



Final Report
Microbicide Stakeholders Meeting

29 November 2010
Washington, DC

Table of acronyms and abbreviations

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| ADIP | Accelerated Development and Introduction Plan |
| ART | Anti-retroviral therapy |
| ARV | Anti-retroviral |
| BAT 24 | Acronym to describe and help participants remember gel dosing in CAPRISA 004 trial (B efore, A fter and no more than Two in 24 hours) |
| CAPRISA | Centre for the AIDS Programme of Research in South Africa |
| CDC | (US) Centers for Disease Control and Prevention |
| DFID | (UK) Department for International Development |
| DST | (SA) Department of Science and Technology |
| FACTS | Follow-on African Consortium for Tenofovir Studies |
| FC | Female condom |
| FDA | (US) Food and Drug Administration |
| GAVI | The Global Alliance for Vaccines and Immunisations |
| GHI | (US) Global Health Initiative |
| HSV-2 | Herpes Simplex Virus type 2 |
| iPrEX | Pre-Exposure Prophylaxis Initiative |
| LSHTM | London School of Hygiene and Tropical Medicine |
| MCC | (SA) Medicines Control Council |
| MDP | (UK) Microbicides Development Programme |
| MRC | (SA) Medical Research Council |
| NIAID | (NIH) National Institute of Allergy and Infectious Diseases |
| NIH | (US) National Institutes of Health |
| OGAC | (US) Office of the Global AIDS Coordinator |
| PEPFAR | (US) President's Emergency Plan For AIDS Relief |
| PMTCT | Prevention of Mother to Child Transmission |
| PPP | Public Private Partnership |
| PrEP | Pre-exposure Prophylaxis |
| R&D | Research and Development |
| STD | Sexually Transmitted Disease |
| STI | Sexually Transmitted Infection |
| TIA | (SA) Technology Innovations Agency |
| UNAIDS | Joint United Nations Programme on HIV/AIDS |
| USAID | United States Agency for International Development |
| VOICE | Vaginal and Oral Interventions to Control the Epidemic |
| WHO | World Health Organization |

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Background

The results of the CAPRISA 004 clinical trial of 1% tenofovir gel were the first to demonstrate that a vaginal microbicide could reduce the risk of HIV infection. This announcement, in July 2010, captivated many and focused attention on the need to confirm the product's safety and effectiveness, and to prepare for introduction. To build agreement on the best way forward, WHO and UNAIDS convened a meeting near Johannesburg in August 2010 on "Next Steps with 1% Tenofovir Gel". Following this meeting and based on the expectation that 1% tenofovir gel will receive regulatory approval for HIV prevention within the next few years, USAID developed a two-stage process to focus on next steps needed for introduction of 1% tenofovir gel as well as other ARV-based microbicides. On November 29, 2010, the USAID Administrator convened a high-level "Microbicide Stakeholders" meeting to define the major steps needed over the next two years to expedite licensure and prepare for the introduction of 1% tenofovir gel after regulatory approval in the US, South Africa and other African countries. The meeting's objectives were:

1. To highlight microbicide development progress to date
2. To outline next development steps in licensure of 1% tenofovir gel
3. To develop a shared vision on the major product introduction issues to be addressed
4. To identify coordinating mechanisms and a list of agreed-upon major next steps

This is the first of two stakeholders meetings to address next steps in microbicide development and to plan for strategic introduction of microbicide products. It will be followed by a technical meeting in South Africa during the first half of 2011 to outline plans and specific actions in more depth.

The November 29th meeting was by invitation and included nearly 90 participants, with senior leaders from a number of US agencies (USAID, OGAC, NIH, CDC and the Department of State) and the South African government, along with worldwide leaders in microbicide research, product development, policy and civil society. The meeting was formatted as sessions with dynamic discussions between panelists representing key stakeholders, formal presentations to provide focal points as needed, and questions, commentary, and additional discussion by other participants in the audience. These lively discussions touched on a range of needed initiatives: additional clinical research and regulatory processes, building and forecasting demand, manufacturing and distribution, challenges and opportunities in health systems, ensuring affordability and access, and policy and guideline development.

This report captures the key issues that emerged from the panelists, presentations, and discussions in each of the sessions.

Opening Session: Rajiv Shah, Administrator, USAID
Melanne Verveer, Ambassador-at-Large, Global Women's Issues,
US Department of State

In his opening remarks, USAID Administrator Dr. Rajiv Shah underscored his own and USAID's enthusiasm about the potential of tenofovir gel to change the ways that HIV/AIDS is tackled around the world. Both Dr. Shah and the Agency are committed to move aggressively to ensure that this potential can be realized for women and communities as rapidly as possible. Dr. Shah stated that the CAPRISA 004 results offer hope that the world may soon have a tool to empower women to protect themselves from HIV, and he underscored women's important role in development around the world. Referring to the announcement of the iPrEX trial results made the week before (that showed that daily use of oral Truvada can reduce the risk of HIV infection in men who have sex with men by 41%), Dr. Shah emphasized the renewed sense of possibility for HIV prevention technologies and the responsibility to build on these scientific breakthroughs. He acknowledged that introducing these new products will be challenging, and will require thoughtful approaches that use realistic marketing and introduction strategies that reflect and are tailored to specific settings and populations.

Administrator Shah went on to say that the Global Health Initiative, which brings together all elements of the US federal government involved with global health, is fostering an integrated approach to bring about better outcomes for more people in a more lasting way. He noted that collaboration between the US and South African governments will be vital to the regulatory review process, as well as many of the other elements critical to moving from research to implementation. USAID is committed to supporting country-led sustainable roll out and implementation for microbicides in a broad range of countries, and the many aspects critical to the success of this approach: early planning, mobilization across the public and private sectors, fostering creative and innovative approaches, market analyses, understanding barriers to uptake, policy development, preparatory research and a host of other issues.

Melanne Verveer, Ambassador-at-Large for Global Women's Issues at the US Department of State, stated that women's rights and human rights are increasingly integrated into the US government's development approaches and policies. This commitment is exemplified in the joint program, *Together for Girls*, that aims to put a focus on girls and violence and build evidence to better understand the relationship between violence and HIV. Amb. Verveer noted that, fittingly, the program was being launched the same day as this meeting, at the start of the annual *16 Days of Activism Against Gender Violence* and just prior to World AIDS Day. She said that the link between violence against women and AIDS is just one dimension of the fact that – globally – AIDS has a woman's face, and is now the leading cause of death for women of reproductive age in low and middle income countries, as well as a significant contributor to maternal mortality. While the global health community has rightly celebrated the impact that antiretroviral therapy has had in changing the course of the disease for many, emphasis on prevention remains critical. Amb. Verveer mentioned that the HIV epidemic is fueled by structural inequalities that exacerbate women and girls' biological vulnerability to infection, including lack of

education and control over resources, child marriage, and the low status and value placed on girls. Efforts to address HIV will only be successful if they allow women broader control over their own lives. Amb. Verveer said that, while only one part of a comprehensive approach, in this context tenofovir gel represents a potentially game-changing tool by addressing a gap in the existing spectrum of HIV prevention strategies – one that offers a woman the possibility of initiating protection that may not require the active involvement of her partner.

Amb. Verveer acknowledged that the potential of tenofovir gel will require coordinated and concerted action across a number of areas: further research; product development; regulatory approval; building demand; and ensuring affordability and access. She said that it will be important to contextualize this work within the broader context of development, including the Millennium Development Goals. Microbicides can potentially impact on Goal 3 related to gender equality and women’s empowerment, as well as Goal 6 on HIV and AIDS. Amb. Verveer concluded with the statement that the US government’s commitment to continuing work on tenofovir gel and microbicides exemplifies its commitment to protecting women’s health for their own sake, as well as the positive impact it has on families and communities.

Session I. Building on Success: Collaborative Vision for Advancing HIV Prevention for Women

Moderator: Rajiv Shah, USAID

Panelists: Kevin DeCock, Center for Global Health, CDC
Carl Dieffenbach, Division of AIDS, NIAID, NIH
Stefano Bertozzi, Bill & Melinda Gates Foundation
Debra Birnkrant, Division of Antiviral Drug Products, FDA
Mitchell Warren, AVAC Global HIV Prevention
Glaudina Loots, Health Innovation; Department of Science & Technology, Republic of South Africa

The panelists responded to questions from the Moderator, which resulted in a rich and wide-ranging discussion. Overall, the panelists stressed the urgent need for tenofovir gel, the interest and commitment of many in moving the product forward and facilitating access as soon as possible, and the importance of considering tenofovir gel within the context of other emerging antiretroviral based HIV prevention approaches, including oral PrEP and test and treat. While underscoring their overall commitment to building on the promise of tenofovir gel, they also cautioned that it will be important – and difficult – to manage expectations, given the many challenges still ahead. Key points included:

- The uneven use of the test products in both the CAPRISA 004 and iPrEX trials reinforces that these “biomedical” prevention technologies depend on behavior, and as such are also behavioral interventions. It will be very important to articulate and implement a research and distribution agenda that places the new technology in the context of user behavior. The challenge is not just to identify an effective product, but the combination of product and adherence that will be effective at the community level.

- In South Africa, both the Department of Science and Technology and the Department of Health are committed to supporting and facilitating further research to confirm tenofovir gel's effectiveness, and to implementing programs to deliver the product if it is confirmed to be safe and effective.
- Medical male circumcision is the most recent innovation to be incorporated into HIV prevention programs, and is an instructive example of how research findings can serve as the basis for policy, guidelines, and program implementation. At the same time, ambitious plans to scale up male circumcision are behind schedule, and it would be useful to look at the plans, processes and resources invested to tease out any lessons that can be applied to microbicide introduction and scale up.
- The field needs to drive toward regulatory approval as efficiently and quickly as possible, and focus on what is needed to make tenofovir gel affordable, deliverable and useable. New expertise is needed to complement the field's focus to date on science and clinical research.
- The FDA has been involved in the microbicide field from the beginning and remains committed to providing clear guidance and expedited review to move products forward. It is important to identify what steps are needed to license tenofovir gel outside the US. The FDA is committed to working with other countries when appropriate and feasible; a joint review could send a strong message about the importance of tenofovir gel and the commitment to making it available.
- Product development partnerships have typically faced challenges in moving from proof of concept to impact on the ground. The global health community overall has not been very effective at driving uptake of new technologies or innovations. Observing how drug companies pursue profitable markets may be useful in determining how to aggressively drive uptake.
- Measures of community level effectiveness will be needed as soon as possible but few reliable approaches are available.

These points were further debated and supplemented during questions and discussions among the audience and panelists, with the following main outcomes:

- While regulatory processes are critical, other policy development is also vital. Many players will have a say in whether tenofovir gel is manufactured, introduced, paid for, recommended and used; each one can, in effect, "veto" such a new health innovation before it ever reaches a client. It is therefore important to engage national ministries of health and finance, providers, and a range of other key opinion leaders early on.
- Many national governments and donors, including PEPFAR, look to guidance from WHO in determining whether to incorporate or support a new product or innovation. Guidelines from normative agencies such as WHO require evidence not just of effectiveness but also of cost and feasibility. This will involve answering important service delivery questions such as the frequency of HIV testing and retesting, how and where the product would be delivered (i.e., integrated with PMTCT, sexual and reproductive health, family planning, maternal health, etc.), the degree of medical monitoring and level of provider, and so forth. Some work in this area is already moving forward: HIV testing would be studied in a proposed follow up trial at CAPRISA,

and the Gates Foundation is sponsoring work to develop a reliable HIV self-test that could facilitate HIV testing and re-testing. Identifying and answering questions needed for WHO guidelines is a high priority.

- An important factor will be the level of effectiveness and how a range of actors – including policymakers, providers, donors, and users – understand and act on the level of effectiveness identified in a trial, and how this would relate to perfect use. Some participants noted that policy development is needed for both topical and oral PrEP to determine the minimum level of effectiveness that would warrant licensure or implementation. Others felt it more appropriate to consider the whole body of evidence rather than a precise figure. A dilemma is that most regulators and policymakers consider effectiveness for a product used “as recommended,” but in both the CAPRISA 004 and iPrEX trials many participants did not use the product as recommended. More work is needed to determine how best to convey the implications of trial results for “effectiveness” to users, providers and policymakers.
- Ideally, the HIV prevention field, like family planning, will have a portfolio of different products to meet diverse user needs and preferences.
- Several lessons from medical male circumcision can be applied to work on tenofovir gel immediately. While there are many factors, the slow uptake underscores the real need for a long lead time for developing guidance and policy, and working with key opinion leaders at the country level. Country consultations started well before confirmatory trials were finished on the strength of the initial trial results; with support from the Gates Foundation, WHO and UNAIDS are conducting a similar process with oral PrEP. Beginning these processes while clinical research is ongoing can help build capacity for understanding the trial results when they are announced, and underscores the long lead time needed. While being mindful of the need to manage expectations, this work should begin for tenofovir gel.
- “Integration” into existing services is appealing, but putting new health innovations into failing and overburdened health systems may undermine success. For example, in Soweto, it was decided to implement PMTCT services vertically because existing health systems could not absorb the integration.
- Ultimately the issues around implementing tenofovir gel or oral PrEP are part of a broader context of how to best use antiretroviral drugs for prevention and for treatment, for individuals and communities. This is a significant agenda that is beyond the purview of any one agency or country, and will require a coordinated approach.
- Bearing in mind the general experience of the “slow walk” of new health technologies, USAID and others across the government are committed to taking an aggressive approach.

The first panel and the questions and comments it generated highlighted the urgency and complexity of preparing for access to tenofovir gel. Examples from other technologies reinforced that regulatory processes are critical but not sufficient for policy development and the need to engage new and different actors. Many of these points were further explored over the course of the meeting.

Session II. State of the Microbicide Field

Moderator: Carl Dieffenbach, Division of AIDS, NIAID, NIH
Presenter: Catherine Hankins, UNAIDS
Panelists: Gita Ramjee, MRC, South Africa
Renee Ridzon, Bill & Melinda Gates Foundation
Ward Cates, FHI
Polly Harrison, AVAC Global HIV Prevention

In a summary presentation, Dr. Hankins reviewed the overall state of the microbicide field: major objectives, history, achievements to date, and what is needed to advance microbicide development and cooperation mechanisms.

- HIV infection moves from a small founder population at the portal of entry to systemic infection over the course of a few days. Candidate microbicides have worked to target different points in the process of infection and replication through: viral disruption; inhibiting fusion or absorption; inhibiting reverse transcriptase; and inhibiting HIV uptake by dendritic cells. Other potential mechanisms of action have included: providing a physical barrier and lubrication (gel and cream formulations); helping maintain normal microflora in the reproductive tract; and preventing other sexually transmitted infections.
- Clinical effectiveness trials of the first two “classes” of candidate products, surfactants and polymers, did not show a reduction in the risk of HIV infection when compared with a placebo, and even suggested that two of the products may have increased the risk of infection.
- Tenofovir gel is among the third class of microbicides: ARV-containing preparations that specifically target HIV attachment, fusion and replication. The next ARV-based product that is most advanced in the pipeline is a vaginal ring containing dapivirine. There are a number of additional products in the pipeline but it is uncertain how likely they are to make it into clinical testing.
- ARV-containing microbicide candidates are sometimes referred to as “topical PrEP”. Available data, while limited, indicate that there are major advantages of topical over oral use of tenofovir: higher concentration at the point of infection, much lower systemic absorption and much lower risk of resistance.
- The microbicide field has faced a number of challenges in product selection and proving effectiveness. For example, the lack of robust, validated surrogate markers of protection means that the only way to measure effectiveness is through large, complex and expensive clinical effectiveness trials. Effectiveness also depends on adherence, and it has been difficult to measure product use in trials.
- The microbicide field has faced criticism that poor coordination and use of non-validated scientific markers has compromised its efficiency in selecting products to move into effectiveness trials and its credibility. The HIV Vaccine Enterprise, which recently launched its scientific strategic plan for the HIV vaccine field that involved more than 400 scientists, may offer a model for the field as it moves forward.

- Philanthropic sector investment in the microbicide field has declined while public sector investment has continued to rise.

Acknowledging the unique product development challenges for microbicides, Session Moderator Carl Dieffenbach invited panelists to outline priorities to complement ongoing product development efforts. Panelists offered the following observations and recommendations:

- Local governments, providers and communities need to be engaged as work moves from relatively well-resourced trial sites into broader health systems with sometimes limited capacity. Communities near trial sites are very keen to have the product available, and it is important to specify parameters for moving forward with implementation.
- Donor investment decisions could be made more strategically if the microbicide field had a rational drug development pipeline. A consensus driven, prioritized plan with a clear research agenda that reflects the limited resources and critical path activities could help drive decision making by some donors, including the Gates Foundation.
- Developing such a consensus document should be possible but will be challenging. Even with such consensus recommendations, funders often de facto define the agenda at the interface of recommendations from the field and their own priorities.
- Support for microbicides is now at a critical crossroads between different funders that focus on different aspects of health innovations: the main funders of product development in the microbicide field to date (NIH, USAID, Gates and DFID), and those focused more on implementation and health service provision.
- The microbicide field has made a great deal of effort to coordinate and work together. These efforts have succeeded in several areas, including a working group on clinical trials that provided a forum for organizations to openly raise and address ongoing challenges in clinical trial design and implementation.
- While the microbicide field has at times been challenged to manage and prioritize its product development pipeline like a pharmaceutical company, it is, in fact, more like an industry in that no one entity controls the products and/or investment funds. Competition in product development may indeed be beneficial.
- It is too soon to know whether the Vaccine Enterprise can or should serve as a “model”, nor whether its efforts will ultimately prove to be strategic and cost-effective.
- Given the limited resources available for microbicides, there is some concern that moving into implementation research will come at the expense of other work: early stage work needed to maintain a healthy pipeline of products, including combination products and multipurpose products that aim to prevent other STIs or pregnancy; and the considerable resources needed for proof of concept and licensure trials of the dapivirine ring, rectal microbicides, and other product formulations and delivery modes.
- Current donors need to determine what role they can and will play in underwriting the shift from product development to product delivery. The striking similarities in results from the iPrEX and CAPRISA trials strongly suggest that tenofovir-containing products work to prevent HIV

infection, and there needs to be some consensus on how best to deliver the drug and to whom. Despite the challenges in coordination, it is likely that donors will need to jointly fund implementation research and it is important to engage and attract donors working on implementation and service delivery now.

- The microbicide field needs structural approaches to draw in new expertise, perspectives and people to complement and move beyond the field's scientific and clinical research focus to date.

Session III. Advancing 1% Tenofovir Gel Licensure for HIV Prevention in Women

Moderator: Caroline Ryan, OGAC

Presentations: *Overview of Safety and Efficacy Results with 1% Tenofovir Gel*

Salim Abdool Karim, Nelson Mandela School of Medicine, University of KwaZulu-Natal

Scenario Planning for Late-Stage 1% Tenofovir Gel

Trish Stroman, Boston Consulting Group

Panelists: Debra Birnkrant, FDA

Shabir Banoo, Medicines Control Council, South Africa

Stefano Bertozzi, Bill & Melinda Gates Foundation

Ian McGowan, Microbicide Trials Network

Salim Abdool Karim presented an overview of the results of the CAPRISA 004 trial and follow up work by the CAPRISA team.

- The trial assessed the safety and effectiveness of 1% tenofovir gel using a dosing schedule called BAT 24. Participants were instructed to use one dose of the gel up to 12 hours before sex, one as soon as possible after sex, and to use no more than two doses in 24 hours.
- Overall there was a 39% lower HIV incidence among women assigned to the tenofovir gel group than among those assigned to the placebo group ($p=0.017$; 95% CI 6-60). Adherence played a key role in the effectiveness of tenofovir gel -- effectiveness among those women who reported most consistent use (both doses used in more than 80% of sex acts) was 54%, among intermediate users (both doses used in 50-85% of sex acts) it was 38%, and among low adherers (<50% adherence) it was only 28%.
- Tenofovir gel also provided 51% protection against HSV-2 infection ($p=0.003$; 95% CI: 22-70%), and the CAPRISA team is conducting additional analyses of the HSV-2 data.
- Overall there were no safety concerns, and the very limited data on resistance and safety in pregnancy also suggested no concerns.
- With respect to policy development and implementation, safety in pregnancy will be one of the main obstacles to implementation for both topical and oral PrEP; it is important to establish that trials underway to assess safety in pregnancy will meet regulatory requirements.
- Two follow up studies have been proposed to explore issues important to implementation by:

- Providing ongoing access to tenofovir gel under a research designation to former trial participants while answering questions about service delivery (CAPRISA 008); and,
- Providing care, treatment and monitoring to sero-converters from CAPRISA 004 trial and comparing outcomes for those who receive combined ART, including and excluding tenofovir (CAPRISA 009).
- Responsibility for supporting the CAPRISA 004 trial was shared between the governments of the United States and South Africa, and following up on these results is also considered a shared responsibility.

Trish Stroman from the Boston Consulting Group described a scenario analysis that BCG is conducting at the request of the Gates Foundation, NIH and USAID.

- This analysis is designed to map out the possible alternative paths to licensure for tenofovir gel; the risks and benefits of each scenario; and the implications and trade-offs of different funding decisions for tenofovir gel, the microbicide pipeline, and the HIV prevention field overall.
- This analysis, expected in early 2011, may also help inform the sequence, priority and timing for key activities related to preparing for access.

The panel and audience raised a number of issues related to coordinating the work moving forward, especially related to regulatory processes:

- The field has a comprehensive portfolio of studies on tenofovir gel for vaginal and, increasingly, rectal use. Gaps in clinical data on tenofovir gel – including safety in pregnancy, in adolescents, and post-menopausal women – are being addressed through ongoing and proposed trials.
- In considering whether 39% protection is “good enough” to warrant licensure, regulators will look at the totality of the data to ensure that the gel is safe and effective, and to consider the potential public health impact rather than setting an absolute threshold. Creating a label that accurately conveys the gel’s qualities to patients and practitioners will be a key part of the process. Regulatory authorities will seek opportunities to collaborate to expedite and strengthen the review process, and to bring other agencies into the process.

Regulatory processes and ongoing clinical work

Planning for access must be informed by and coordinated with regulatory processes and clinical research. During an August meeting in South Africa convened by WHO and UNAIDS and hosted by the South African Department of Science and Technology, participants determined that, given uncertainty in the regulatory requirements and differences in dosing between the CAPRISA 004 trial and VOICE, it would be prudent to move forward with planning additional effectiveness studies. Two trials were proposed: the FACTS 001 trial would replicate many elements of the CAPRISA 004 trial, and gather data on safety in adolescents by lowering the age of eligibility from 18 to 16. The MDP 302 trial would test a single pre-coital dose in an effort to lower costs and improve acceptability and adherence. In late October, the FDA indicated that it would consider CAPRISA 004 and VOICE as pivotal trials for tenofovir gel despite the differing dosing strategies. At the same time, the South African MCC indicated informally that additional evidence using the BAT 24 dosing regimen would be useful, and encouraged submission of the FACTS 001 protocol for review. These differing responses from major regulatory bodies have created uncertainty about the path to licensure and the implications for next steps, investment and timelines.

- Data from CAPRISA are compelling but need to be confirmed. The iPrEX finding helps to confirm that tenofovir-containing drugs work to reduce the risk of HIV infection.
- The MCC will drive the real decision about whether VOICE is sufficient or whether another confirmatory trial is also needed. While it has not yet formally stated a position on this, the MCC is in the process of engaging stakeholders, reviewing the data, and determining next steps.
- It is critical to determine whether FACTS is necessary as soon as possible as this will likely have a significant impact on resources and timelines for product availability and access.

What is VOICE?

VOICE stands for **V**aginal and **O**ral Interventions to Control the **E**pidemic. Conducted by the NIH Microbicide Trials Network (MTN), it is studying the safety and effectiveness of daily antiretroviral tablets and 1% tenofovir gel to reduce the risk of HIV infection in women. VOICE is a five group randomized phase 2B trial, with 3 oral arms (tenofovir, Truvada and placebo) and 2 vaginal arms (1% tenofovir gel and placebo). Trial participants are instructed to use the tablet or gel daily, whether or not they have sex on that day. VOICE is studying the effectiveness of tenofovir gel for preventing HIV through daily dosing, a different strategy than the before and after sex strategy used in CAPRISA 004. While the FDA stated that these trials would be considered pivotal despite the different dosing regimens, it is not clear how other regulatory or policy agencies will respond.

Regulatory pathways remain uncertain, but there is a great deal of momentum and effort being invested in clarifying this, addressing outstanding clinical questions, and ensuring collaboration to move forward as expeditiously as possible. Ongoing efforts aim to share expertise and make the best decisions possible in this new and uncertain arena.

Lunchtime Fireside Chat

Speakers: Eric Goosby, Office of the US Global AIDS Coordinator
Ezekiel Emmanuel, Office of Management and Budget

Moderator: Robert Clay, USAID

In a lively and thought-provoking discussion, these two leaders in US efforts on global health highlighted some of the key priorities and challenges facing the US Global Health Initiative, and where microbicide access planning fits into the US government’s work on HIV/AIDS and global health. Some of the highlights of this discussion included:

- New prevention technologies – microbicides and PrEP – and the innovative opportunities they present may be a way to reenergize the world about HIV/AIDS.
- In initially responding to the urgent need for treatment, PEPFAR began its work as an “emergency response”; it is now moving into a more “sustainable response” mode. Since its inception PEPFAR has played a critical role in moving discoveries into the field and it is committed to doing the same for microbicides, building on its extensive infrastructure including professionals, procurement and distribution systems, laboratories, and other resources.
- PEPFAR’s structures, designed and working largely for treatment, will need to be adapted and supplemented to effectively reach people with prevention innovations. While PEPFAR has

always included prevention, these efforts will need to be enhanced with an explicit strategy to reach negative people where they already go for services – such as family planning services, STD clinics, maternal and child health programs – to help them stay negative. Such integration is one of the pillars of the new Global Health Initiative.

- Microbicides are now at the point where funding and innovation need to “bridge” between R&D and implementation. Given that the GHI does not explicitly address R&D, it is important to clarify which players within the GHI are responsible for providing resources to build this bridge. Innovation and research – evaluation, impact assessment, operations research and other areas – is an important aspect of the GHI. The Initiative is working to incorporate more rigorous and innovative evaluation, recognizing the need to balance investing in program evaluation and impact evaluation.
- The field must develop ways to convey the complexity, subtleties and urgency of implementing tenofovir gel – and the importance of investing in it – to diverse constituencies in order to build sustained support.

Session IV. Product Introduction – Approaches and Lessons Learned

Moderator: Wendy Taylor, USAID

Presentation: *Successful Introduction and Scale Up: The Accelerated Development and Introduction Plan (ADIP) Model for Pneumococcal Vaccines*

Orin Levine, Johns Hopkins University

Panelists: Jeff Spieler, USAID

Maggie Kilbourne-Brook, PATH

To illustrate some of the elements of successful product introduction and scale up, Orin Levine presented the ADIP model used for pneumococcal vaccines (in particular, the Hib vaccine). This example illustrates the importance of policy development, substantial donor investment, and dedicated staff, as well as the dampening effect that uncertain demand can have on relations with the private sector, pricing and supply.

- The Hib vaccine was developed by the private sector and was not readily available in resource-poor settings where it could have the biggest impact in preventing pneumonia, a significant cause of childhood mortality and morbidity. Realizing the Hib vaccine’s potential to save lives required finding overlap among willingness of countries to introduce a product, of donors and countries to pay for it, and of industry to supply it. Some \$30 million was invested by public and philanthropic donors to launch ADIP.
- Moving to the next level required a combination of investment through advanced market commitments, securing the manufacturers’ commitment to increase supply, and policy development by WHO and by Ministries of Health. One of the keys to moving this agenda forward was producing a strategic demand forecast that also laid out what each stakeholder

group needed to contribute and do. The entire process was jeopardized when initial demand estimates proved to be far too optimistic.

- Work on the Hib vaccine offers important lessons that can be applied to microbicides: making microbicides available will require parallel work by a dedicated team in compiling evidence, developing policies and recommendations, financing, advocacy, and monitoring impact.

The ADIP model has some clear lessons and parallels with microbicides, as well as some important differences. Panelists and meeting participants identified some of these issues, as well as some priority actions:

- While the Hib vaccine is a useful case study, there are clear differences between the experience with the Hib vaccine and microbicides – the vaccine had an established, paying market with existing manufacturing capacity; targets children and is delivered through a health system; does not require ongoing supply and use; and could build on international infrastructure for vaccine supply and purchase at GAVI.
- Building a parallel process for microbicides would require a substantial up-front investment of funds and a global structure to purchase and oversee the process. It is not clear which donors and global health agency or agencies are best positioned and willing to do this.
- Realistic forecasting is critical to estimate demand and uptake that does not conflate the clear *need* for microbicides with *demand* for this product – especially challenging given that microbicides are a completely new product category. Reliable demand forecasting is both art and science. In the past, industry has cited building reliable demand as one of the biggest obstacles to working with the public sector. It will be important to build credible demand forecasts and then test every underlying assumption. A number of key elements of preparing for access will hinge on this forecasting, which needs thoughtful, dedicated, informed and nuanced work to begin immediately.
- Demand for tenofovir gel will need to be created, and demand creation will be an ongoing process. One key component will be to determine whether roll out will be done through targeting specific user groups or through a more general approach.
- It is important to articulate specific questions that could speed up or slow down the process of product introduction and roll out, and develop approaches to answer them. This will help target research and policy development to address these specific questions and issues.
- GAVI buys the Hib vaccine and passes it along at a low co-payment to countries and programs. The ADIP program has not tested how willing the programs would be to invest in unsubsidized purchase of the vaccine.
- Pre-introductory and introductory trials are essential to preparing for access by offering a context within which to examine key questions related to information provision, service delivery, acceptability, improving adherence and a host of other issues.
- In parallel with research to confirm effectiveness, tenofovir gel is now ready for a market development approach whereby a technology is turned into a product. This involves creating product identity, positioning, and branding; given that microbicides are a user-controlled

product, it will be important to understand what factors will influence whether women seek out and use the product, including issues around sex, couple dynamics and pleasure.

- The female condom (FC) has important parallels with microbicides, and its introduction and roll out was largely a missed opportunity. It was a new product category without an established market in well-resourced settings, and fell into a vicious cycle of uncertainty with regard to demand, price, and production. Policy development was very slow, and policymakers, donors and providers had clear biases against the technology and its market. The FC was perceived and dismissed as too expensive and never had sufficient policy or donor backing to increase demand or bring down costs through economies of scale. Experience with the FC illustrates the many actors and processes that can in effect “veto” a new product before it ever reaches a user.
- The very different experiences with Hib vaccine and the FC demonstrate that tenofovir gel will need strong champions, significant investment, strong infrastructure and targeted policy development to maximize its chances for success.
- Important questions remain regarding who is going to pay for and supply tenofovir gel, and what public policy options are available to share the risks. These issues need leadership in the global health community.

Session V. Estimating Impact of Microbicides

Moderator: Deborah Birx, CDC Global AIDS Program

Presentation: *Estimating Impact and Cost Effectiveness of Microbicides*
Lori Heise, London School of Hygiene and Tropical Medicine

Discussant: Glenda Gray, University of the Witwatersrand

Using modeling developed by the LSHTM, Dr. Heise underscored the urgency of preparing for and managing access and uptake to maximize tenofovir gel’s impact and cost-effectiveness. This dynamic impact model uses actual behavioral and biological data from a particular setting, and unlike many impact models that use optimistic assumptions for uptake and coverage, it assumes a modest coverage of 20% to mirror the historically slow uptake and low coverage actually achieved by health interventions. The model highlights the following issues:

- The rate of uptake and adherence will drive impact, and the relative success of microbicide programs will likely hinge on early decisions about positioning, targeting user groups or settings, promoting adherence and taking programs to scale.
- Condom substitution is not likely to be a substantial concern with microbicides or PrEP except in settings where consistent condom use is already high. Unless handled carefully, condom substitution could possibly undermine benefits of new technologies like PrEP or microbicides, especially among sex workers.
- It will be important to select impact measures based on the stage of the epidemic in a given setting. The potential impact varies by the stage of the epidemic and the extent to which it is

generalized. It is harder to decrease HIV incidence in mature, saturated epidemics although a large number of infections may be averted.

- Modeling and economic analysis can be used to estimate the impact of microbicide introduction in different settings. This is important as the impact on HIV will vary by epidemic setting.
- All modeling projections for South Africa conclude that, if reasonable coverage can be achieved, gel use is likely to avert substantial HIV infection, despite differing specific conclusions. Cost-effectiveness varies depending on the input assumptions for different models.
- The LSHTM model factors in a variety of costs, including: the product itself, HIV tests and counseling, facility visits, training, and mass media for education and advertising, with most of the costs in the first two areas. These suggest clear opportunities to reduce costs that could be explored through research: using a single dose of gel rather than 2 doses; reducing the frequency of HIV tests; and reducing the cost per dose of the gel. It also raises questions about the feasibility of daily dosing from a cost perspective.
- Given that a wide range of programmatic factors will influence future impact and costs, increased policy focus is needed to determine how to maximize uptake and reduce costs.
- Modeling demonstrates that coverage and adherence are the main drivers of microbicide effectiveness, underscoring the importance of preparing for “access” now. The overall impact of a partially effective product is determined by coverage and how quickly programs can scale up.
- It is very important to balance modeling to demonstrate the potential of a microbicide with some realistic sense of what can be accomplished.
- Given the critical importance of adherence, implementation trials should start experimenting with how much adherence can be increased through counseling or other approaches as this will make interventions much more effective and cost effective.

As Discussant, Dr. Gray drew on the experience of preventing mother-to-child transmission with HIV in South Africa. She outlined the complex array of factors that must be in place to deliver an intervention like tenofovir gel, and also offered a cautionary tale of PMTCT which has had relatively little impact despite being a very effective and relatively simple regimen. She used examples and some simple models and assumptions to illustrate how easy it would be for tenofovir gel to fall short of its potential.

- Analyses of the potential impact and cost-effectiveness of health innovations often are compromised by consistently underestimating: the cost of enhancing the health system to deliver the programs; the limitations of health systems to provide counseling, HIV testing, drug procurement and delivery, clerical and administrative functions; and the difficulty in training health care workers.
- Rational implementation of tenofovir gel will require clear consideration of: what health system structure should be in place, how the gel as a prevention method should be prioritized, and how this prevention method matches local needs; who should be targeted; where the programs and product should be offered; and how the programs should be delivered and managed.
- Even the best interventions can fall far short of expectations and potential. PMTCT has been both an astounding success – in settings like the US where prenatal transmission of HIV is now

near zero – and a resounding failure in many settings where even years after program roll out for this highly effective and relatively simple intervention, relatively few women who need them receive the drugs.

- Coverage is the most important factor in impact.

Following this very compelling if rather sobering presentation, meeting participants had only a brief time to make suggestions about how to adapt and use the models, and made several specific suggestions:

- It is important to include anal sex among both women and men as a variable in impact modeling when possible, recognizing the challenges in obtaining reliable data.
- In calculating cost effectiveness it would be useful to factor in the costs of treatment for those infections avoided to make a more compelling case.

Session VI. Building and Estimating Demand for Successful Introduction

Moderator: Orin Levine, Johns Hopkins University

Panelists: Tim Farley, WHO

Pamela Norick, International Partnership for Microbicides

Yasmin Halima, Global Campaign for Microbicides

Martha Brady, Population Council

Lori Heise, London School of Hygiene and Tropical Medicine

Building and estimating demand emerged as a key theme and clear priority for action throughout the meeting, providing the speakers in this panel with a useful context for their comments and observations. It is critical that acceptability and use considerations inform the demand forecasting exercises described above. The panelists emphasized the importance of drawing on knowledge about microbicides from clinical trials and existing acceptability and market research, as well as experiences in introducing other health innovations, especially contraception. Echoing other speakers and discussions throughout the day, they also reiterated the importance of understanding and addressing acceptability among multiple actors, not only users, and how product quality interacts with other personal and social dynamics. Key points included:

- A critical analysis of introduction and provision of contraceptive methods can offer perhaps the most useful lessons for microbicides, given their many parallels: a sexual health product used for prevention, by sexually active women, likely user-controlled but with some medical monitoring, likely initiated by a woman but may potentially require negotiation with a partner, and so forth.
- A number of products in the microbicide pipeline have innovative intellectual property agreements which allow them to be competitively priced for the market in resource- poor settings. Affordability to individuals, health systems, donors and other actors is an important dimension of acceptability.
- Balancing demand building with raising expectations is an important practical and ethical consideration that needs to take into account how ready donors, health systems, providers and others are to actually make a product available and sustainable.

- Acceptability derives from many factors in addition to a product’s intrinsic characteristics. Research and experience shows that different women like different products and product characteristics, and that acceptability is mutable: individuals’ preferences can shift with time, relationships, risk perception and actual risk, and other factors.
- Different market segments and user groups will likely need different characteristics to interest them in tenofovir gel and support their use. It is important to explore what different platforms will be needed to reach and retain different user groups.
- “Acceptability” of a product is critical not only for users but also for a range of gatekeepers: policymakers, providers, funders, and others. Experience with many technologies – male and female condoms, emergency contraception, and many others – demonstrate that provider and policy bias can undermine availability of a product, effectively precluding client “choice”. This in turn undermines continuation and adherence.
- Tenofovir gel’s effectiveness against HSV-2 may create a market in the US and other developed economies that could defray costs for the public sector.
- Experience with other health innovations can inform how to manage the multifaceted and complex process of shifting from clinical research to preparing for access, to product introduction and implementation.
- A key element to determining where the product can be provided is identifying how much medical monitoring, including HIV testing, will be needed. This will determine whether provision will be through a provider/facility model or more of a consumer model.
- Pricing will influence demand and uptake. Even if the price for the end user is very low, cost and pricing models will need to determine costs all along the pathway.
- It is very important to determine and cultivate a donor base for the field as it moves from research to implementation. For services, most of the donor funding will likely come from global development monies, and donors will want impact measured in terms of the Millennium Development Goals. It will be important to underscore with donors that, after the substantial investment they have already made in microbicide R&D, they will need to maintain their investment in order to eventually provide an affordable and effective product.

Session VII. Ensuring Affordability, Access, and Sustainable Supply

Moderator: David Stanton, USAID

Panelists: Skhumbuzo Ngozwana, Cipla Medpro
 David Walwyn, iThemba Pharmaceuticals
 Henry Gabelnick, CONRAD
 James Rooney, Gilead Life Sciences
 Carl Montague, Technology Innovations Agency, Republic of South Africa

The meeting's final panel brought together the key actors involved with development and production of tenofovir gel, and described the collaborations among public, not-for-profit and private agencies in the unusual history and arrangements going forward.

- Development of tenofovir (then called PMPA) started some 15 years ago through a collaboration between Gilead and the NIH, with product development supported largely for in vivo through early clinical testing.
- In 2005 Gilead licensed tenofovir gel for use as a vaginal microbicide to CONRAD and IPM, granting the two organizations a worldwide license to carry forward development.
- In addition to substantial funding from the US government via USAID, the CAPRISA 004 trial was also supported by the South African Department of Science and Technology (DST) through Lifelab, a precursor to the current Technology Innovations Agency (TIA). TIA is primarily funded by the DST with a mandate to develop and bring to market innovative products across a range of sectors. TIA is working to ensure that tenofovir gel is registered in South Africa as soon as possible and is accessible in South Africa and other high-incidence settings in Africa. TIA explored possible partners to produce and distribute tenofovir gel and identified CIPLA Medpro and iThemba Pharmaceuticals; the three groups are forming a public-private-partnership (PPP) to take forward registration, production and distribution of tenofovir gel in Africa.
- The PPP team is confident that it can establish and scale up capacity to make tenofovir gel available rapidly despite many unknowns, including the timing of registration, demand estimates and the concomitant scale of production that would be needed. CIPLA Medpro would need to build additional manufacturing capacity to produce the gel, and this will require substantial investment. The company estimates that it would take approximately 18 months to validate the production process.
- DPT Laboratories, the company in Texas that has produced tenofovir gel for the trials, can continue to produce gel until production can begin in South Africa.
- CIPLA Medpro has partnerships and extensive distribution networks linked with different distribution systems (public sector, community based organizations and the private sector) in many countries in Africa, and indicated that can build on these arrangements to distribute tenofovir gel.
- A brief review of costs and pricing underscored that the single dose applicator and overwrap accounts for 90% of the cost of a dose of tenofovir gel as currently packaged. PATH and CONRAD are testing a user-filled paper applicator as one approach to reduce costs, and the field should continue to explore different delivery systems to lower costs. Aiming to ensure that the product is affordable, the license with CONRAD, established as part of the PPP, specifies that pricing should be at cost plus a small margin.
- These collaborators have momentum and have made considerable progress in putting these arrangements in place. However, there are still many unknowns in terms of timing, financing, forecasting and marketing which underscore the need for careful coordination, scenario planning and leadership in taking tenofovir gel forward.

The panelists outlined plans and potential for producing and distributing tenofovir gel in South Africa, and the presentations also made clear that this work is still very much in process, with many uncertainties and unanswered questions. Comments and questions underscored the uncertainties and possibilities, the importance of demand estimates, and clarifying regulatory requirements. Key points made during the discussion included:

- Estimating demand and uptake will be critical to scale initial production and scale up appropriately. As highlighted in the discussion of pneumococcal vaccine, forecasting and distinguishing between need and demand can be difficult for public health innovations, and is particularly challenging for a new product category, and for products that will need to be used over a long period of time. This will require inventive thinking about how the product can be branded and positioned.
- Scaling up production will require substantial capital investment to build manufacturing capacity and a long lead time. One critical dimension of timing is uncertainty about what the MCC will require for regulatory approval. It will be difficult to plan or raise the substantial funds needed without resolving and clarifying the regulatory requirements.

Session VIII. Going Forward

Speakers: Nita Lowey, US Congress
Susan Brems, Deputy Assistant Administrator for Global Health, USAID
Rajiv Shah, Administrator, USAID

Meeting participants were honored to be joined by US Congresswoman Nita Lowey, a longstanding congressional supporter of microbicides. She reiterated the excitement that she and many others felt about the CAPRISA 004 results, how they energized people about the potential of microbicides, and how the results illustrate the possibilities of smart use of science and technology to address critical problems. Rep. Lowey thanked the many people in the room who had worked over the years on microbicide development and advocacy, and acknowledged the many brave women who had participated in the trials. She noted that the possibility of providing women with a tool to protect themselves from HIV infection could help turn the tide of the AIDS epidemic. Rep. Lowey promised to continue to support and fight for funding for microbicide research, and charged the participants with ensuring that the funding is used wisely, and that pieces are put in place to ensure wide and equitable roll out. She reiterated that this is critical to assuring the incoming Congress and the public that funds are being used as efficiently as possible and continuing support from the US government, the biggest donor to microbicide development.

Dr. Susan Brems presented a summary of issues that had emerged over the course of the day:

- To prepare for access to tenofovir gel, the field needs to frame the right questions, identify research priorities, and be disciplined in staying with this agenda.

- Collaboration is needed to tackle the range of research needed to license, implement and scale microbicides, and a committee could be useful in mapping the strategic research needed for licensure and implementation.
- Additional expertise needs to be brought into the field to bridge development and implementation.
- Regulatory representatives from the FDA and MCC expressed interest in collaborative review of 1% tenofovir gel; these groups should work together to facilitate regulatory collaboration on microbicides, starting with 1% tenofovir gel.
- Some uncertainty remains around the need for a third confirmatory trial.
- Strategic demand forecasting is critically important; experts in demand forecasting should begin working with experts in product introduction and access to work on a specific forecasting process that draws on the wealth of knowledge about user needs and preferences around microbicides.
- While many users and gatekeepers are interested in microbicides, significant uptake and impact will require ongoing activities to actively build a market.
- Ultimately the impact and cost-effectiveness of a microbicide will be driven by coverage and adherence.
- Implementation science and market research are urgently needed to answer many of the key questions around tenofovir gel implementation, including: the needed frequency of testing and medical supervision; counseling and approaches to conveying partial efficacy; approaches to integrating with other health services; identifying and engaging gatekeepers; optimal platforms for delivery for different user groups; drivers of demand; and so forth.
- Need to explore the potential for a total market approach that would include one or more branded products for the private and public sectors.
- Coordinated planning is needed around transitioning the manufacturing of the tenofovir gel in South Africa. Efforts to reduce the cost through different applicators or other delivery approaches are important.

Administrator Shah closed the meeting by thanking everyone for coming and noting that while the community doesn't agree on everything, the meeting represented a major step forward. He charged the USAID microbicides team to accomplish the following actions in the coming months as part of the Agency's leadership in responding to recent advances in the microbicide field:

- 1) By January 1, 2011, transition the management of the microbicides portfolio within the Global Health Bureau to the Office of HIV/AIDS.
- 2) By January 31, 2011, establish a USAID External Microbicide Advisory Group to transparently advise on accelerated development and implementation, and to make the deliberations of that committee subsequently available via website.

- 3) By January 31, 2011, develop, with consultation, a strategic plan for microbicide development and rapid introduction. The plan will lay out a late-stage coordination framework and a product introduction strategy, based on initial feedback from the November 29 meeting. To enhance transparency of decision-making and progress, the plan will include Agency milestones and deliverables.

The Administrator also requested that a USAID Microbicide Program Website be established by early 2011 that will present the deliberations of the External Advisory Group, the Development Plan and Introduction Strategy, USAID program deliverables, and quarterly progress updates, including any negative results.

Dr. Shah announced that USAID's second stakeholders' meeting will be co-hosted with the government of South Africa, WHO and UNAIDS, and convened in South Africa in the spring of 2011. This second meeting will focus on developing a detailed introduction strategy for tenofovir gel.

The Administrator reiterated his and USAID's commitment to moving aggressively along parallel tracks to complete product development and regulatory approval as well as to plan strategically for product introduction, and thereby make tenofovir gel available as soon as possible. Dr. Shah noted the many examples where new health innovations had been made available slowly if at all, and underscored the importance of driving uptake as aggressively as possible. He stressed the importance of key opinion leaders in driving product introduction and uptake, and that they need to be engaged beginning now. Dr. Shah asked for a single aggressive validated plan that emphasizes marketing and implementation, and pledged to find the resources necessary to support it. He said that the results of the CAPRISA and iPrEX trials underscore the importance of developing a broader framework for thinking about the role of antiretrovirals in prevention, but also noted that *not every problem needs to be solved nor every question answered before we begin to act.*