STAKEHOLDER CONSULTATION ON PRIORITY IMPLEMENTATION RESEARCH TO INFORM DEVELOPMENT OF WHO NORMATIVE GUIDANCE ON TOPICAL PRE-EXPOSURE PROPHYLAXIS

26-28 MARCH 2014, DURBAN, SOUTH AFRICA
STAKEHOLDER CONSULTATION ON PRIORITY IMPLEMENTATION RESEARCH TO INFORM DEVELOPMENT OF WHO NORMATIVE GUIDANCE ON TOPICAL PRE-EXPOSURE PROPHYLAXIS

26-28 MARCH 2014
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meeting Purpose and Objectives</td>
<td>5</td>
</tr>
<tr>
<td>Welcome and Context</td>
<td>7</td>
</tr>
<tr>
<td>WHO Normative Guidance</td>
<td>8</td>
</tr>
<tr>
<td>Clinical Testing and Path to Approval: Tenofovir Gel and Dapivirine Ring</td>
<td>9</td>
</tr>
<tr>
<td>User Perspectives, Acceptability and Adherence</td>
<td>10</td>
</tr>
<tr>
<td>Cost Effectiveness Models and Investment Case for New Woman-Initiated HIV Prevention Methods</td>
<td>11</td>
</tr>
<tr>
<td>Introducing Tenofovir Gel and Dapivirine Ring in a Rapidly Evolving HIV Prevention Landscape</td>
<td>12</td>
</tr>
<tr>
<td>Current Knowledge, On-Going Research and Information Gaps</td>
<td>14</td>
</tr>
<tr>
<td> Resistance: monitoring, HIV testing, care and support for people who become infected with HIV</td>
<td>14</td>
</tr>
<tr>
<td> Topical PrEP and potential users in the context of other HIV prevention options</td>
<td>15</td>
</tr>
<tr>
<td> Integrating HIV prevention products into health services for women</td>
<td>15</td>
</tr>
<tr>
<td> Identifying the best methods to support adherence to topical PrEP and retention in an HIV prevention programme</td>
<td>16</td>
</tr>
<tr>
<td> Pharmacovigilance: monitoring safety of topical PrEP</td>
<td>17</td>
</tr>
<tr>
<td> Tenofovir gel specific issues: single pericoital dose and paper applicator</td>
<td>17</td>
</tr>
<tr>
<td> Identifying priority countries for pilot introduction</td>
<td>18</td>
</tr>
<tr>
<td> Potential resources for operational and implementation research</td>
<td>19</td>
</tr>
<tr>
<td>Priority Research</td>
<td>20</td>
</tr>
<tr>
<td>Policy Analysis and Synthesis</td>
<td>22</td>
</tr>
<tr>
<td>References</td>
<td>23</td>
</tr>
<tr>
<td>Agenda</td>
<td>24</td>
</tr>
<tr>
<td>List of Participants</td>
<td>27</td>
</tr>
</tbody>
</table>
MEETING PURPOSE AND OBJECTIVES

WHO's Department of Reproductive Health and Research (RHR) and the Centre for the AIDS programme of research in South Africa (CAPRISA) convened a stakeholder consultation to identify priority implementation research on tenofovir gel and dapivirine ring to inform development of WHO normative guidelines on use of topical pre-exposure prophylaxis (PrEP). The Stakeholder Consultation brought together researchers, policymakers, programme managers, NGOs, donors, representatives of industry and other experts (see Appendix A). Through discussions informed by a series of technical presentations, the group worked to determine what issues were most critical for development of WHO guidelines, and the research approaches and timing where they can be addressed. WHO jointly convened the meeting with CAPRISA, which had led the CAPRISA 004 trial of tenofovir gel, the only clinical trial to date to demonstrate efficacy of a topical PrEP product. [1] The Consultation addressed both of the vaginal microbicide products currently in Phase 3 clinical trials – tenofovir gel and the dapivirine ring.

Based on a series of presentations, debate and discussions, participants worked to identify and prioritize issues in programme implementation of tenofovir gel and dapivirine ring and to determine what could be addressed in each of three phases of research: 1) open label extensions (OLE) of the on-going clinical trials; 2) pilot introductory studies and operations research after confirmation of safety and effectiveness, but before product licensure; and 3) programmatic research following product licensure (see table 1 below). The group strongly affirmed that implementation research and roll out should be prioritized in communities and countries that have hosted clinical trials of microbicides, and it was important to support and fully fund OLE studies in the sites where trials of tenofovir gel and dapivirine ring are on-going. The clear priorities for the OLE studies are to generate additional safety data for the regulatory dossiers, and to continue to provide study product to trial participants while learning more about some of the programming requirements and the acceptability of the product to users after it has been shown to be safe and effective. While several topics were identified that can be examined in OLE studies, it was considered important not to overburden the studies with complex implementation research questions as this might jeopardise the practical need to provide product to former trial participants and collect additional safety data.

This report summarizes the presentations and rich discussions, and concludes with a section on recommendations and next steps. The structure of the report follows the meeting agenda (Appendix B) although in a few cases discussions on similar topics have been combined.

Table 1: Research phases and characteristics

<table>
<thead>
<tr>
<th>Phase of research</th>
<th>Settings/key characteristics</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before product licensure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open label extension of efficacy trials</td>
<td>Efficacy trial sites</td>
<td>Additional safety data to support licensure</td>
</tr>
<tr>
<td></td>
<td>Participation limited to efficacy trial participants</td>
<td>Key questions to allow less restrictive labeling: e.g.</td>
</tr>
<tr>
<td></td>
<td>All are former trial participants who have successfully completed the trial.</td>
<td>– frequency of HIV testing, product resupply</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– adherence support models</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– alternative service delivery settings</td>
</tr>
<tr>
<td>Phase of research</td>
<td>Settings/key characteristics</td>
<td>Key outcomes</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pilot introductory studies and operations research (following safety and effectiveness, prior to licensure)</td>
<td>New users&lt;br&gt;Can be in trial sites or other settings&lt;br&gt;Research requires ethical and regulatory approvals and individual informed consent</td>
<td>Inform guidance and product labeling&lt;br&gt;Inform initial programme design (e.g. minimum service package, efficient adherence support models, feasible and sustainable service delivery models)&lt;br&gt;Extend to new user groups (e.g. extended age range, relaxed eligibility criteria and extension to users previously excluded due to minor contraindications)</td>
</tr>
<tr>
<td>After product licensure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demonstration Projects/ Implementation Research</td>
<td>New users&lt;br&gt;Projects developed to inform programme design&lt;br&gt;Research designed and conducted in the context of ongoing programmes</td>
<td>Inform successful programme scale up and adaptation&lt;br&gt;Inform development of updated guidance as experience with product delivery and use accumulates.&lt;br&gt;Address public health use of products</td>
</tr>
</tbody>
</table>
WELCOME AND CONTEXT

At the invitation of the Provincial Department of Health, the Consultation was hosted in Durban, near the epicentre of the HIV epidemic, and Dr. Sibongiseni Dhlomo, Health Member of Executive Council (MEC) of KwaZulu-Natal (KZN), opened the meeting with a compelling and eloquent overview of HIV in the province. KZN province has made important progress in reducing mortality from HIV through rapid expansion of HIV treatment programmes, and in lowering the number of new HIV infections through prevention programmes targeting vertical transmission. The provincial government is highly receptive to science and research and implementation of new innovations. For example, they have engaged the King to champion voluntary medical male circumcision (VMMC), and have opened camps and clinics to perform VMMCs throughout the Province. At the same time, the rate of new infections among young women in particular, remains among the highest in the world. Given the need for new HIV prevention approaches, especially for young women, Dr. Dhlomo voiced his commitment to implementing new HIV prevention approaches that are grounded in a comprehensive sexual and reproductive and human rights approach. He commended CAPRISA’s work and gave his support to helping ensure rapid roll-out of topical PrEP once its safety and effectiveness had been confirmed. He suggested that it should be appropriate to engage nurses to deliver ARV-based prevention as they have done so successfully with treatment. Recognizing the ongoing epidemic in South Africa, and in KwaZulu-Natal in particular, Dr. Dhlomo underscored the importance of the consultation’s objectives in helping to determine how best to ensure that effective HIV prevention products can be delivered appropriately and as soon as possible.

Manjulaa Narasimhan (WHO/RHR) and Salim Abdool Karim (CAPRISA) opened the Consultation and emphasized the importance of developing new HIV prevention products in the context of sexual and reproductive health given the continued high rate of new infections among women, especially young women in generalized HIV epidemics.
WHO guidelines are influential in shaping policy and facilitating access to new drugs and innovations. They are complementary to national regulatory review, and provide guidance on whether the product or intervention should be used or introduced, as well as the circumstances and policies necessary to ensure that they are used safely and successfully. Tim Farley (Sigma3 Services), Nathalie Brouet (WHO) and Rachel Baggaley (WHO) described the process of guideline development, and provided examples and lessons from developing guidance for VMMC, HPV Vaccines, oral PrEP and preventing mother to child transmission (PMTCT). According to the WHO Handbook for Guideline Development, “a WHO guideline is any document … that contains WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources.” [2] Recommendations are judgements based on the quality of evidence, the trade off between benefits and harms, costs, and values and preferences. WHO issues several types of Guidelines of varied scope and through different processes (see Box).

Following a 2007 review in the Lancet [3] that found that WHO guidelines rely heavily on opinions of experts rather than systematic reviews of evidence or inputs from those that will need to implement the Guidelines, WHO established formal procedures to develop recommendations, overseen by a Guidelines Review Committee to ensure that the procedures and standards are applied. The procedures are consistent with internationally accepted best practices and ensure that the recommendations are based on a comprehensive and objective assessment of the available evidence, and the process to develop the recommendations is transparent. The Guideline Development Group (GDG) defines key questions that specify the population, intervention, comparison or control, outcome and time (PICOT) against which evidence is retrieved and compiled in a systematic manner. The GDG assesses the quality of the evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, and makes recommendations according to the quality of the evidence (high, moderate, low, very low) and balance between benefits and harms. The strength of the recommendation is determined by additional factors including values and preferences of patients, providers and programme managers, as well as the resource implications and potential opportunity costs of the new intervention. The GDG, which comprises experts with a range of relevant disciplines and a reasonable global geographic representation, normally makes recommendations by consensus. Widely divergent opinions usually result in a conditional recommendation, while consistent opinions between the experts lead to strong recommendations. The new approach has allowed WHO to develop guidelines that are high-quality and evidence-based through a process with oversight and accountability. Nevertheless challenges remain, including applying the GRADE system where evidence is of low quality and limited, and ensuring that global recommendations are applicable in many diverse geographic and health care settings.

### Types of WHO Guidelines

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Advice</td>
<td>Response to acute need, informed by evidence, limited consultation</td>
<td>9-12 months</td>
</tr>
<tr>
<td>Standard/focused Advice</td>
<td>Limited topic area; 10-20 ‘questions’; evidence based</td>
<td></td>
</tr>
<tr>
<td>Full guideline</td>
<td>Complete coverage of health topic or disease area</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Compilation of Guidelines</td>
<td>Recommendations from WHO and other sources; no new recommendations</td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL TESTING AND PATH TO APPROVAL: TENOFOVIR GEL AND DAPIVIRINE RING

The sponsors of tenofovir gel and dapivirine ring summarized completed, on-going and anticipated research necessary for regulatory submission. Results from on-going effectiveness trials for both products are expected in early 2015. These similar timelines underscore the importance of joint guideline development and planning follow on and implementation research for both products. Both products will need to accumulate safety data in the OLE studies in order to meet the minimum woman-years of exposure and duration of use required in the regulatory dossiers. Summarizing the extensive portfolio of research on each product is beyond the scope of this report; additional information can be found for tenofovir gel (www.conrad.org) and dapivirine ring (www.ipm-microbicide.org).

**Tenofovir Gel:** Gustavo Doncel (CONRAD) outlined the rationale behind testing tenofovir as a preventive agent, and described planned and on-going clinical and implementation studies. The FACTS 001 Phase 3 safety and effectiveness trial is underway in nine sites in South Africa. The primary endpoints for FACTS 001 are safety and effectiveness in preventing HIV acquisition; preventing HSV-2 acquisition is a secondary endpoint. The protocol also calls for secondary analysis to determine the effectiveness of the product stratified according to different levels of adherence. Safety studies among adolescents are planned for the US and South Africa, although the South Africa trial is still awaiting approval by the Medicines Control Committee (MCC), the national regulatory authority. Consistent with advice from the US Food and Drug Administration (FDA), other studies are assessing drug-drug interactions, safety and pharmacokinetics in post-menopausal women, and safety and pharmacokinetics in women with reproductive tract infections.

The CAPRSIA 008 study, a follow-on to CAPRISA 004, is comparing two service approaches to delivering tenofovir gel to former CAPRISA 004 participants. Participants are randomized to receive the gel through public sector family planning services every two to three months (scheduled to coincide with each participant’s routine family planning visit) or through the trial research clinics every month.

A separate study currently in development will assess the acceptability of less expensive, user-filled paper applicators to deliver the required volume of tenofovir gel instead of the pre-filled plastic applicators used in the clinical research studies. The MCC has indicated that a new protocol is under development. FACTS 001 OLE will provide trial participants with on-going access to product, complete adequate safety measures, measure adherence to a known effective intervention, and evaluate socio-behavioural barriers to gel use.

The **Dapivirine Ring** is being evaluated in two separate Phase 3 effectiveness studies: the Ring Study (IPM) in seven research centres in South Africa and Uganda, and ASPIRE (MTN) in 15 research centres in South Africa, Uganda, Zimbabwe and Malawi. Both trials have enrolled women 18-45 years of age and include monthly subjective and objective measures of adherence. In addition to numerous completed studies, safety studies are being conducted among adolescents and post-menopausal women, both in the US. Other studies are assessing drug-drug interactions, compatibility with male and female condoms, and pharmacokinetics with extended ring use. The follow-on studies being planned by IPM and MTN will provide the active ring to all former trial participants and will focus on long-term safety and adherence. The two studies will also vary the follow-up regimens (1-monthly vs. 3-monthly in the ASPIRE follow-on study and 3 monthly vs. 6-monthly for the Ring Study follow-on) to explore the safety, acceptability and feasibility of different intervals in clinical practice.

**Discussion and recommendation**

- Priority for the follow-on studies for both gel and ring must be to generate the safety data needed for regulatory submission. This may limit the feasibility of examining other implementation questions in the context of these studies, although some questions (such as the intervals between visits, service delivery models and different gel applicators) can be explored.
USER PERSPECTIVES, ACCEPTABILITY AND ADHERENCE

Research on user perspectives and acceptability has been a key part of microbicide research trials and ancillary studies from the earliest studies of these products. There is a rich literature about microbicide acceptability, although much of this information refers to early products that did not contain ARVs. However, high reported rates of adherence and acceptability of coitally dependent products in the early studies was not borne out in the VOICE study in which adherence to daily product use was very low. In light of this low adherence, increased attention has been focused on reconceptualising constructs and methods for assessing acceptability that are more nuanced and predictive of product use. Mitzi Gafos (University College London) outlined some of these approaches. First, she noted that there is no common definition of acceptability; while this can limit comparability it has also provided a breadth of information. Acceptability constructs have generally included some combination of attention to product characteristics, willingness to use the product, experience using the test product, trial procedures, and correct and consistent use. Use can also be affected by influencing factors associated with the individual (age, education), partner (number, type, risk or experience of intimate partner violence), household (resources, members, rooms), broader context (norms, practices, HIV prevalence), and how the product is being provided (a trial of a product with unknown efficacy or a placebo). Non-use can be either intentional or unintentional (forgetting, not having product when and where needed). Use can also be influenced by beliefs about medicines overall or about the specific product being tested. Interestingly, Gafos noted that while gender inequalities have been among the drivers for microbicide development, she was unable to find any instances where factors related to gender were measured in relation to product acceptability and use.

It is uncertain how use and non-use in trials will predict or relate to use of a product once it is shown to be effective, by women who choose to obtain and intend to use the product. To maximize the utility of what can be known before the effectiveness studies are completed, Gafos called for a new conceptual model of acceptability and use that explores the association between the two. This model can frame revisiting extensive existing data from past microbicide trials and be tested in on-going and future studies. Given how central gender is to the concept of microbicides, such a model should adopt a clear measure of gender equity and test its associations with use. Once effectiveness has been demonstrated, it will likely be necessary to reconceptualise constructs of adherence to a microbicide that is known to reduce HIV risk.

Discussion and recommendations:

• Several participants questioned the utility of examining existing data from early trials and acceptability studies. Given that reported use did not correlate well with objective measures of use, it is not known whether women in these early trials actually used the products. Some meeting participants felt that data from any trials of an unproven product will have little relevance to a product that is known to work and is how it is marketed and used outside a trial setting.

• There was some debate as to whether objective measures of use (such as measuring tissue drug levels) in early roll out studies would be worth the expense and complexity to assess whether different adherence interventions were having an impact.

• Although some studies have addressed stigma and discrimination associated with microbicide use, these have not been adequately measured in most acceptability studies or clinical trials.
COST EFFECTIVENESS MODELS AND INVESTMENT CASE FOR NEW WOMAN-INITIATED HIV PREVENTION METHODS

Three complementary models were presented that examined different aspects of cost-effectiveness of new woman-initiated HIV prevention methods.

John Stover (Futures Institute) presented a model developed by the Gates Foundation and Futures Group that analysed cost effectiveness of four forms of PrEP (oral, tenofovir gel, dapivirine ring, and injectable) in sub-Saharan Africa. Incorporating detailed costs for different program design scenarios, the models showed that all these forms of PrEP can be as cost-effective as existing HIV prevention interventions. The main factor driving their cost-effectiveness was the populations prioritized to receive the products. These populations could be defined by geography, behaviour or risk situation. Importantly, even when PrEP interventions were not as cost-effective as other approaches (such as VMMC) they could fill gaps in demand and coverage for HIV prevention methods, and thereby play an important role in “getting to zero” new HIV infections by reducing HIV incidence in hard to reach groups.

Another model developed by Imperial College London and presented by Ide Cremin examined the potential role for PrEP within the context of existing HIV prevention interventions (VMMC, behaviour change, and early ART initiation), along with a detailed analysis of the impact and cost-effectiveness of PrEP for female sex workers in Nairobi. Both models looked at oral PrEP, although the principle would be similar for topical PrEP. As in the previous model, impact and cost-effectiveness can be improved by prioritizing those at highest risk, and both are highly sensitive to adherence. For several high-transmission locations in Kenya an optimal combination prevention package may include PrEP provided to key populations. More data are needed on the efficacy of the gel (or ring), trends in condom use, and unit costs to adapt the analyses to the specifics of topical PrEP.

Finally, Fern Terris-Prestholt (LSHTM) presented highlights from models and discrete choice experiments for microbicides developed over a number years at the London School for Hygiene and Tropical Medicine that examined cost effectiveness, as well as women’s preferences for product characteristics, service delivery and advertising. Cost effectiveness and threshold prices were modelled for tenofovir gel in a specific setting in Gauteng Province South Africa under varying assumptions. Outcomes were highly dependent on these assumptions, including the discount rate and programming issues: dosing regimen (single or multiple doses), frequency of HIV testing, ART coverage (costs averted) and levels of effectiveness, uptake and use. A discrete choice experiment conducted in Johannesburg in 2005 found that women’s key preferences were the product’s effectiveness in preventing HIV and/or pregnancy. In general women would prefer health sector outlets, such as clinics and pharmacies, as distribution points over non-health sector outlets such as shops or market stalls. Impact on sexual pleasure was an important product attribute, but women overall did not want “suggestive” packaging. These data are somewhat dated so it is not clear how relevant they are to the current ARV-based products which require regular HIV testing and delivery through health facilities, so the LSHTM group is developing protocols to update both of these projects.

Discussion and recommendations

- With rapid developments in biomedical HIV prevention the models and parameters rapidly become out of date. It was important to update the models to reflect the characteristics of the two most advanced products and current expansion of other HIV prevention methods.
- While it may be possible to reduce the cost of goods, service provision will account for substantial cost for both oral and topical PrEP. In making a case for investments in topical and oral PrEP delivery it would be important to emphasize that costs associated with infrastructure and service delivery can benefit other programs. Synergies can be expected with family planning and other sexual and reproductive health services.
- It is important to clarify how efficacy, adherence and use of different HIV prevention methods are parameterized, compared and presented in the models.
- It was not possible in the context of this large meeting to identify specific parameters and data points that could be elaborated during implementation research. Convening a small, focused follow on meeting to draw together modellers for an in-depth discussion and decisions was considered a priority next step.
New topical PrEP products will be introduced into a rapidly evolving HIV prevention landscape, with new technologies and use patterns, shifting epidemiology, and changing political realities. Quarraisha Abdool Karim (CAPRISA) provided thoughtful background to help participants anticipate some of these changes and what they will mean for prioritizing implementation research. A confluence of recent scientific advances has led to some optimism that the HIV epidemic may be approaching a turning point, with incidence decreasing in many populations and settings, prevalence stabilizing, and substantial scale up of ART coverage. It is also encouraging that new HIV prevention approaches have been identified and are available to varying degrees. However, in some settings, infection rates, especially among young women, remain very high. This reflects the diversity of epidemics within and between communities, regions and countries, with stubborn reservoirs of infection among key populations. The epidemic has also demonstrated repeatedly that preventing HIV is a complex challenge, with no quick fixes, and no single approach that will work for everyone.

Accumulating evidence makes clear that both oral and topical PrEP work well – if people use it. As noted throughout the meeting, it is important to characterise and understand the determinants of adherence, including how a product known to be effective influences adherence. It is uncertain whether new technologies – intravaginal rings, long-acting injectables, and technologies that prevent both HIV and pregnancy – will increase adherence, and whether PrEP roll-out is feasible, affordable and practical.

South Africa provides some encouraging examples of successful implementation of HIV prevention and treatment with dramatic increases in HIV testing, VMMC, PMTCT, scale-up of ART provision, and tuberculosis detection. While concerns are often voiced about oral and topical PrEP with respect to partial effectiveness and adherence, South Africa – and many other countries – have rolled out interventions even that are partially effective (VMMC, PMTCT) and where adherence is uneven and challenging (ART provision). The HIV prevention landscape in 2017, when tenofovir gel and dapivirine ring are expected to be licensed, would likely include further scale up of VMMC and PMTCT, increasing ART coverage and initiation of Treatment as Prevention (TasP) as an intense response to epidemic hotspots, and some availability of oral PrEP in key populations. In this context, tenofovir gel and dapivirine rings could fill an important niche for female-initiated HIV prevention for vulnerable women. Additional information about adherence and safety in younger women will be needed to maximize the potential of these products.

The HIV epidemic and HIV prevention technologies are evolving rapidly. Increased ART coverage may have a dramatic impact on the dynamics of the epidemic, as may a host of other contextual factors such as increased migration and changing social norms. Therefore niches for different technologies will change over time, so it is important to maintain a multi-faceted approach and not rely on any one technology to fit the needs of all individuals. Approaches to prevention programmes should facilitate adaptation within the evolving epidemic and social contexts, and to community-specific prevention strategies. Targeted, customised combination interventions may be needed to address the evolving and diverse contours of the epidemic in different settings. Strong surveillance, monitoring and evaluation and evidence-based modelling will all play a crucial role in shaping the role of new tools and technologies within a truly adaptive response.

Discussion and recommendations

• Work on topical PrEP should draw on experience with oral PrEP. Technically, there may be some similarities with implementation and roll out (testing frequency, resupply, etc.). At a policy level, WHO guidance for oral PrEP is not well developed as there is currently little programmatic experience in how to deliver the product. It is important to ensure that an adequate evidence base from operations research and on pilot implementation studies are available in time so that WHO guidance for topical PrEP can be developed and released soon after licensure.

• Engaging with regulatory authorities and policymakers will be necessary to help them clearly understand the different determinants of efficacy and effectiveness as they weigh the balance of benefits and harms as they review the licensure applications and develop national policies on topical PrEP.
• Given the social, gender and economic factors underlying the HIV epidemic, new biomedical prevention technologies and interventions will not be sufficient to extinguish the epidemic among women. One participant suggested that issues like employment for women and schooling for girls be considered as “adjuvants” for biomedical prevention technologies.
CURRENT KNOWLEDGE, ON-GOING RESEARCH AND INFORMATION GAPS

Summary presentations identified current knowledge, on-going research and information gaps in areas critical to conceptualizing topical PrEP introduction: drug resistance; use in the context of other HIV prevention options; integrating new products into health services for women; supporting adherence to product and retention in HIV prevention programs; pharmacovigilance; tenofovir gel specific issues; identifying priority countries for product introduction; and potential resources for operational and implementation research.

Resistance: monitoring, HIV testing, care and support for people who become infected with HIV

Due to concerns about HIV resistance with ARV based prevention, periodic HIV testing will need to be incorporated into topical PrEP services. Dawn Smith (US CDC) reviewed evidence and considerations related to resistance, including the implications for program issues and future treatment. Available evidence suggests that resistance related to ARV based prevention may not be as significant a concern as once thought. Models indicate that most resistant virus will come from the considerably larger population of people on ARV treatment rather than those using ARVs for prevention. Limited evidence available to date does not show resistance with use of topical PrEP agents (tenofovir gel or dapivirine ring), nor with breakthrough infections occurring in people using oral PrEP. With respect to limiting or compromising future treatment options, treatment is not needed immediately after infection and resistant viruses are dominated by wild type virus in the absence of drug pressure. However, it is possible that dapivirine resistance may confer cross-resistance to other NNRTIs. Care for persons who acquire HIV infection during gel or ring use would be the same as for all other persons with HIV infection. However, ARV treatment decisions may need to factor in detecting resistant virus soon after sero-conversion and/or at treatment initiation, possibly delaying treatment initiation, and/or choosing first line regimens based on possible resistance that will benefit the woman’s health and prevent any transmission during pregnancy (perinatal transmission).

Programs should work to minimize gel or ring related HIV resistant infections through: (1) minimizing HIV infections during use by supporting adherence and reducing other HIV acquisition risks; and (2) reducing the duration of gel use by people unaware that they are infected through detecting acute infection before starting gel or ring use, and frequent HIV testing to detect incident HIV infection during gel or ring use so that the product can be stopped. HIV tests will need to be chosen with these needs in mind, and oral rapid antibody tests, while acceptable and convenient, have limited sensitivity for detecting acute infection. Key knowledge gaps echoed those raised throughout the meeting: how to accurately measure adherence to the regimens, how best to achieve adherence to maximize efficacy and minimize resistance, and defining messages about adherence, efficacy and resistance for specific populations of potential users, non-users, and providers.

Discussion and recommendations

- Given the low adherence in CAPRISA 004, VOICE, FemPrEP and other trials many of the participants who seroconverted may have not used the products. In addition, these trials also conducted monthly HIV testing and a product hold was initiated for all seroconverters, resulting in minimal exposure to the drug and therefore less resistance. This means that resistance data from sero-converters in earlier trials may not be especially relevant, and a rigorous monitoring program is needed to determine how to address resistance as the new products are used in programmes.

- Resistance monitoring for PrEP may be able to build on WHO programmes to monitor ARV resistance from treatment, although programme capacity and effectiveness is uneven. A key concern is whether ARVs for prevention will compromise future treatment options, and it may be necessary to pool data from multiple user cohorts to address this question.

- Existing HIV rapid testing technology is not able to detect acute HIV infection and the oral antibody tests are not as sensitive as whole blood tests to signs of early seroconversion. If oral testing technology is used programmes can expect women to have HIV for fairly lengthy periods before it is detected.

- It is important to understand more clearly the acceptability, costs and risks associated with different HIV testing strategies and testing intervals as topical PrEP programmes are implemented. Similar concerns apply to oral PrEP programmes, but they will not provide all answers relevant to topical PrEP
• Resistance is a nearly universal concern among policymakers and providers, and may become a significant barrier to oral and topical PrEP implementation. A brief, clear, evidence-based policy summary is needed to lay out the evidence, outstanding questions, and approaches to monitoring and addressing resistance induced by topical PrEP programmes.

Topical PrEP and potential users in the context of other HIV prevention options

Jenni Smit (MatCH) reviewed users’ decision-making and choices for successful and sustained use of HIV prevention tools, and appropriateness of topical PrEP for different potential users in the context of other HIV prevention options. Although there are still few HIV prevention options that women can initiate, female condoms are now available in 70-80% of public sector clinics in South Africa, and newer designs have mitigated some of the acceptability and cost concerns that limited availability and uptake. Evidence suggests that strong policymaker and provider bias against the product remain. A multiyear evaluation of the national female condom programme in South Africa is on-going and may provide additional insights that can be applied to the gel and ring. The female condom is only now becoming widely available in South Africa, long after its first introduction and after newer models addressed some of the limitations of the first polyurethane female condom. Experience with the slow scale up of female condoms should temper expectations around how rapidly topical or oral PrEP can be made widely available.

Other programmes at service settings may also have an impact on the feasibility of delivering topical PrEP. The SILCS diaphragm is being evaluated as a reusable delivery system for tenofovir gel, which could offer protection against HIV and pregnancy. New emphasis on Long-Acting Reversible Contraception (LARCs) will mean that women using those methods have fewer reasons for regular attendance at clinics than women using injectable contraception.

Key knowledge gaps were similar to those raised in other consultations and discussions, and cover the range of issues related to products, programmes, context and socio-behavioural dynamics (see Box).

Discussion and recommendations

• Several participants noted that women are not prioritized in policies, programmes or expenditures in South Africa, or in other countries in the region. It is important to be aware of and work to overcome this institutional gender bias when planning woman-initiated prevention programmes.

• No technology will or should be expected to meet the needs of all potential users. It is important to acknowledge that topical PrEP may fill an important role for some women and men, even if it is not acceptable to everyone who tries it. The challenge is to identify those women who want to use the product and supporting them to use it successfully.

• It will be important to establish an aspirational but achievable metric for success at different points. Uptake may not be the only or most appropriate measure, and success may be more appropriately defined as continuation over an extended period. Different measures of success will need to be explored.

• Understanding how younger women make and operationalize decisions about product use will be critical if they are one of the prime user groups.

• Prioritizing and implementing new health innovations is a political as well as a technical process. Information from pilot implementation programmes is essential to understanding the factors that drive the political and technical considerations.

Integrating HIV Prevention Products into Health Services for Women

Saïqa Mullick (Population Council) outlined a range of health delivery systems and service types that could deliver topical PrEP to different segments of women, using examples to illustrate what services focused on women actually deliver and to whom. Family planning clinics are an obvious setting for delivering topical PrEP, and linking family planning and HIV services is considered beneficial and feasible in family planning clinics, HIV counselling and testing centres, and HIV clinics. However, in some countries and settings relatively low contraceptive prevalence figures suggest that women who may be at risk of HIV may not be reached by family planning services. High unmet need for contraception among married women does not always correlate with high rates of HIV in women. The 2011 DHS found that difficulties and barriers related to access account for only about one-third of the reasons women cite for not using modern contraception, with method-related concerns accounting for the other two-thirds.

Ensuring that new HIV prevention approaches are integrated into existing service delivery platforms is a strong finding of a recent Population Council review of key opinion leader (KOL) attitudes about ARV-based prevention for women. Though most recognize the need for new HIV prevention options for women, and support their use, the
KOLs echoed questions heard in other formal and informal studies: efficacy levels, potential for resistance, cost, feasibility of testing, and acceptability. Finally, in settings where young women would benefit from new prevention technologies, it is critical to understand their needs, preferences and lifestyles in designing services, paying special attention to how and where to reach young women as they may not use traditional family planning and health services.

**Discussion and recommendations**

- The field may face a real dilemma in trying to introduce a somewhat complex new technology into existing services given that many of these systems are weak. New HIV prevention methods and programmes for women should draw and build on current investments in health system strengthening.

- Identifying target groups or individual women at risk will be a significant challenge in delivering ARV-based prevention for women. One clinician noted that in his experience women’s perception of risk is based largely on her partners, and it is difficult for women to acknowledge or articulate this risk, or for providers to assess it. Making the products available preferentially to “high risk” groups such as sex workers, risks stigmatizing their use in other contexts. One great potential for these new HIV prevention methods is that they may be able to be used by women at high risk of HIV infection but not in any identified traditional core group or key population.

- PMTCT has been a significant success in HIV prevention. It was implemented as a defined, core package that was understandable and feasible, and was attractive to politicians and policymakers. It has been refined and adapted but always presented as a clear intervention package. This approach should inform efforts to introduce topical PrEP.

**Identifying the best methods to support adherence to topical PrEP and retention in an HIV prevention programme**

Drawing on experience from trials of oral and topical PrEP and implementing other technologies, Helen Rees (WHRU/FACTS) outlined some of the complex issues related to adherence and retention in clinical trials and in programmes. Numerous trials have demonstrated that ARV-based prevention works if people use it, but adherence to product use has been uneven, and low in several trials. The VOICE trial exemplified both the challenges and importance of adherence for topical and oral PrEP. While self-reported adherence in all three active arms was approximately 90%, only 25-30% of participants in these arms had detectable drug levels in their blood. Many of the correlates of low adherence across a number of topical and oral PrEP trials correspond closely with those factors that put women at risk of HIV: younger age; no regular partner; low perception of risk; and perceived stigma. The FACTS 001 trial is using a comprehensive approach to bolstering and assessing adherence. It draws on counselling, social science and biologic measures, and social behaviour reinforcing strategies such as SMS reminder messages and peer discussion clubs. The FACTS consortium will evaluate the effect of this package, but it is unlikely that such an approach is sustainable or feasible in the service delivery context.

Adherence is a pervasive challenge across many prevention and treatment approaches, including contraception and ART, examples that may be especially relevant to topical PrEP. Rees outlined a wide range of approaches likely to improve adherence and retention for topical PrEP, echoing the literature on quality of care in health and family planning services: creating a positive social environment with sufficient policy and budgetary commitment and advocate buy-in; choosing appropriate, accessible service outlets where trained, positive staff can provide quality services; defining a topical PrEP package recognizing that users do not like complex, time consuming processes or procedures; offering choice; developing and using tools and approaches that provide clear information and foster open communication about products and side effects; and supporting adherence through counselling, social support and social media. Cash transfers have been effective in changing behaviour related to HIV and other outcomes such as discouraging early marriage and promoting retention in school. In providing compensation for clinic visits and participation, clinical trials in some ways mirror these programs, but it is important to align incentives with desired outcomes. VOICE study participants adhered well with the visit schedules and reported high compliance with the product schedule, but in fact most did not use the products as instructed.

Finally, Rees outlined a number of knowledge gaps related to delivering topical PrEP, while noting that it may be neither possible nor necessary to answer them all before starting a programme. Although there is much discussion about the need to identify women at risk, it is not clear whether it is possible to target specific populations, nor whether doing so is equitable especially in a generalised epidemic. If adherence and retention in programmes are affected by structural drivers, is it feasible and possible to evaluate the impact of these drivers on product use, and to address these issues in the context of biomedical prevention programmes? Given that conditional cash transfers have been effective in some areas, are they feasible and desirable for a prevention package that
includes PrEP for young women? What are the elements of a PrEP package that ensure safety and optimal use of a product without making product access and use so complex and demanding that there is little uptake? To what extent can community readiness and quality of service be expected to be built to support a single product?

Discussion and recommendations

• In general, meeting participants agreed that defining the core elements of the PrEP package is critical and the priority must be on developing a package that can be delivered and then experimenting with this package. As one participant noted, a challenge is to balance making the service so perfect that no one will use it with making it so imperfect that no one will use it.

• While recognizing the key role that structural drivers play in conditioning women’s HIV risk as well as use of any new intervention, most participants felt that it is not feasible for PrEP programs to address structural issues in a significant way. It may be worth exploring further cash transfers for specific behaviours, such as returning for HIV testing on schedule, given that HIV testing and its relation to resistance is critical for quality services and for addressing concerns of policymakers.

• VMMC is an evolving success in HIV prevention. While many of the details are quite distinct from PrEP, several lessons from VMMC are key: setting bold targets to drive ambitious programmes; securing major investment; and maintaining commitment to the vision through initial setbacks and programme adjustments.

• A clear, specific and realistic research agenda for supporting and measuring adherence in targeted, short term studies should be outlined to be included in roll-over studies and other initial research following effectiveness trials.

Pharmacovigilance: Monitoring Safety of Topical PrEP

Zeda Rosenberg (IPM) outlined considerations for pharmacovigilance, or drug safety, the pharmacological science relating to the collection, detection, assessment, monitoring and prevention of adverse effects with pharmaceutical products. Because clinical trials are conducted in a well screened and closely monitored subset of the target population, it is important to verify that the safety profile of the drug product is similar in a broader population of product users when it is on the market. Pharmacovigilance is an increasingly important regulatory issue, with the sponsor required to collect, analyse and report safety information following the launch of a new product; results can result in labelling changes. This requirement is generally the most intense in the first few years a new drug is on the market though it continues for with adverse drug reaction (ADR) reports for generic products. From a practical standpoint, there is a long history of safety data on tenofovir, and none on dapivirine. A new system must be established for dapivirine so the challenge is likely to be much greater.

In Africa some coalitions are emerging to discuss coordination on pharmacovigilance, but at present requirements are driven by NRA regulations and differ between countries. These requirements are generally quite strict though it is unclear the extent to which they are enforced. In practice safety data collection is driven more by the clinical setting and data analysis requirements than the regulations, and constructing databases can be challenging. Data sources and inputs depend on voluntary participation by physicians. It is important to determine how best to encourage their participation which is highly variable in the sometimes fragmented and under resourced systems where topical PrEP will be used.

Discussion

• Efforts have been made to coordinate reporting on ADR through WHO, the Gates Foundation and other entities but these systems are still not well developed and collecting adequate safety information is difficult.

• Based on experience, it seems unrealistic to suggest that a pharmacovigilance system be established in resource-limited settings for a single product. South Africa tried to set up a dedicated pharmacovigilance system for ARVs when they were rolled out but it has been difficult to manage and not that successful. It may be more feasible to set up sentinel sites to monitor use in women with different background health characteristics than those of women in clinical trials.

• Regulators have made clear to the sponsors that pharmacovigilance is part of the review process, and the sponsors will need to submit a proposal that is feasible. Pharmacovigilance will also be needed as part of the WHO prequalification process.

• Pharmacovigilance will be an important aspect of topical PrEP registration and implementation, but is not a central concern for implementation research at this time.

Tenofovir Gel Specific Issues: Single Pericoital Dose and Paper Applicator

Jill Schwartz (CONRAD) outlined several on-going research efforts aimed at decreasing the cost of tenofovir gel use. Trials to date have tested two dosing regimens: BAT-24
(one dose before and one dose after sex), and daily (one dose every day). A single pericoital dose is likely to be safe, less expensive and more convenient, but it is not clear whether it would be as effective as BAT-24. A study currently in analysis will provide pharmacokinetic data on the three different dosing regimens through assessing drug levels in plasma, aspirate and tissue (tenofovir) and in cells and tissue (tenofovir-diphosphate). In practice, missed doses, convenience, and lower cost mean that a single pericoital dose will be used by some women if tenofovir gel is approved, even if the labelling specifies two doses.

Replacing the pre-filled, plastic, single dose applicators used in the trials with user-filled paper applicators is another approach to reducing cost. Clinical and laboratory research are comparing safety, dose delivery and acceptability of these two applicators. An initial clinical study showed that neither applicator caused any signs or symptoms of irritation, the paper applicator was considered easy to fill, and women expressed a slight preference for the user-filled paper applicator. CONRAD, PATH and CAPRISA are planning additional research to assess the acceptability, dose delivery, adherence and user instructions for the user-filled paper applicator among women who had previously used the plastic applicator in CAPRISA 008. Data from this study will also be submitted to the FDA and MCC to help support registration and distribution of gel packaged in either configuration in Africa and the United States.

Discussion and recommendations

- There is uncertainty whether pharmacokinetic data would be sufficient to support regulatory approval of effectiveness of a single dose.

- A timeline that includes the sequencing of these studies and the planned regulatory submissions would be useful to specify the timeframe in which data would be available on paper applicators, multiple dose tubes and effectiveness of a single pericoital dose, and the implications for regulatory review, demonstration projects and product roll-out. Information on timing could also help determine how to approach messaging to avoid possible confusion around different dosing and delivery approaches.

Identifying priority countries for pilot introduction

Tim Farley (Sigma3 Services) outlined a number of issues to consider in identifying priority countries and locations for pilot introduction and implementation research. The top priority is countries and settings with on-going and recently completed HIV prevention research trials. In addition to an ethical obligation to provide products to communities which participated in the clinical testing program, these countries and communities have demographic and epidemiological characteristics that indicate a need for new prevention products for women: a large number of sexually active women age 15-49 years with high HIV incidence. Other contextual factors are also key to facilitating successful introduction and should be considered. The regulatory environment would need to be conducive to approving introductory research before licensure and prompt licensure following regulatory approval in the US or EU. Indicators that suggest that potential users can be reached by relevant health services (such as high contraceptive prevalence) should be considered along with indicators of political will and commitment. These could include, for example, investments in HIV prevention, the proportion of PEPFAR funds invested in prevention (such as VMMC), a demonstrated willingness to innovate, HIV testing rates, and previous formative research on microbicide introduction. Gender issues and the presence of champions for topical PrEP and/or HIV prevention are also important to consider.

Discussion and recommendations

- The group strongly endorsed the ethical and practical imperative of prioritizing countries and communities where Phase 3 trials have been conducted for demonstration projects and product implementation. Countries that hosted safety trials should also be considered for early implementation.

- Funding committed to date is not sufficient to support OLE studies to continue to provide product to participants in all of the FACTS 001 trial sites. Securing funding for these OLE follow on studies is an urgent ethical and political priority.

- Implementation should begin in settings where success is most likely. Some country settings may have political or technical barriers to new product regulatory approval and introduction. For example, despite South Africa hosting sites for almost all HIV prevention trials, the MCC has been slow to approve the CAPRISA 008 study (a follow-on study to CAPRISA 004), clinical safety studies for gel and ring in adolescents, and requiring that follow-on study protocols are submitted as fully separate from clinical trials. Several South African researchers at the meeting expressed concern that the MCC could be a barrier to prompt implementation and underscored that they will need to have proactive discussions about the anticipated regulatory filings. An additional complication is that the MCC is being restructured but the timing and impact on review and approval of tenofovir gel and the dapivirine ring are uncertain.
• Implementation in South Africa could begin in provinces with the best political support for studies before licensure. This will provide a testing ground to assess start-up challenges such as procurement and distribution mechanisms. Others noted that it may be more useful and realistic to start with a hybrid model of settings where implementation is likely to go smoothly as well as areas where it may be more challenging.

• Discipline will be needed to allocate what is likely to be limited initial quantities of product to a few settings to build traction and success.

Potential resources for operational and implementation research

Lee Claypool (USAID) outlined potential resources available to support implementation and operational research. Global health donors, including PEPFAR, USAID, CIDA, DFID and other European bilateral donors are potential sources of funding, as are national governments of some implementing countries, including South Africa. Private foundations including the Bill and Melinda Gates Foundation are also potential supporters of this research. Through the Department of Science and Technology, the South African government has joined with USAID (Washington and South Africa) and the Mac AIDS Fund to support the CAPRISA 008 study, the open label follow on to CAPRISA 004. USAID Washington has committed some funds to support the FACTS 001 OLE study, but this is not sufficient to fund all of the sites so additional sources and funds are needed. Some funding for follow on trials for the dapivirine ring may come from the donors supporting the trials NIH (ASPIRE) and Gates Foundation, USAID and other IPM donors (The Ring Study). It may be possible to garner funding for one-time support for an introduction initiative for topical PrEP as a whole new class of product, and to leverage OLE studies and other microbicides research platforms. Once licensure it obtained it is anticipated that new funding sources that focus on commodity procurement, programmes and implementation will become available. The Global Fund will take its lead from WHO so facilitating WHO guideline development and prequalification are key to mobilizing Global Fund resources. Similar considerations apply to UNFPA and other UN agencies.

Discussion and recommendations

• NIH, USAID and the Gates Foundation have been the three main donors supporting research on topical PrEP. It is likely that UNITAID, PEPFAR and the Global Fund will join as major supporters of scale up. The Mac AIDS Fund may be another possible donor. It has supported work at CAPRISA including preparing toolkits for providers and users and may be especially interested in marketing.

• FACTS 001 has nine sites and there is insufficient funding to support rollover studies in all of these sites. Securing funding commitments to provide tenofovir gel to trial participants in all of the FACTS 001 sites through follow on studies is a top priority.

• The field should be bold in setting targets, requesting funds, and articulating a vision for why investment in topical PrEP is needed and what it could mean. This vision should acknowledge that some investments will need to be made at risk before knowing the level of effectiveness or licensure decisions.
PRIORITY RESEARCH

The group was tasked with identifying priority research activities that could and needed to be implemented in the immediate period after closure of the phase 3 trials and results have been announced, but before the products are licensed for use. Even under the most optimistic assumptions there is likely to be a 2-3 year gap between end of Phase 3 and licensure. Particular consideration was given to questions that would inform development of programmatic guidance from WHO that would be drafted and prepared for release soon after the first favourable regulatory approval. WHO guidance is complementary to the regulatory process and in addition to considering the balance of benefits and harms assessed by the regulators, considers the values and preferences of users, providers, programme managers and policy makers as well as the financial and opportunity costs of making or not making the intervention available. WHO Guidelines are global so it is important to ensure that the guidelines are applicable and consider evidence from a range of settings.

The top priority was to define the core service package to deliver tenofovir gel and dapivirine ring safely and appropriately. This would include defining HIV testing and retesting models (including frequency, location, and self-testing or provider-led testing), prescribing and resupply models (location of initial supply and refills, frequency of product dispensing), counselling approaches, whether and how to monitor for drug resistance in newly infected product users, and frequency and methods for measuring adherence. Written materials for users should be developed and tested, and a training curriculum developed for providers. Particular attention should be paid to barriers to use, such as travel, time spent in the clinic, length of counselling sessions, and other factors. The goal should be to develop a minimum or core package of elements that are essential to ensure safe and effective product use with high coverage of those most at risk of HIV infection. Additional elements could be added in selected service delivery settings where resources allow or where special safety or acceptability concerns apply.

Defining the elements of the minimum service package can begin in the OLE studies in former trial participants, and the following priority topics that should be varied and tested in OLE studies were identified: adherence support and counselling models, frequency of HIV retesting and product resupply, and service delivery settings (for example, family planning clinics or HIV testing sites in contrast to research sites). Participants in these studies will, by definition, be former or continuing users who have successfully completed Phase 3 trials, so information generated may not be generalizable to other settings and new users of the product. To ensure that these OLE studies can be initiated as soon as possible following the end of the Phase 3 trials, protocols should be developed, costed, reviewed and provisionally approved conditional on a clear demonstration of safety and effectiveness from the Phase 3 studies.

Focused research will be needed to determine how best to provide topical PrEP to adolescents and young women (age 15-24 years). Clinical safety studies in women below age 18 years are essential and the top priority. These are necessary before regulatory authorities will approve use in younger women as all clinical studies to date have only included women age 18 years and over. However, safety studies must be accompanied by complementary programmatic research to assess the feasibility and acceptability of delivering tenofovir gel and dapivirine rings to young women, their willingness and ability to use the product, how to offer topical PrEP without undermining condom use, and young women’s beliefs about the products, risks and how these might affect adherence. Ideally topical PrEP will be provided within the context of comprehensive sexual and reproductive health and human rights. Since many young women do not use traditional health or family planning services, site specific situation analyses will be needed to identify where young women go, or would go, to access topical PrEP for HIV prevention. This could include determining how to make existing health service delivery outlets more acceptable to young women and to making them aware these services exist and encouraging young women to use these services if needed.

Supporting consistent product use will be an important dimension of topical PrEP introduction and programme design, especially given that product adherence has been low in many ARV-based prevention trials in women. Tools should be developed to determine which factors influence use, and identify reasons for non-use, both unintentional and intentional. Such efforts should examine factors at multiple levels (partner, peer group, household, and community) that influence product use, and can be complemented by objective measures of adherence. Such approaches would allow support to be tailored to the individual user according to her situation and perceived and actual risk factors. While much has been learnt about supporting product adherence in Phase 3 clinical studies, it is not evident that this will also apply to users who know that they are receiving a product that has been shown to be safe and effective.
Provider training materials should be developed, tested and adapted as more experience with implementing programmes and supporting users accumulates. These materials should draw on clinical trial documents and evidence as well as available training materials from other sexual and reproductive health and HIV prevention technologies. A priority element is to develop and test practical tools for screening potential users that can be used by providers and by women themselves to help identify those at high risk of HIV, those likely to adhere to product use, and other approaches for defining users.
POLICY ANALYSIS AND SYNTHESIS

Building an enabling environment for topical PrEP is essential if the products are to be made available rapidly to women. This will require anticipating and addressing a number of issues which go beyond implementation and programmatic research. A number of barriers and facilitators to product introduction and use have been identified among advocates, providers, programme managers, policy makers and donors. New issues may emerge in this area, but the following topics can and should be addressed now as a priority.

- **Drug Resistance**: Drug resistance has consistently emerged as a key policy concern for ARV-based prevention. Available clinical data from previous and current trial participants who have become infected with HIV while using active product show no signs of selection for drug resistance, though the number of women involved is limited and due to low adherence in early trials it is not clear how many used the study drug. Modelling suggests that drug resistance and treatment failure generated by use of ARV-containing prevention products is unlikely to be a major concern even with widespread use. However, concerns regarding drug resistance need to be addressed and managed. Information from existing clinical studies, modelling, and other sources should be compiled into a policy brief on drug resistance and topical PrEP. For tenofovir gel, this would include an assessment of existing data from topical and oral PrEP trials, on-going PrEP demonstration projects, and data on use of tenofovir in ARV treatment regimens. For the dapivirine ring there is much less supportive safety data as there has been no use of the product outside HIV prevention research trial settings. It will be important to ensure that registries or other mechanism established for the Phase 3 studies are available or can be extended to include information on incident infections in further HIV prevention studies and programmes so that selection for drug resistance can be monitored.

- **Safety in Pregnancy**: While the safety of topical PrEP use in pregnancy is primarily a concern of national regulatory authorities, who will determine whether to allow use in pregnancy and the product labelling, it is also a key policy concern. Topical PrEP will most likely be used by young, sexually active women at high risk of HIV infection who will also be at risk of pregnancy. A policy brief must be developed that summarizes available data on safety of topical PrEP in pregnancy and data on use of systemic tenofovir in pregnancy from DAART and other studies. This should include a discussion of the likely relevance of these data on systemic use to topical use given data on absorption.

- **Risk compensation** is a concern with the introduction of any new HIV prevention method, especially one that offers only partial protection against HIV infection. Modelling and programmatic research on HIV prevention interventions suggests that risk compensation is unlikely to be a major concern, particularly in communities and individuals with low or intermittent condom use. In order to inform policymakers, programme managers and providers, it is important to develop a policy brief summarizing available data and modelling the potential for and implications of risk compensation, as well as laying out approaches to assessing risk compensation so that any adverse effects on risk behaviour can be monitored.

- Several issues about introduction of topical PrEP echo those being examined in the oral PrEP demonstration projects now starting to be implemented. However, many of the oral PrEP demonstration projects are being conducted among MSM and serodiscordant couples and in developed countries and therefore have limited relevance to use of topical PrEP among women in resource-limited settings. A detailed analysis of oral PrEP demonstration projects is needed to identify those areas where evidence generated from oral PrEP demonstration projects can inform topical PrEP guidance, and where gaps remain so they can be addressed. Such an analysis can be started immediately.

- **Modelling costs and cost-effectiveness** of any new HIV prevention methods is necessary in order to justify financial and human resource investments in making the products available to those in need. Several models have been developed to assess and compare costs and cost-effectiveness of different HIV-prevention interventions including tenofovir gel, the dapivirine ring and oral PrEP. In order to facilitate comparison between models and estimates it is important to ensure a consistent approach to which costs are included or excluded from the models (e.g. costs of programme delivery including initiation of new users and support to existing users, in addition to costs of the individual products). While different models are designed to address different issues, it is also helpful if one or more standard baseline scenarios with identical inputs are developed and run through each of the models for comparison. Building a common modelling approach should be started as soon as possible, particularly since this will help identify critical, poorly determined model parameters for which new data on costs can be generated from programmatic and implementation research. This is best achieved by convening a small meeting of the various modelling consortiums and supporting further model development.
REFERENCES


# AGENDA

<table>
<thead>
<tr>
<th>Session</th>
<th>Duration (mins)</th>
<th>Topic and issue</th>
<th>Presenter or lead</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TUESDAY, 25 MARCH 2014</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Buffet Lunch (12h30 – 14h00)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Afternoon Session (14h00 – 18h00)</strong></td>
<td><strong>Chair: Mike Chirenje (U. of Zimbabwe)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Context and background</strong></td>
<td>10 mins</td>
<td><strong>Welcome, introductions, meeting objectives and expectations</strong></td>
<td>Manjulaa Narasimhan (WHO), Leila Mansoor (CAPRISA)</td>
</tr>
</tbody>
</table>
| | 20 mins | **Keynote Address: Dr Sibongiseni Dhlomo**  
KwaZulu-Natal Health MEC | Tim Farley (WHO consultant) |
| | 10 mins | **Overview and importance of normative guidance in accelerating product introduction and adoption in priority countries and settings** | |
| **Current status of new HIV prevention methods in late stage clinical trials** | 25 mins | **Tenofovir Gel: Clinical testing and path to approval**  
Review status of clinical research and implications for regulatory timelines to provide all participants with a common understanding and "baseline" for discussions  
– Safety and effectiveness studies: status and timelines  
  Completed: CAPRISA 004, VOICE  
  Ongoing: FACTS 001  
– Additional clinical research: status and timelines  
  Ongoing: CAPRISA 008  
  Planned: FACTS001 follow-on studies  
– Regulatory scenarios and timelines | CONRAD: Gustavo Doncel  
Clarification of key questions |
| | 25 mins | **Dapivirine Ring: Clinical testing and path to approval**  
Review status of clinical research and implications for regulatory timelines to provide all participants with a common understanding and "baseline" for discussions  
– Safety and effectiveness studies: status and timelines  
  Ongoing: ASPIRE, The Ring Study  
– Additional clinical research: status and timelines  
  Planned: follow-on studies  
– Regulatory scenarios and timelines | IPM: Analene Nel  
Clarification of key questions |
| **Tea Break (15h30 – 16h00)** | | | |
| **User perspectives** | 30 Mins | **User perspectives, acceptability and adherence Brief review of what is known and can be known from completed and ongoing clinical research, challenges to assessment before products available within service delivery program** | Mitzy Gafos, University College London  
Discussion |
<table>
<thead>
<tr>
<th>Session</th>
<th>Duration (mins)</th>
<th>Topic and issue</th>
<th>Presenter or lead</th>
</tr>
</thead>
</table>
| Cost-effectiveness, positioning and HIV prevention context | 40 mins | Cost-effectiveness and investment case models for new woman-controlled HIV prevention methods  
- Key results from cost-effectiveness models suggesting efficiency and suitability of different service delivery models  
- Identify key model parameters that are poorly determined yet have strong influence on model outcomes  
Key knowledge gaps to inform cost-effectiveness models, development of investment cases and sustainable financing | John Stover, Futures Institute  
Ide Cremin, Imperial College  
Fern Terris-Prestholt, LSHTM  
Clarification of key questions |
| | 30 mins | Anticipated evolution of HIV-prevention programmes in early adopter countries, context in which pre-licensure research will be conducted and HIV prevention landscape when products likely to enter market place | Quarraisha Abdool Karim, CAPRISA  
Discussion |
| | 20 mins | WHO normative guidance – purpose, value, development process, content  
Examples and lessons from developing guidance for male circumcision, HPV vaccines and oral PrEP, and PMTCT, and impact of guidance | Nathalie Broutet (WHO/RHR), Rachel Baggaley (WHO/HIV)  
Discussion |

**WEDNESDAY, 26 MARCH 2014**

**Morning Session (09h00 – 12h30)**  
**Chair: Peter Godfrey-Faussett (UNAIDS)**

<table>
<thead>
<tr>
<th>Session</th>
<th>Duration (mins)</th>
<th>Topic and issue</th>
<th>Presenter or lead</th>
</tr>
</thead>
</table>
| Key implementation challenges (1) | 15 mins | Summary of previous day | Liz McGrory, Tim Farley  
Introduction: Dawn Smith, CDC  
Discussion |
| | 75 mins | Current knowledge, ongoing research, information gaps  
- HIV testing and retesting – methods, safety, acceptability and resource requirements of different testing and retesting strategies; providing appropriate care and support for women who become infected while using topical PrEP, including monitoring for selection for drug resistance  
- Appropriateness of topical PrEP for types of potential user in the context of other available HIV-prevention methods; understanding users’ decision making processes and choices leading to successful and sustained use of HIV prevention tools | Introduction: Jenni Smit, MatCH, Durban  
Discussion |
| Coffee Break (10h30 – 11h00) | | | Introduction: Saiqa Mullick, Population Council, Johannesburg  
Discussion |

**Key implementation challenges (2) | 90 mins | Current knowledge, planned research, information gaps  
- Identifying suitable service delivery models for topical PrEP initiation and resupply to reach different types of users  
- Linking topical PrEP delivery with sexual and reproductive health programs, in particular contraception service delivery | Introduction: Saiqa Mullick, Population Council, Johannesburg  
Discussion |
<table>
<thead>
<tr>
<th>Session</th>
<th>Duration (mins)</th>
<th>Topic and issue</th>
<th>Presenter or lead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffet Lunch (12h30 – 14h00)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afternoon Session (14h00 – 17h30) Chair: Dawn Smith (US CDC)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Key implementation challenges (3)** | 60 mins | Current knowledge, planned research, information gaps  
– Identifying best methods to support adherence to topical PrEP and retention in an HIV-prevention program  
Discussion |
| **Key implementation challenges (4)** | 30 mins | Tenofovir gel specific issues. Current knowledge, planned research, information gaps  
– Safety and effectiveness of alternate dosing regimen (single dose vs. BAT24 regimen)  
– Safety, acceptability, practicality and dose delivery of user-filled applicators | Introduction: Zeda Rosenberg, IPM  
Discussion |
| **Tea Break (15h30 – 16h00)** | | | |
| **Opportunities to generate answers to key questions** | 60 mins | Process for identifying priority countries for product implementation, priority locations, service delivery models, and political support | Introduction: Tim Farley (WHO Consultant)  
Discussion |
| | 30 mins | Potential resources to address key operational and implementation research questions | Lee Claypool, USAID and Matt Barnhart |
| **THURSDAY, 27 MARCH 2014** | | | |
| **Morning Session (09h00 – 12h30) Chair: Salim Abdool Karim (CAPRISA)** | | | |
| 30 mins | Summary of previous day | Liz McGrory, Tim Farley |
| 30 mins | Matching high priority questions to feasible research opportunities before product licensure | |
| 30 mins | Prioritizing operational and implementation research agenda | |
| **Coffee Break (10h30 – 11h00)** | | | |
| 60 mins | Prioritizing operational and implementation research agenda (continued) | |
| 30 mins | Summary of key points and next steps | Manjulaa Narasimhan (WHO) |
| **Meeting Closure** | | | |
| Buffet Lunch (12h30 – 14h00) | | | |
LIST OF PARTICIPANTS

Quarraisha ABOOOL KARIM
Associate Scientific Director
Centre for the AIDS Programme Research in South Africa (CAPRISA)
Nelson Mandela School of Medicine
2nd Floor, DDMRI
719 Umbilo Road
Durban, 4041 – South Africa
Email: abdoolq2@ukzn.ac.za

Salim ABOOOL KARIM
Director: CAPRISA
President: South African Medical Research Council
Chair: UNAIDS Scientific Expert Panel
Pro Vice-Chancellor: University of KwaZulu-Natal
Professor of Clinical Epidemiology, Columbia University
Adjunct Professor of Medicine, Cornell University
Associate, Ragon Institute of MGH, MIT and Harvard
Nelson Mandela School of Medicine
2nd Floor, DDMRI
719 Umbilo Road
Durban, 4041 – South Africa
Email: karims1@ukzn.ac.za

Jared BAETEN
Medical Director, International Clinical Research Center
Associate Professor of Global Health and Medicine
Associate Professor, Allergy and Infectious Dis.
Adjunct Associate Professor, Epidemiology
Office: Box 359927
International Clinical Research Center
908 Jefferson St.
Box 359927
Seattle, WA 98104
Email: jbaeten@u.washington.edu

Rachel BAGGALEY
HIV Department
World Health Organization (WHO)
1211, Geneva 27, Switzerland
Email: baggaley@who.int

Matthew BARNHART
Senior Advisor
USAID Washington
Washington, DC
United States
Email: mbarnhart@usaid.gov

Nathalie BROUTET
Department of Reproductive Health & Research
World Health Organization (WHO)
Avenue Appia 20
1211 Geneva 27, Switzerland
Email: broutet@who.int

Elizabeth Anne BUKUSI
Chief Research Officer
Deputy Director Research & Training
Kenya Medical Research Institute (KEMRI)
P O Box Director (Research & Training) KEMRI Co-Director
Research Care Training Programme (RCTP) Centre for Microbiology Research, KEMRI
Box 19464, 00202
Nairobi – Kenya
Email: ebukusi@rctp.or.ke

Delivette CASTOR
Senior Epidemiologist
Office of Research and Science
Office of the U.S. Global AIDS Coordinator (PEPFAR)
401 4th St. SW, Washington, DC – USA
Email: castord@state.gov

Otto CHABIKULI
Director, East and Southern Africa Regional Office
FHI 360
4th Floor, Building 3, Hatfield Square |1115 Burnett Street,
Hatfield, Pretoria 0083
Email: ochabikuli@fhi360.org

Nomita CHANDHIOK
Scientist
Indian Council of Medical Research
Ansari Nagar
New Delhi – 110029 – India
Email: n_chandhiok@hotmail.com

Manju CHATANI
Senior Program Manager
AVAC: Global Advocacy for Prevention Research
9 3/4 Market Street
Apt. B, Northampton, MA, 01060
New York, USA
Email: manju@avac.org
Michael CHIRENJE  
Executive Director  
University of Zimbabwe  
UZ-UCSF Collaborative Research Programme  
15 Phillips Road, Belgravia  
Harare, Zimbabwe  
Email: chirenje@uz-ucsf.co.zw

Lee CLAYPOOL  
Biologist  
U.S. Agency for International Development  
Washington, DC, USA  
Email: lclaypool@usaid.gov

Ide CREMIN  
Research Associate  
Imperial College London  
Department of Infections Disease Epidemiology  
Imperial College London  
St Marys Campus  
Paddington  
W2 1PG  
Email: ide.cremin05@imperial.ac.uk

Gustavo DONCEL  
Scientific and Executive Director  
CONRAD  
CONRAD-Eastern Virginia Medical School  
601 Colley Ave  
Norfolk, VA 23507  
United States  
Email: DoncelGF@evms.edu

Tim FARLEY  
WHO Consultant  
Sigma3 Services SARL  
Scientific and Statistical Solutions  
Nyon  
Switzerland  
Email: Tim.Farley@Sigma3services.com

Virginia FRANCIS  
Gender Advisor  
USAID – PRETORIA  
100 Totius Street  
Groenkloof  
Pretoria – South Africa  
Email: VFrancis@usaid.gov

Mitzy GAFOS  
Social Scientist  
MRC Clinical Trials Unit  
University College London  
Aviation House  
125 Kingsway  
London  
WC2B 6NH  
UK  
Email: m.gafos@ucl.ac.uk

Peter GODFREY-FAUSSETT  
Senior Science Adviser  
Office of the UNAIDS Science Panel  
UNAIDS  
20 Avenue Appia  
CH-1211 Geneva 27 – Switzerland  
Email: godfreyp@unaids.org

Andy GRAY  
Senior Lecturer  
Division of Pharmacology  
Discipline of Pharmaceutical Sciences  
School of Health Sciences  
Consultant Pharmacist (Research Associate)  
Centre for the AIDS Programme of Research in South Africa (CAPRISA)  
University of KwaZulu-Natal  
Private Bag 7, Congella 4013  
South Africa  
Email: graya1@ukzn.ac.za / andy@gray.za.net

Glenda GRAY  
Executive Director  
Perinatal HIV Research Unit  
12th Floor, New Nurses Home  
Baragwanath Hospital  
Pretoria – South Africa  
Email: gray@pixie.co.za

Tian JOHNSON  
Sexual & Reproductive Health and Rights Portfolio Manager  
Stakeholder Relations Consultant  
Sonke Gender Justice  
Lead Strategist at The African Alliance for HIV Prevention  
Advocate at International Rectal Microbicide Advocates  
Johannesburg – South Africa  
Email: tian@genderjustice.org.za
Benjamin LAMBERT
Manager, New Market Opportunities Team
Clinton Health Access Initiative (CHAI)
1271 Avenue of the Americas
42nd Floor New York
NY 10020 – United States
Email: blambert@clintonhealthaccess.org

Amy LIN
Senior Market Access Advisor
USAID
Washington, DC
United States
Email: amylin@usaid.gov

Manjulaa Narasimhan
Department of Reproductive Health & Research
World Health Organization (WHO)
Avenue Appia 20
1211 Geneva – Switzerland
Email: narasimhanm@who.int

Paul MAHANNA
Deputy Director for Health Team
USAID South Africa
100 Totius Street, Groenkloof.
Pretoria
South Africa
Email: pmahanna@usaid.gov

Leila MANSOOR
Senior Scientist
Centre for the AIDS Programme Research in South Africa (CAPRISA)
Nelson Mandela School of Medicine
2nd Floor, DDMRI
719 Umbilo Road
Durban, 4041 – South Africa
Email: mansoor@ukzn.ac.za

Tim MASTRO
Group Director, Global Health, Population & Nutrition at FHI 360
Professor (Adjunct), Gillings School of Global Public Health
359 Blackwell Street, Suite 200 Durham,
North Carolina 27701 – United States
Email: Tmastro@fhi3.org

Sheena McCORMACK
Senior Clinical Scientist
MRC Clinical Trials Unit at UCL
Aviation House, 125 Kingsway
London WC2B 6NH, UK
Email: smccormack@ucl.ac.uk

Ian McGOWAN
Professor
University of Pittsburgh School of Medicine
Co-principal investigator
Microbicide Trials Network
Magee-Womens Research Institute
204 Craft Avenue, Room B608
Pittsburgh, PA 15213
Email: jmcegowan@pitt.edu

Liz McGRORY
WHO Consultant
Nyack, New York
Email: emcgrory@gmail.com

Saiqa MULLICK
Country Director and Senior Associate
Population Council
The Office Zone, Suite 1, Sheldon Place,
5 Lone Close, Lonehill Extension 9
Sandton
South Africa
Email: smullick@popcouncil.org

Annalene NEL
Chief Medical Officer at International Partnership for Microbicides
121 Main Street
Paarl
Western Cape, 7646
South Africa
Email: anel@ipmglobal.org.za

Kevin O’REILLY
WHO Consultant
1109 Consulting Services SÀRL
Nyon, Switzerland
Email: kr.oreilly@gmail.com

Kevin OSBORNE
Programme Leader
PATH
Block A, 1st Floor, Regent Place
Cradock Avenue, Rosebank
South Africa
Email: kosborne@path.org

Vera PAIVA
University of Sao Paulo
Av. Prof. Almeida Prado, nº1280 – Butantã, São Paulo – SP, 05508-070, Brazil
Email: veroca@usp.br
Gita RAMJEE  
DIRECTOR HIV Prevention Research Unit  
Medical Research Council (MRC)  
123 Jan Hofmeyer Road  
Westville, Durban  
South Africa  
Email: Gita.Ramjee@mrc.ac.za

Helen REES  
Executive Director of Wits RHI and Ad Hominem Professor in the Department of Obstetrics and Gynaecology, Honorary Professor in the Department of Infectious and Tropical Diseases of the Clinical Research Unit at the London School of Hygiene and Tropical Medicine.  
Hillbrow Health Precinct  
22 Esselen Street, Hillbrow  
South Africa  
Email: hrees@whri.ac.za

Jim ROONEY  
Managing Director, Vice President, Medical Affairs  
Gilead Sciences  
333 Lakeside Drive  
Foster City, CA 94404  
United States  
Email: jim.rooney@gilead.com

Zeda ROSENBERG  
International Partnership for Microbicides  
Silver Spring, MD USA  
Email: ZRosenberg@ipmglobal.org

Jill SCHWARTZ  
Medical Director  
CONRAD  
1911 North Fort Myer Drive  
Suite 900  
Arlington, VA 22209  
Email: jschwartz@conrad.org

Jennifer SMIT  
Deputy Divisional Head  
MatCH  
University of the Witwatersrand  
155 Juniper Road  
Overport, 4091  
Durban, South Africa  
Email: jsmit@match.org.za

Dawn SMITH  
Biomedical Interventions Implementation Officer, Epidemiology Branch, DHAP, NCHHSTP at CDC  
1600 Clifton Rd  
Atlanta, GA 30333  
United States  
Email: dks0@cdc.gov

William SPREEN  
Managing Director Infectious Diseases US RD Infectious Disease R&D  
GSK  
5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States  
Email: william.r.spreen@gsk.com

Petrus STEYN  
Department of Reproductive Health & Research  
World Health Organisation (WHO)  
Avenue Appia 20  
1211 Geneva – Switzerland  
Email: SteynP@who.int

John STOVER  
Vice President  
Futures Institute  
41-A New London Tpke  
Glastonbury, CT 06033 – United States  
Email: jstover@futuresinstitute.org

Fern TERRIS-PRESTHOLT  
Lecturer in the Economics of HIV  
202 LSHTM  
15-17 Tavistock Place  
London WC1H 9SH  
United Kingdom  
Email: fern.terris-prestholt@lshtm.ac.uk

Mitchell WARREN  
Executive Director  
AVAC  
423 West 127th Street, 4th Floor  
New York, NY 10027  
United States  
Email: mitchell@avac.org

Peter WILLIAMS  
Non-Executive Director  
Jannsen  
Beerse  
Belgium  
Email: Pwilli14@its.jnj.com
For more information, contact:

World Health Organization
Department of Reproductive Health and Research (RHR) and the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP)
20, avenue Appia
1211 Geneva 27
Switzerland

E-mail: hrp_rhr@who.int

www.who.int/hiv