnancy</td>
<td>MTN/CONRAD</td>
<td>MTN (others?)</td>
<td></td>
<td>Confirm that doing all necessary for FDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clarify that MTN has regulatory pathway to obtain approval for use in pregnancy</td>
</tr>
<tr>
<td>Safety in women with hepatitis B, impaired renal function</td>
<td>TBD</td>
<td>2011</td>
<td></td>
<td>Small safety studies (Hepatitis B and impaired renal function are exclusion criteria for CAPRISA 004, VOICE and proposed confirmatory trials)</td>
</tr>
<tr>
<td>Additional safety studies TBD</td>
<td>TBD</td>
<td></td>
<td></td>
<td>TBD pending:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Feedback from regulatory authorities</td>
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<tr>
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<td></td>
<td></td>
<td>• Comprehensive file and identify gaps</td>
</tr>
<tr>
<td>Safety - high-frequency use (more than 2x/day)</td>
<td>MTN ?</td>
<td></td>
<td></td>
<td>Daily use from VOICE</td>
</tr>
<tr>
<td>Safety HIV+ men</td>
<td>MTN? CONRAD? IPM?</td>
<td></td>
<td></td>
<td>Small safety study for higher frequency use</td>
</tr>
<tr>
<td>Study of user filled paper applicator</td>
<td>PATH/CONRAD/Profamilia</td>
<td>Q42010</td>
<td>USAID</td>
<td>Study to be started Q4 2010 pending IRB and FDA submissions</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Results expected 2011</td>
</tr>
<tr>
<td>Follow on applicator study/studies in other settings</td>
<td>PATH/CONRAD</td>
<td></td>
<td>USAID</td>
<td>Depending on regulatory review?</td>
</tr>
<tr>
<td><strong>Regulatory</strong></td>
<td></td>
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<tr>
<td>Meeting with FDA</td>
<td>CONRAD</td>
<td>October 2010</td>
<td>CONRAD</td>
<td>Identify gaps and outstanding issues based on CAPRISA 004 data and forthcoming VOICE data</td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td><strong>Organization Lead</strong></td>
<td><strong>Timing</strong></td>
<td><strong>Funding</strong></td>
<td><strong>Comments</strong></td>
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<tr>
<td>EMA Scientific Opinion Technical Review</td>
<td>IPM to take lead; work with EMA and WHO</td>
<td>Q4 2010</td>
<td>IPM</td>
<td>IPM to submit request to EMA for scientific advice/review under Article 58 (same Qs and dossier as sent to FDA) &lt;br&gt;Involve WHO and developing country technical experts in advice. &lt;br&gt;Possibility of joint review with FDA.</td>
</tr>
<tr>
<td>Dialogue with/Submission to MCC</td>
<td>TIA</td>
<td>Sept/Oct 2010</td>
<td></td>
<td>Will submit materials and Qs sent to FDA &lt;br&gt;Will include SA Consortium representatives and possibly manufacturing partner (if identified)</td>
</tr>
<tr>
<td>Convene regional meeting of regulators</td>
<td>WHO</td>
<td>Q4 2010</td>
<td>WHO</td>
<td>Provide background on HIV prevention studies and tenofovir gel. Timed to provide developing country NRA perspective before EMA issues final scientific opinion</td>
</tr>
<tr>
<td>Clarify other studies/data needed for regulatory process</td>
<td>CONRAD, IPM, TIA, regulatory agencies</td>
<td>Q4 2010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product development team to develop and share Gantt charts for regulatory process, additional studies</td>
<td>CONRAD, IPM, TIA, others</td>
<td>Q4 2010</td>
<td></td>
<td>Transparency re: timing and process for regulatory review, additional studies involving other agencies</td>
</tr>
<tr>
<td>Clarify level of training required for who can/will prescribe to inform operations research</td>
<td></td>
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</table>

**Manufacturing**

<table>
<thead>
<tr>
<th><strong>Activity</strong></th>
<th><strong>Organization Lead</strong></th>
<th><strong>Timing</strong></th>
<th><strong>Funding</strong></th>
<th><strong>Comments</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete validated, scaled-up commercial process for regulatory submission</td>
<td>CONRAD</td>
<td>Ongoing</td>
<td></td>
<td>Final steps to be completed by CONRAD</td>
</tr>
<tr>
<td>Technology transfer to SA; validate commercial process</td>
<td>TIA, CONRAD, partner company TBD</td>
<td>TBD</td>
<td>TIA, partner company TBD</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>Organization Lead</td>
<td>Timing</td>
<td>Funding</td>
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<tr>
<td><strong>Policy, Program, Implementation Research</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implementation research on delivery approaches with former CAPRISA 004 participants and communities</td>
<td>CAPRISA</td>
<td>Immediate (protocol development) for 2011 start</td>
<td>USAID Pretoria (TBC) Other TBC</td>
<td>CAPRISA 008 Answer critical research questions relevant to programme design &amp; provide ongoing access to gel under research designation in former trial populations &amp; communities. Determine needed frequency of HIV testing and approaches in gel users (including self-tests)</td>
</tr>
<tr>
<td>Seroconverter Treatment Study</td>
<td>CAPRISA</td>
<td>Immediate (protocol development) for 2011 start</td>
<td>TBD</td>
<td>CAPRISA 009- study to provide care, treatment and monitoring to seroconverters from CAPRISA 004 trial and compare outcomes for those who receive combined ART including and excluding tenofovir.</td>
</tr>
<tr>
<td>Identify needed frequency of HIV testing and approaches in gel users feasible for programs</td>
<td>Confirm CAPRISA, MTN, MDP 302 Others?</td>
<td>?</td>
<td>TBD</td>
<td>Key program question (monthly testing in trials not feasible in programs); partially addressed in CAPRISA 008 and MDP 302, MTN?</td>
</tr>
<tr>
<td>Identify gaps in information re: resistance and approaches to resistance monitoring feasible for programs</td>
<td>CAPRISA, MTN, NIH, WHO, UNAIDS, others</td>
<td>2011</td>
<td>TBD</td>
<td>Small group to review existing evidence and ongoing research; identify missing information and approaches to filling gaps</td>
</tr>
<tr>
<td>Convene meeting to develop research agenda for implementation (clinical and service delivery) and policy questions</td>
<td>WHO, UNAIDS, FHI, others?</td>
<td>Q4 2010</td>
<td>TBD</td>
<td>Targeted discussion around implementation and operations research to inform service delivery strategies, maximize coverage and impact</td>
</tr>
<tr>
<td>Define evidence base needed for WHO guidelines</td>
<td>WHO</td>
<td>Ongoing at WHO</td>
<td></td>
<td>Needed to prepare for WHO guidelines &amp; plan for additional information required</td>
</tr>
<tr>
<td>Consolidate approaches and define research for determining how to explaining partial effectiveness, levels of effectiveness</td>
<td>TBD</td>
<td>Q1 2011</td>
<td></td>
<td>Main concern/source of confusion from civil society and community consultations. Implications for policy decisions, positioning, user education.</td>
</tr>
<tr>
<td>Activity</td>
<td>Organization Lead</td>
<td>Timing</td>
<td>Funding</td>
<td>Comments</td>
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</tr>
</tbody>
</table>
| Elaborate plans for pre-introductory studies/ongoing access for trial participants & communities  
  • Testing, retesting (inc. self tests)  
  • Less frequent monitoring | CAPRISA, MTN, others? | Ongoing      |         | Can meet joint goals of answering critical research questions & providing ongoing access under research designation in trial populations & communities. |
| Define marketing/branding agenda                                         |                   |              |         | Review historical and current acceptability and market research  
  Consider demand creation as well as delivery                           |
| **Strategic Communications**                                             |                   |              |         |                                                                          |
| Communications around outcome of consensus meeting                       | WHO UNAIDS        | Immediate    | Press release  
  Meeting report                                                           |
| Community research/education around partial efficacy & implications in trial sites & other settings | TBD               | Ongoing, continue | Key for users & others to understand partial effectiveness (rather than dichotomy presented around trials that a product will “work” or “not work” to prevent HIV). |
Appendix 2: Summary of completed, ongoing and planned clinical studies of 1% tenofovir gel

This summary is organized in the following sections:
- Completed Safety and Pharmacokinetic Studies
- Ongoing Safety and Pharmacokinetic Studies
- Ongoing Observational Studies
- Pending and Planned Safety Studies
- Pending Observational Study
- Completed Effectiveness Study
- Ongoing Effectiveness Study

Completed safety and pharmacokinetic studies

**HPTN 050: Phase I safety and acceptability study vaginal microbicide agent PMPA gel**
- **Summary:** Phase I safety and acceptability study of 0.3% or 1% tenofovir gel applied once or twice daily for 14 days; sequential cohorts
- **Sponsors/Implementers:** NIAID, HPTN
- **N** = 84; HIV-negative and HIV-positive women (18-45 yrs)
- **Research centres:** Harlem Hospital Center, New York (New York); University of Pennsylvania, Philadelphia (Pennsylvania); Miriam Hospital and Women’s and Infants’ Hospital, Providence (Rhode Island) (United States)
- **Status:** Completed, Results 2006
- **Results:**
  - Two-week course of 1% tenofovir gel was well tolerated in sexually active and abstinent HIV-negative and HIV-positive women
  - Low serum but detectable levels in 56% of participants
  - No new resistance mutations evolved, and no patients had high-level tenofovir mutations, such as K65R.
  - Tenofovir gel generally safe and acceptable.

  - **Citation:** Mayer KH et al. Safety and tolerability of tenofovir vaginal gel in abstinent and sexually active HIV-infected and uninfected women. AIDS. 2006 Feb 28; 20 (4): 543-51
  - **Links:** [http://www.hptn.org/research_studies/hptn050.asp](http://www.hptn.org/research_studies/hptn050.asp)
    [www.clinicaltrials.gov/ct2/show/NCT00028132](www.clinicaltrials.gov/ct2/show/NCT00028132)

**CONRAD A04-099: Phase I male tolerance study of 1% tenofovir gel**

Summary: Phase I randomized, blinded, male safety and tolerance study following multiple topical exposures; 7 days of once-daily 1% tenofovir gel or K-Y Jelly

- **Sponsors/Implementers:** IPM, CONRAD / CONRAD, FHI
- **N** = 36; HIV-negative men
- **Research centres:** Advances in Health, Houston (Texas)(United States)
- **Status:** Completed
- **Results:**

Page 24
35 men completed the study
13% of men in the tenofovir group reported symptoms of genital irritation vs. 18% in the K-Y
group; overall both products were well tolerated.

Citation: Schwartz JL, et al. Safety evaluation of 1% tenofovir gel in healthy men. Int J STD AIDS
2009;20:384-386. http://ijsa.rsmjournals.com/cgi/content/abstract/20/6/384

HPTN 059: Phase II expanded safety & acceptability study of the vaginal microbicide 1%
tenofovir gel

- **Summary:** Phase II placebo-controlled expanded safety and acceptability study of 1% tenofovir
gel in sexually active HIV-negative women. Randomized into 4 arms comparing tenofovir 1% gel (daily &
coitally-dependent) to placebo; 24 week duration with 48-week follow-up. Outcome
measures: macroscopic evidence of damage to the cervical, vulvar, or vaginal epithelium, severe
erythema, or severe edema, related or not related to the study gel or applicator.
- **Sponsors/Implementers:** NIH, Gilead / HPTN (MTN)
- **N = 200:** HIV-negative, sexually active women (18-50 yrs)
- **Research centres:** University of Alabama at Birmingham, Birmingham (Alabama); Bronx-Lebanon Hospital Center, Bronx (New York) (United States); Jehangir Hospital/ NARI Clinic, Pune (India)
- **Status:** Completed
- **Results:**
  - Tenofovir gel was safe, acceptable, and feasible for both daily and sex-dependent
    application over 6 months. No differences in safety measured by liver, blood and kidney
    function. Only minor genital symptoms such as itching and burning reported by some
    women, with no differences between sites or study groups.
  - Adherence (80% and 83%) and acceptability similar in both dosing groups; 90% reported
    they would use gel if it reduced risk of HIV infection.
  - Some women preferred daily use. The majority of participants were married.
- **Links:**
  - http://www.hptn.org/research_studies/hptn059.asp
  - http://clinicaltrials.gov/ct2/show/NCT00111943
- **Citation:** Hillier SL: Safety and acceptability of coitally dependent use of 1% tenofovir over six
  No. 655

CONRAD A04-095: Phase I pharmacokinetic study to assess local & systemic absorption of 1%
tenofovir gel in HIV-negative, abstinent women

- **Summary:** Phase I open label, uncontrolled, pharmacokinetic study to assess local & systemic
  absorption of 1% tenofovir gel in HIV-negative, abstinent women.
- **Sponsors/Implementers:** IPM, USAID, NIH, Gilead / CONRAD, FHI
- **N = 49** (45 completed, 4 discontinued early); HIV-negative, abstinent women (18-45 yrs)
- **Research centres:** University of Pittsburgh Medical Center, Pittsburgh (Pennsylvania); Advances in
  Health, Houston (Texas) (United States); Profamilia, Santo Domingo (Dominican Republic)
- **Status:** Completed
- **Results:**
  - Single and multiple dose tenofovir gel exposure led to high genital tract levels up to 24 hours post
dose and support further study of pericoital and once-daily dosing of tenofovir gel
  - TFV exposure low in blood plasma and high in cervicovaginal fluid up to 24 hours after vaginal
  application
• TVP-DP concentration high in endocervical cells and detectable in about 40% of vaginal tissue biopsy samples at exposures similar to or higher than seen in PMBCs after oral exposure.

• Links: [www.clinicaltrials.gov/ct2/show/NCT00561496](http://www.clinicaltrials.gov/ct2/show/NCT00561496)

• Citation: Schwartz JL, Rountree R, Kashuba A, Brache V, Creinin MD, Poindexter A, Kearney, BP. A Multi-Compartment, Single and Multiple Dose Pharmacokinetic Study of the Vaginal Candidate Microbicide 1% Tenofovir Gel. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Cape Town, SA, July 20-22, 2009. Abstract #: LBPEC03

**TFV 010: Phase I safety and pharmacokinetic study of repeated dose of 1% tenofovir gel in abstinent HIV negative women**

• **Summary:** Phase I randomized, double-blind, placebo-controlled safety and pharmacokinetic study of 14 daily tenofovir gel applications. Study to assess whether any measurable response to daily vaginal applications of 1% tenofovir gel in women at low risk for HIV infection. Measured mucosal response to daily intravaginal applications of 1% tenofovir gel versus placebo in two groups of women. Primary outcome measures: changes in cytokines, chemokines, and other mediators of innate immunity.

• **Sponsors/Implementers:** NIAID

• **N = 30;** sexually abstinent HIV negative women with normal lower vaginal tract (18-50yrs). 26 completed trial (12 TFV, 14 placebo)

• **Research centres:** Montefiore Medical Center, Albert Einstein College of Medicine (New York) (US)

• **Status:** Completed

• **Results:**
  - Gels well tolerated and adverse events similar in tenofovir and placebo groups and mild in severity (vaginal itching/burning). Small but significant increase in vaginal pH in tenofovir group on day 14.
  - Repeated vaginal application of TFV gel not associated with reduction in endogenous antimicrobial activity, loss of protective mediators or proinflammatory response.
  - CVL from women using tenofovir had significantly increased anti-HIV activity compared to those using the placebo

• **Citation:** Keller M, Madan R, Torres N, Cho S, Eisinger S, et al. A phase I study to assess genital tract mucosal immunity following repeated vaginal application of 1% tenofovir gel. Abstract 212; Microbicides 2010; Pittsburgh, PA. 24 May 2010.

• **Links:** [http://clinicaltrials.gov/ct2/show/NCT00594373](http://clinicaltrials.gov/ct2/show/NCT00594373)

**MTN 002: Phase I study of the maternal single dose pharmacokinetics and placental transfer of tenofovir 1% vaginal gel among healthy term gravidas**

• **Summary:** Phase I single site, open label study of pharmacokinetic parameters and placental transfer of single dose 1% tenofovir gel. Gel administered vaginally to 16 full-term pregnant women approximately 2 hours prior to caesarean delivery. Secondary aims: characterize systemic safety profile of single dose tenofovir gel; compare 3rd trimester absorption of tenofovir gel to absorption in non-pregnant recent historical controls; and assess amniotic fluid, cord blood, endometrial tissue and placental tissue levels following administration of a single dose of 1% tenofovir gel.

• **Sponsors/Implementers:** NIH, CONRAD / MTN

• **N = 16;** HIV-negative healthy term pregnant women (18-45 yrs)

• **Research centres:** University of Pittsburgh Medical Center: Pitt CRS, Pittsburgh (Pennsylvania) (United States)

• **Status:** Completed
• **Preliminary Results:**

  Only small amounts of tenofovir absorbed in mother’s blood, amniotic fluid, and umbilical cord (fetal) blood. Levels of drug absorption similar to that seen in non-pregnant women. Drug levels much lower than seen in umbilical cord blood (40 times lower) and maternal blood (50-100 times lower) among pregnant women administered oral tenofovir (600mg) for prevention of maternal to child transmission of HIV.

  No serious side effects associated with tenofovir in mothers or newborns in 1st 2 weeks of life (time followed).

  **Citation:** Beigi R, Noguchi L, Macio I, Kunjara R, Hendrix C et al. Maternal single dose pharmacokinetics and placental transfer of tenofovir 1% vaginal gel among healthy term gravidas. Abstract 9; Microbicides 2010; Pittsburgh, PA. 23 May 2010.

  **Links:** [http://www.mtnstopshiv.org/node/1846](http://www.mtnstopshiv.org/node/1846), [www.clinicaltrials.gov/ct2/show/NCT00540605](http://www.clinicaltrials.gov/ct2/show/NCT00540605)

**Ongoing safety and pharmacokinetic studies**

**MTN 001: Phase II adherence and pharmacokinetic study of oral and vaginal preparations of tenofovir**

- **Summary:** Phase II, multi-site, randomized, six sequence, three period open label cross over study of safety, acceptability, adherence, and pharmacokinetics. Three daily regimens studied: tenofovir gel, tenofovir tablet (300 mg), and the two together. Participants followed each regimen for six weeks, with one week between when no study product was used.

- **Other outcomes:** factors associated with product adherence and potential variations in sexual activity and male condom use associated with different regimens; tenofovir levels in rectum following vaginal administration of tenofovir gel (NY site only).

- **Sponsors/Implementers:** NIH, Gilead, CONRAD / MTN

- **N** = 144; sexually active, HIV-negative women (18-45 yrs)

- **Research centres:** Bronx-Lebanon Hospital Center (New York), Alabama Microbicide CRS (Alabama), Univ of Pittsburgh CRS (Pennsylvania), Case Western Reserve Univ Cleveland (Ohio) (United States); South African Medical Research Council: Botha’s Hill CRS, Umkomaas CRS (South Africa); Makerere Univ-JHU Uganda (Uganda)

- **Status:** Closed to follow up; results expected early 2011


**MTN 006 / RMP-02: Phase I safety, acceptability and pharmacokinetic trial of tenofovir gel applied rectally compared with oral tenofovir**

- **Summary:** Phase I, two site, partially blinded, placebo-controlled trial. Measuring safety, acceptability and pharmacokinetics of topical, vaginally formulated tenofovir 1% gel applied rectally compared with oral tenofovir (300 mg) in HIV-1 seronegative adults. Primary objective: evaluate systemic safety profile of 1% tenofovir gel applied rectally during a single exposure followed by once daily dosing for 7 days compared to a single oral dose of tenofovir. Study will measure acceptability and compare whole tissue, rectal fluid, intracellular, mucosal mononuclear cells and plasma concentrations of tenofovir applied topically with the same parameters for oral dosing.

- **Sponsors/Implementers:** NIH, Gilead, CONRAD / MTN

- **N** = 18 HIV-negative men and women (18+ yrs)

- **Research centres:** UCLA Center for Prevention Research (California), Univ of Pittsburgh CRS (Pennsylvania) (United States)
WHO/UNAIDS MTN Ongoing

Next Steps with 1% Tenofovir Gel Appendix 2 Final Draft WHO/UNAIDS Meeting Report 23 November 2010

- **Status:** Closed to follow-up; results expected early 2011
- **Link:** [http://www.mtnstopshiv.org/node/911](http://www.mtnstopshiv.org/node/911)

**Ongoing observational studies**

**MTN-003C (VOICE-C): Household and community factors associated with study product adherence in VOICE**

- **Summary:** Behavioral and ethnographic sub study to explore household and community factors associated with study product adherence in VOICE, including: factors participants identify as influencing product use (and non-use); if these factors differ between participants in vaginal product arm vs. oral product arm; perceptions of the importance of adherence, and barriers and facilitators to adherence.
- **Sponsors/Implementers:** NIH/ MTN
- **N = 275** target sample size (including VOICE participants, male partners of participants, members of Community Advisory Boards, and key community stakeholders).
- **Research centres:** Reproductive Health & HIV Research Unit (RHRU): **RHRU Research and Training Centre CRS (South Africa)**
- **Status:** Enrolling
- **Link to Sponsor:** [http://www.mtnstopshiv.org](http://www.mtnstopshiv.org)

**MTN-015: Observational cohort study of women following HIV-1 seroconversion in microbicide trials**

- **Summary:** Multi-site, prospective, observational cohort study of women following HIV-1 seroconversion in microbicide trials. Study will compare plasma HIV-1 RNA level twelve months after HIV-1 seroconversion among antiretroviral treatment (ART) naïve participants assigned to an active topical or oral agent compared to control participants. Provide prospective data on clinical progression of HIV disease and prevalence of drug resistance mutations among seroconverters from ARV-based oral and topical HIV prevention studies.
- **Comparisons will also include:** trajectory of CD4+ T-cell counts after HIV-1 seroconversion; plasma HIV-1 RNA levels six months after seroconversion; prevalence of HIV-1 drug resistant mutations in plasma and genital tract specimens after seroconversion; virologic response to initiation of ARV; CD4+ T-cell response to initiation of ARV therapy over time; HIV-1 drug resistance profile among ARV recipients at time of virologic failure; and HIV-1 progression. Study specific subclasses of seroconverters will be assessed for prevalence and persistence of HIV drug resistant mutations in plasma and cervical lavage fluid.
- **Sponsors/Implementers:** NIH/MTN
- **N = 165** target sample size for primary objective; anticipate enrolling approximately 500 women from sites designated by the MTN Executive Committee.
- **Research centres:** College of Medicine Johns Hopkins University: **College of Med. JHU CRS**, University of North Carolina (UNC) Lilongwe: **UNC Linlongwe CRS (Malawi)**; South African Medical Research Council (MRC): **Botha’s Hill CRS**, Isipingo CRS, Overport CRS, **RK Khan CRS**, Umkomaas CRS, Verulam CRS, Tongaat CRS; **CAPRISA: Aurum CRS**, eThekwini CRS; **PHRU:** Soweto MTN CRS; RHRU: Research and Training Centre CRS **(South Africa)**; Makerere University-Johns Hopkins University Research Collaboration: **MUJHU CARE LTD CRS (Uganda)**; University of Zimbabwe-University of California San Francisco (UZ-UCSF): **Seke South CRS, Spilhaus CRS, Zengeza CRS (Zimbabwe)**; Centre for Infectious Diseases Research in Zambia: **Kamwala Clinic CRS (Zambia)**
- **Status:** Enrolling
- **Link to Sponsor:** [http://www.mtnstopshiv.org](http://www.mtnstopshiv.org)
MTN-016: Prevention agent pregnancy exposure registry

- **Summary:** Prospective observational cohort study of maternal exposure to investigational HIV prevention agents. Registry will enroll approximately 500 pregnant participants who become pregnant during microbicide or PrEP trials, or who have had planned exposures in pregnancy safety studies. Study will also include approximately 300 live infants resulting from those pregnancies. Participants will be enrolled as early in pregnancy as possible to maximize validity of the data.

- Primary objectives: evaluate prevalence of spontaneous pregnancy loss, and of major malformations in infants of mothers exposed to active study agent during pregnancy compared to those events in mothers not exposed to an active study agent during pregnancy. Monitor for adverse pregnancy outcomes, evaluate growth parameters of infants during the first year of life, and provide a cohort of infants not exposed to active study agents during pregnancy. Monitor for select risks of prevention agents by trimester of exposure, evaluate prevalence and persistence of HIV drug resistance mutations in HIV-infected infants, and compare the results of developmental screening at select time points in the first year of life among participating infants. Collaborating with FEM-PrEP to enable pooling of pregnancy outcome data.

- **Sponsors/Implementers:** NIH/MTN
- **N** = 500 pregnant women and 300 live infants (target sample size)
- **Research centres:** College of Medicine Johns Hopkins University: *College of Med. JHU CRS*; University of North Carolina (UNC) Lilongwe: *UNC Linlongwe CRS (Malawi)*; South African Medical Research Council (MRC): *Botha’s Hill CRS, Isipingo CRS, Overport CRS, RK Khan CRS, Umkomaas CRS, Verulam CRS, Tongaat CRS*; *CAPRISA: Aurum CRS, eThekwini CRS; PHRU: Soweto MTN CRS; RHRU: Research and Training Centre CRS (South Africa); Makerere University-Johns Hopkins University Research Collaboration: *MUIHU CARE LTD CRS (Uganda)*; University of Zimbabwe-University of California San Francisco (UZ-UCSF): *Seke South CRS, Spilhaus CRS, Zengeza CRS (Zimbabwe)*; Centre for Infectious Diseases Research in Zambia: *Kamwala Clinic CRS (Zambia)*
- **Status:** Enrolling
- **Link to Sponsor:** [http://www.mtnstopshiv.org](http://www.mtnstopshiv.org)

Pending and planned safety studies

MTN 007: Phase 1 safety and acceptability study of tenofovir 1% gel applied rectally

- **Summary:** Phase I randomized, blinded, 4 arm, placebo-controlled rectal safety and acceptability study. Study products are: vaginally formulated 1% tenofovir gel and 2% nonoxynol-9 (N-9) gel and trial has 4 arms (tenofovir 1% gel, 2% N-9 gel, HEC placebo gel, no product). Gel applied once rectally; then administered for 7 daily doses with 1 week in between. Study will also examine: whether rectal use of tenofovir gel is associated with rectal mucosal damage using N-9 as a positive control; acceptability of rectal use of 1% tenofovir gel; and safety of HEC placebo gel applied rectally.

- **Sponsors/Implementers:** NIH, CONRAD / MTN
- **N** = 63; HIV-negative men and women (18+ yrs)
- **Research centres:** University of Alabama at Birmingham (Alabama): *Alabama Microbicide CRS*, Univ of Pittsburgh CRS (Pennsylvania), Fenway Institute CRS (Massachusetts) * (United States)
- **Status:** Pending
- **Link:** [http://www.mtnstopshiv.org/node/912](http://www.mtnstopshiv.org/node/912)
MTN 008: Expanded safety investigation of tenofovir gel in pregnancy and lactation

**Summary:** Phase 1 trial expanded safety and pharmacokinetics trial of tenofovir 1% gel used daily for 7 days in pregnancy and lactation. Mother-infant pair study; will initially enroll and evaluate safety and PK parameters among women at ≥ 37 weeks gestation. Pending safety data from this group same assessment to be done at earlier gestational phase (≥ 34 weeks). Study will assess presence of tenofovir in the blood of infants in both the pregnancy and lactation cohorts, and will also examine the impact of tenofovir gel exposure on the presence of select organisms in the vagina, vaginal flora characteristics and changes, and effects of tenofovir gel on biomarker expression in vaginal and cervical secretions of pregnant and lactating women.

- **Sponsors/Implementers:** NIH/MTN
- **N** = 90 mother-infant pairs; pregnant and lactating women.
- **Research centres:** University of Alabama at Birmingham (Alabama): Alabama Microbicide CRS, Univ of Pittsburgh CRS (Pennsylvania) (United States)
- **Status:** Pending

Pending observational study

MTN-009: HIV-1 Resistance at Screening for HIV Prevention Studies

**Summary:** Multi-site, cross-sectional study to assess frequency of HIV drug resistance mutations among women who test HIV-positive at screening for HIV prevention trials to assess prevalence of drug resistance and to understand if certain risk behaviors are associated with resistance. Secondary aims: identify and evaluate behavioral indicators including self or sexual partner(s) exposures to antiretroviral (ARV) drugs as risk factors for drug resistant HIV infection; characterize degree of immunodeficiency and risk of disease progression by quantifying plasma HIV-1 RNA and CD4-positive T cells. Study will also explore identification of polymorphic or subtype-specific sequence changes in HIV-1 that may impact susceptibility to ARVs, and estimate the proportion of HIV-positive women with chronic versus recent HIV infection.

- **Sponsors/Implementers:** NIH/MTN
- **N** = Up to approximately 1000 women: 350 newly diagnosed HIV-positive women and approximately 650 HIV-negative women all between the ages of 18 and 45.
- **Research centres:** South African Medical Research Council (MRC): Botha’s Hill CRS, Isipingo CRS, Overport CRS, RK Khan CRS, Umkomaas CRS, Verulam CRS, Tongaat CRS (South Africa)
- **Status:** Pre-implementation

Completed effectiveness study

CAPRISA 004: Phase Ib safety and effectiveness trial of tenofovir 1% gel for prevention of HIV infection in women in South Africa

- **Summary:** Phase Ib, two arm, double blind, randomized, placebo controlled trial to assess effectiveness and safety of 1% vaginal gel formulation of tenofovir for the prevention of HIV acquisition in women. Trial compared tenofovir gel with placebo gel in sexually active, HIV uninfected women. Active and placebo gels were used before and after sex in the “BAT24” regimen (one dose up to 12 hours before sex, one dose up to 12 hours after sex and no more than two doses in 24 hours). Serostatus, safety, sexual behavior and gel and condom use were assessed at monthly follow up visits for 30 months.
- **Sponsors/Implementers:** Centre for the AIDS Program of Research in South Africa (CAPRISA), the United States Agency for International Development (USAID), FHI, LIFElab of the South African Department of Science and Technology, CONRAD, and Gilead Sciences.
• **N** = 889 sexually active HIV-negative women risk of sexually transmitted infection

**Research centres:** CAPRISA eThekwini Research Clinic (Durban) and CAPRISA Vulindlela Research Clinic (Vulindlela) (South Africa)

**Status:** Completed

**Results:**
- HIV incidence in the tenofovir gel arm was 5.6 per 100 women-years (38/680.6 women-years) compared to 9.1 per 100 women-years (60/660.7 women-years) in the placebo gel arm (incidence rate ratio = 0.61; \( P = 0.017 \)).
- In high adherers (gel adherence > 80%), HIV incidence was 54% lower (\( P = 0.025 \)) in the tenofovir gel arm. In intermediate adherers (gel adherence 50 to 80%) and low adherers (gel adherence < 50%) the HIV incidence reduction was 38% and 28% respectively.
- Tenofovir gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence.
- No increase in the overall adverse event rates was observed.
- There were no changes in viral load and no tenofovir resistance in HIV seroconverters.

**Citation:** Karim, QA, Karim SSA, Frohlich JA, Grobler AC. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. Science 2010

Ongoing effectiveness study

**MTN 003 (VOICE): Phase Ib safety and effectiveness study of tenofovir 1% gel, tenofovir tablet, and Truvada tablet for prevention of HIV infection in women**

**Summary:** Phase Ib, five-arm, multi-site, partially-blinded, randomized, controlled safety and effectiveness study to estimate effectiveness of daily1% tenofovir gel compared to a vaginal placebo gel, and effectiveness of daily oral tenofovir and daily oral Truvada compared to an oral placebo, in preventing HIV infection among women at risk for STI. Study double-blinded within each mode of administration, but open-label with respect to mode of administration (vaginal or oral).

Other outcomes: extended safety of study products; adherence/behavioral factors; HIV-1 drug resistance (among those who become HIV-infected during the study); pharmacokinetic parameters; and potential for delayed seroconversion during an off-product period scheduled at the end of participants’ study participation. VOICE will also explore impact on vaginal microenvironment, and assess potential relationships between method of contraception and HIV seroconversion, product adherence, and adverse events.

Study will provide parallel comparisons of oral and topically applied antiretroviral strategies for prevention of HIV infection in women. Protocols should allow for comparison across VOICE and other PrEP studies.

**Sponsors/Implementers:** NIH, CONRAD, Gilead/MTN

\[ N = \text{target sample size approximately 5000 (approximately 1,000 in each arm) HIV-negative women at risk of sexually transmitted infection} \]

**Research centres:** South African Medical Research Council (MRC): Botha’s Hill CRS, Isipingo CRS, Overport CRS, RK Khan CRS, Umkamaa CRS, Verulam CRS, Tongaat CRS; CAPRISA: Aurum CRS, eThekwini CRS; PHRU: Soweto MTN CRS; RHRU: Research and Training Centre CRS (South Africa); Makerere University-Johns Hopkins University Research Collaboration: MUJHU CARE LTD CRS (Uganda); College of Medicine Johns Hopkins University: College of Med. JHU CRS (Malawi); University of Zimbabwe-University of California San Francisco (UZ-UCSF) Seke South CRS, Spilhaus CRS, Zengeza CRS (Zimbabwe)

**Status:** Enrolling (first enrollment September 2009); results anticipated 2013

**Link to Sponsor:** [http://www.mtnstopshiv.org/](http://www.mtnstopshiv.org/)
Acknowledgements: Thanks to colleagues at the Microbicide Trials Network (Lisa Rossi), CONRAD (Marianne Callahan), International Partnership for Microbicides (Pam Norick and Heather Campbell) and AVAC (Polly Harrison) for providing summaries and background information.
## Appendix 3: List of Participants

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td><strong>Salim ABDool Karim</strong></td>
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</tr>
<tr>
<td>3</td>
<td><strong>Edward Abwao</strong></td>
<td>Pharmacy and Poisons Board Nairobi - Kenya</td>
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<tr>
<td>4</td>
<td><strong>Shabir Banoo</strong></td>
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<tr>
<td>5</td>
<td><strong>Deborah Baron</strong></td>
<td>Consultant Reproductive Health and HIV Research Unit University of the Witwatersrand Johannesburg - South Africa</td>
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<tr>
<td>6</td>
<td><strong>Jonathan Berger</strong></td>
<td>Senior Researcher &amp; Head of policy and Research Section 27 Incorporating the AIDS Law projects Braamfontein - South Africa</td>
</tr>
<tr>
<td>7</td>
<td><strong>Debra Birnkran</strong></td>
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</tr>
<tr>
<td>8</td>
<td><strong>Gina Brown</strong></td>
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<tr>
<td>9</td>
<td><strong>Elisabeth Buki</strong></td>
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<td>10</td>
<td><strong>Ward Cates</strong></td>
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<tr>
<td>11</td>
<td><strong>Manju Chatani-Gada</strong></td>
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</tr>
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<td>12</td>
<td><strong>Peter Cherutich</strong></td>
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</tr>
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<td>13</td>
<td><strong>Michael Chirenje</strong></td>
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<td>14</td>
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<tr>
<td>16. <strong>Jessica COHEN</strong></td>
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<td></td>
<td>Program Officer</td>
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<td>PATH</td>
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<td>Seattle, WA- USA</td>
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</table>

| 25. **Henry GABELNICK** |   |
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<thead>
<tr>
<th></th>
<th>Name</th>
<th>Title and Affiliation</th>
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<tr>
<td>68</td>
<td>Alan STONE</td>
<td>Director, MEDSA Ltd, London, UK</td>
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<tr>
<td>69</td>
<td>Doug TAYLOR</td>
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<tr>
<td>70</td>
<td>Carlos TOLEDO</td>
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<td>71</td>
<td>Lut VAN DAMME</td>
<td>FHI, Research Triangle Park, Durham, NC, USA</td>
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<td>Sten H. VERMUND</td>
<td>Amos Christie Chair of Global Health, Vanderbilt University School of Medicine, Nashville, TN, USA</td>
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<tr>
<td>73</td>
<td>Melinda WILSON</td>
<td>USAID, Pretoria, South Africa</td>
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3. **Catherine HANKINS**  
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6. **Michael M. MBIZVO**  
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8. **Morkor NEWMAN**  
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   Harare - Zimbabwe

9. **Catherine SOZI**  
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   Pretoria - South Africa
Appendix 4: Declaration of Interests

All participants, except those representing governments or government agencies, were asked to declare any actual or potential conflicts of interest relevant to the meeting. In this the respect the following declarations were made:

- Jim Rooney declared that his employer Gilead Sciences holds the patent to Viread and tenofovir gel microbicide and had licensed the rights to develop the gel for HIV prevention to CONRAD and IPM. He holds stock in the company as well as patents relevant to the subject matter of the meeting. He therefore did not participate in the formulation of any recommendations.
- Zeda Rosenberg, Pam Norick, Ron Nardi, Annalene Nel declared that the International Partnership for Microbicides held a co-exclusive license to tenofovir gel with preferential pricing conditions for the public sector in developing countries. IPM also holds licenses to develop other compounds containing antiretrovirals for prevention of HIV infection in women.
- Henry Gabelnick and Gustavo Doncel declared that CONRAD held a co-exclusive license to tenofovir gel with preferential pricing conditions for the public sector in developing countries.
- Carl Montague and Suvina Sooknandan declared that the Technology Innovation Agency holds the license to tenofovir gel for distribution in the African region at an affordable price.
- Salim Abdool Karim and Qurraisha Abdool Karim declared that they are part of a patent application, currently with no commercial value, on the use of tenofovir gel for the prevention of HSV-2 infection.
- Angela Kashuba declared that she had received grants from Gilead Sciences to study the pharmacokinetics of tenofovir in the genital tract and mucosal tissues.
- Sharon Hillier and Ian McGowan declared that they were co-chairs of the Microbicide Trials Network that was implementing research on tenofovir gel.
- Mike Chirenje declared that he was the Protocol Chair of the Microbicide Trials Network VOICE (MTN-003) study investigating the effectiveness of daily oral tenofovir and truvada and daily use of 1% tenofovir gel.
- Lut van Damme declared that she was Principal Investigator on the Fem-PrEP trial that was investigating the protective effectiveness of oral tenofovir and emtricitabine in reducing the risk of HIV infection in women.
For more information, please contact:

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