



# MICROBICIDES

EDCTP Stakeholders' meeting

Oslo

8 June 2007

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Version Number:

Date of approval:

15 August 2007

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# EDCTP

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## **1. Introduction**

The EDCTP stakeholders' meeting on microbicides is the fifth stakeholders' meeting in the series of twelve meetings including two consultative ones. It was organised by EDCTP and Norway and hosted by GLOBINF network at the University of Oslo and the Norwegian Research council.

The aim of the meeting was to make recommendations to EDCTP in terms of suitable products in the pipeline for clinical trials; to identify potential sites in Africa to conduct the trials; to identify the capacity strengthening needs for the conduct of clinical trials in Africa; and to formulate an advice on the funding procedure that should be applied to meet these aims. In addition, EDCTP required the participants to provide insight into the financial commitment of the Member States for clinical trials on microbicides.

The meeting was chaired by Dr Margaret Liu. Dr Liu is a pioneer in the field of plasmid based HIV vaccines. She has been honoured as one of the 50 most important women in science and consults in the fields of vaccines and immunotherapy and is a Foreign Adjunct Professor at the Karolinska Institute.

## **2. Overview of participating organisations**

### ***2.1 Africa Centre for Health and Population Studies (ACHPS)***

Africa Centre for Health and Population Studies of the University of Kwazulu Natal run in collaboration with the Medical Research Centre of South Africa. It undertakes research in demography, social and behaviour issues, epidemiology, clinical matters, health services, virology and evaluation of interventions. Its overall objectives are to describe population dynamics of health in response to the HIV challenge; generate evidence on effects of HIV; identify interventions to improve health and to inform policy; improve the assessment of the burden of ill-health and enhance capacity to conduct health, demographic and epidemiological research in sub-Saharan Africa.

For more information visit: <http://www.africacentre.ac.za>

### ***2.2 African Microbicide Advocacy Group (AMAG)***

African Microbicide Advocacy Group (AMAG) is a regional coalition of community advocates, researchers, policy-makers and media actively engaged in microbicides research and/or advocacy in Africa. The AMAG network has an e-forum that has members from 27 countries across Africa and abroad. Its vision is to have a society where equity and justice prevail; the African woman is empowered to protect herself against AIDS and where there is an African-driven agenda for more prevention options and access to information and products.

### **2.3 CONRAD**

CONRAD was established in 1986 under a cooperative agreement between Eastern Virginia Medical School (EVMS) and the U. S. Agency for International Development (USAID), but also receives funding through interagency agreements between USAID and the National Institute of Child Health and Human Development, the Centers for Disease Control and Prevention, and the National Institute of Allergy and Infectious Diseases. Private foundations provide additional support to two subprograms of CONRAD, the Consortium for Industrial Collaboration for Contraceptive Research (CICCR) and the Global Microbicide Project (GMP).

CONRAD is dedicated to improving reproductive health, particularly in developing countries where the need is greatest, by supporting the development of better, safer and more acceptable methods to prevent pregnancy and sexually transmitted infections including HIV/AIDS.

More information on CONRAD can be found at: <http://www.conrad.org>

### **2.4 European Microbicide Project (EMPRO)**

The European Microbicides Project (EMPRO) is a consortium of 24 partners consisting of academic institutions and SME's across Europe and in Africa. The project is coordinated and managed by Kings College London and will run for 5 years, beginning at the start of 2004. EMPRO has been funded by the European Commission as part of the Sixth Framework Programme. The consortium aims to develop a pipeline of novel microbicides and enter the first of these new candidates into the first stages of clinical testing. The drugs developed will be topical microbicides that are designed to block the entry of HIV at mucosal sites such as the vagina and rectum. These microbicides are being designed for women in developing countries in an attempt to give women greater choice and control over their sexual health.

More information on EMPRO can be found at: <http://www.empro.org.uk>

### **2.5 GLOBINF**

Centre for Prevention of Global Infections also known as the Norwegian Forum for Health Research (GLOBINF) of the University of Oslo established in 2002 is a virtual research centre comprising around 30 researchers from the Medical Faculty, University of Oslo, Norwegian Institute of Public Health and the Norwegian Health Services Research Centre. The research within GLOBINF is thematically focussing on HIV/AIDS vaccine development and HIV prevention in adolescents and MTCT; tuberculosis vaccine development, epidemiological modelling and testing of strategies for treatment; meningitis vaccine development; health service research strategies for implementation and capacity development in the South.

### **2.6 Global Health and Vaccination Research (GLOBVAC)**

The programme for Global Health and Vaccination Research (GLOBVAC) consists of two sub-programmes on global health research (2004 – 2010) and on vaccination research (2006 – 2011), respectively, with separate budgets and separate calls for proposals but with a joint programme board

More information on GLOBVAC can be found at <http://www.rcn.no/globvac>

### **2.7 European Commission (EC)**

The European Commission is the main funder of EDCTP through Article 169 of the European Treaty. The EC were presented by a representative of the Directorate-General for Research. Additionally an EC representative reviewing the EDCTP initiative attended the meeting.

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The Infectious Diseases Unit within Research Directorate General is funding research aimed at combating the three major killer diseases (HIV/AIDS, Tuberculosis, and Malaria). They do this through the development of new and promising candidate vaccines and therapies, sponsoring research on the full spectrum from basic molecular research through preclinical tests and proof-of-principle on Poverty-related Diseases and through the EDCTP initiative.

More information about goals and activities of the European Commission can be found at: [http://ec.europa.eu/index\\_en.htm](http://ec.europa.eu/index_en.htm)

### ***2.8 European and Developing Countries Clinical Trials Partnership (EDCTP)***

EDCTP was represented by the Member State Representatives, The Partnership Board (PB), The Developing Countries Coordinating Committee (DCCC), the Executive Director and the Secretariat.

More information on EDCTP can be found at: <http://www.edctp.org>

### ***2.9 International Partnership for Microbicides (IPM)***

IPM is a not-for-profit product development partnership (PDP) established in 2002 to prevent HIV transmission by accelerating the development and availability of a safe and effective microbicide for use by women in developing countries. It promotes the rapid development and delivery of a safe and effective microbicide product by pioneering a "best-practices" approach for screening compounds and designing optimal formulations; developing clinical trial sites and conducting clinical trials; identifying appropriate regulatory pathways; and establishing manufacturing and distribution capacity to ensure rapid access as soon as it. IPM's partners include widely respected academic institutions, major pharmaceutical and biotechnology companies, and leading non-governmental and international organisations.

More information on IPM can be found at <http://www.ipm-microbicides.org>

### ***2.10 Member State representatives***

Each European Member State was invited to send two representatives; the legal European Network Office for EDCTP and with one researcher representing TB treatment research.

The following organisations represented the European Member States (both researchers and governmental representatives):

#### **2.10.1 Carlos III Health Institute (ISCIII) – Spain**

A national public research and scientific support organisation responsible for promoting biomedical and health science research. Its mission is to develop and provide the highest quality scientific-technical services to the National Healthcare System and society in general.

More information on ISCIII can be found at <http://www.isciii.es>

#### **2.10.2 Federal Ministry for Education and Research, "Health Research" - Germany**

The causes of about two thirds of all diseases still cannot be cured. This means that at the best only the symptoms of most diseases can be treated, and even this is not possible with some diseases. Health research is therefore of great importance. Today new or improved methods of diagnosis and therapies are being developed to help sick people more effectively. And new approaches and methods of prevention are being sought so that diseases do not develop in the first place.

More information on the Federal Ministry for Education and Research can be found at <http://www.bmbf.de>

### **2.10.3 Institute of Tropical Medicine Antwerp (ITM) - Belgium**

The Prince Leopold Institute of Tropical Medicine in Antwerp, Belgium (ITM) is one of the world's leading institutes for training, research and assistance in tropical medicine and health care in developing countries. The ITM works with its partners all over the world towards a common goal of "Health Care for All".

More information on the Institute of Tropical Medicine Antwerp can be found at <http://www.itg.be/itg/>

### **2.10.4 Norwegian Research Council - Norway**

The Research Council of Norway is a national strategic and funding agency for research activities. The Council serves as a chief source of advice on and input into research policy for the Norwegian Government, the central government administration and the overall research community. The Research Council works with research institutions as well as the private and public sectors to enhance financial and quality targets in Norwegian research and innovation activities. It is the task of the Research Council to identify Norway's research needs and recommend national priorities. The Council utilises specifically-targeted funding schemes to help translate national research policy goals into action.

More information about the Norwegian Research Council can be found at: <http://www.forskningsradet.no>

## **2.11 SHIVA**

SHIVA project is a consortium funded under the Sixth Framework (FP6) programme whose objective is early (up to phase 1) development of microbicide. Its lead compound is MC1220 (NNRTI), based on the interruption of viral replication at mucosal level. The project has four main components that include basic science research (virology, microbiology and screening of new microbicides); pharmacological and preclinical development; primate challenge models; and toxicological studies in primates and humans.

## **3. Science and products**

### **3.1 Overview of presented products**

#### **Scientific overview**

The background paper on microbicides pointed out the urgent need for the development of additional HIV prevention tools, especially those that can be used by women. Microbicides are within this concept. They are being developed for topical vaginal or rectal application to prevent HIV and possibly other sexually transmitted infections and may or may not have contraceptive properties. They could be formulated as gels, creams, suppositories or vaginal rings. Their development is hampered by various scientific challenges including lack of full understanding of the mechanisms of sexual transmission of HIV; incomplete knowledge of human vagina and sexual intercourse physiology; insufficient data on immunocorrelates of protection, safety and efficacy; and lack of suitable animal models. This is further complicated by the complexity of the microbicides clinical trials including defining of validated surrogate endpoints for biological activity. Currently the current endpoint for microbicides efficacy trials is HIV incidence, thus requiring participation of thousands of women. Moreover, a perfect placebo does not exist for such trials and evaluation of sexual behaviour such as condom and microbicides use is imperfect.

Conduct of clinical trials also requires staff that are trained in ICH-GCP, who may not always be readily available in sub-Saharan Africa. Luckily, significant progress has been made in this area through capacity development by international partnerships

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such as EDCTP, Microbicide Trials Network (MTN) and International Partnership on Microbicides (IPM). However, many more clinical trial sites are still required.

### **Products in the pipeline**

Review of the microbicides at various stages along the pipeline was presented by IPM, SHIVA, and EMPRO. Furthermore there was a presentation from CONRAD that described the cellulose sulphate clinical trial that was prematurely terminated in January 2007.

IPM, whose strategy involves licensing of active compounds from commercial pharmaceutical companies for development as microbicides, described several products and formulations. These include the following:

Dapivirine (TMC120) an NNRTI licensed from Tibotec currently in phase I/II clinical trials and almost ready to enter phase III. It is available as a gel and vaginal ring, but also alternately as intravaginal tablets, emulsion and films. This is the lead IPM candidate microbicide.

M167 licensed from Merck is a CCR5 blocker which is still in a preclinical evaluation stage, with human testing expected to start in the first quarter of 2008.

BMS793 is a gp120 binder licensed from Bristol-Myers Squibb, which is still in early phases of development.

Tenofovir (PMPA) licensed from Gilead individually to both IPM and CONRAD is available in a gel form and is currently undergoing PK and male tolerance studies.

The SHIVA project's presentation was on their lead compound MC1220, an NNRTI which is still in the early development phase and has undergone successful tolerability testing in Macaque monkeys using both a gel and gel plus liposomal forms.

European Microbicides Project (EMPRO) discussed their planned phase I clinical trials on three MAbs combination (2F5, 4E10, 2G12 polymum) and TMC120, the later in collaboration with IPM. They also discussed about their Macaque trials on HHA lecithin from Amaryllis bulb and single domain nanobody. The phase I MAb combination trials of 2F5, 4E10, 2G12 polymum is scheduled to take place in November 2007 in a gel formulation. Other products that were being developed included Acidform lime juice Lactobacillus crispatus and Lactobacillus BufferGel.

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Name of Product	Type	Where in pipeline	Availability	Affordable price
Dapivirine	NNRTI Gel and intravaginal ring	Phase I/II clinical trials	-	IPM receives royalty-free, non-exclusive licences for distributions at affordable price in resource poor countries
M167	CCR5 blocker	First in human Q1-08	-	-do-
BMS793	Gp120 binder	Early formulation	-	-do-
Tenofovir (PMPA)	NNRTI	Advanced stage of development as a gel	-	-
MC1220	NNRTI	Preclinical	-	-
MAB combination (2F5, 4E10, 2G12)	Gel formulation	Phase I	-	-

### ***3.2 Needs identified***

There was a need to continue feeding the pipeline. Since the choice of which products to push forward is hampered by the lack of immunocorrelates of protection, studies to elucidate this is important. This includes studying combination drugs. It was also agreed that it was important to conduct studies to gather more data on the effects of microbicide on normal vaginal physiology and immunology as well as their interaction with sexually transmitted infections.

### ***3.3 Summary of discussion on products and science***

Although there were several products going through various stages of clinical trials, there still was a need to continue feeding the pipeline. Additionally, there was also a great need to gather more data on the vaginal mucosal physiology, immunology, interactions of these drugs with sexually transmitted infections, when to use them in relation to the menstrual cycle and how often to use them.

## 4. Needs in Africa

### ***4.1 Presented needs in the field of microbicides***

It was generally thought that there were not many sufficiently developed clinical trial sites in sub-Saharan Africa that were able to undertake microbicide trials. It was therefore agreed that there was a need to develop such sites. This capacity development should among other things target GCP training, support of quality control and quality assurance, ethics review mechanism, epidemiology and infrastructure upgrade.

It was also agreed that there was a role in strengthening advocacy for microbicides. This included sensitisation and protection of communities, good interaction with the media and informing policy and decision makers. Specific examples were presented from the prematurely terminated CONRAD clinical trial of cellulose sulphate and the work of Africa Centre for Health and Population Studies in Kwazulu Natal, South Africa. Both projects show how well they interact with study participating communities (see Appendices).

Difficulties of getting informed consent were also discussed and the need to involve communities emphasised.

### ***4.2 Overview of presented sites***

The list here is by no means comprehensive. These are clinical sites that work with IPM or are administered by the Africa Centre Health and Population Studies Microbicides Development Programme and the UK Medical Research Council Clinical Trials Unit, some of which also receive funding support from EDCTP. There are of course more clinical trial sites that are working on microbicides than these. Moreover, other clinical trial sites that are working on other fields may also be able to conduct microbicide studies. Furthermore, it was agreed that one of the possible areas of collaboration between EDCTP and IPM could include cofunding from IPM in response to EDCTP to bridge funding of the sites.

<b>Potential sites presented at the meeting</b>	
<b>Name of Institution</b>	<b>Country</b>
Reproductive Health Research Unit (RHRU) – University of Witwatersrand Tembisa Hospital Stanza Bopape Clinic, Clinical Research Centre	3 sites in Gauteng, South Africa
Medical Research Council Reproductive Health Research Unit (RHRU) Ladysmith Madibeng Centre for Research	4 sites in Kwazulu Natal, South Africa
Drakenstein Hospice, Desmond Tutu HIV Centre, University of Cape Town	2 sites in Western Cape, South Africa
Family Health International (US), Kenya Medical	

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Research Institute, Urban Research and Development Centre for Africa	Mombasa and Nairobi, Kenya
Project Ubuzima, Int'l Antiviral Therapy Evaluation Centre (IATEC)	Rwanda
Harvard School of Public Health, Kilimanjaro Christian Medical Centre	Tanzania
Innovative Biotech Ltd.	Nigeria
Mozambican National Institute of Health	Mozambique
Univ. of Zimbabwe Faculty of Medicine	Zimbabwe
Society for Women and AIDS in Africa, Deseret Int'l Foundation Namibia	Namibia
AC, Durban and Johannesburg – ACHPS MDP	3 sites in South Africa
Mwanza – ACHPS MDP	Tanzania
Masaka – ACHPS MDP	Uganda
Mazabuka – ACHPS MDP	Zambia

### ***4.3 Summary discussion on Sites in Africa***

There was an urgent need to develop and prepare more clinical trial sites in sub-Saharan Africa. These should be networked to facilitate cooperative and multicentre trials. Support to these centres should include both personnel and institutional support.

## **5. EDCTP procedures**

### ***5.1 Overview of EDCTP procedures***

EDCTP can fund proposals through an open call or a brokering procedure. Both were explained to the audience. Furthermore, information was given on the new tool “Project Partners” available on the EDCTP website, the EDCTP budget for microbicides and the expected results from the Stakeholders Meeting. More information can be found in the guidelines for Stakeholders Meetings (see Annex 2).

### ***5.2 Summary discussion EDCTP funding procedure and timelines for initiating funding procedure***

#### **Recommended procedure: Open call**

The stakeholders’ meeting participants agreed that while phase III trials were the highest priority, they also made the point that so little is known about other clinical outcomes that determine efficacy and effectiveness, such as the role and effect of concurrent sexually transmitted infections and immune correlates of protection, that phase II studies are the key priority and a critical need, where EDCTP can play an important role. Issues such as the effect of menstrual cycle timing, frequency of use, etc. were also cited as areas that need much more evaluation. The clinical trials should include such studies that may have not been done in the previous phase I or II clinical trials yet may be determining factors in finding efficacious microbicides. The studies should be collaborative and comparative aiming at getting a comprehensive

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picture of the situation and prepare the participating centres for future principle of proof phase III trials

### Possible funding partners:

The table below lists the European countries that were represented at the meeting:

<b>Pledged and potential contributions to topic</b>		
<b>Country</b>	<b>Type of support</b>	<b>Preferred subjects</b>
Spain	Able to cofund projects if a Spanish team is part of the application. Spain therefore performs its own scientific and strategic assessment. In addition the core funding already allocated to EDCTP can be used.	All
United Kingdom	UK has earmarked BSP 350,000 and equivalent of Euro 516,338 to be used in the call. The funding should either go to Africa or to a UK partner of the project. MRC in general accepts principles of EDCTP review procedure.	All
Germany	Recognises that microbicides research is a priority, but will only fund German nationals	All
Norway	Had no funds earmarked for microbicides call, but ready to offer any support on training	
Belgium	Noted that it was already funding IPM at the level of 3 million Euros and was also ready to offer training support.	

It was recognised that for EDCTP and the scientists it remains hard to deal with all cofunding requirements of the Member States.

## **6. Recommendations to EDCTP**

The meeting agreed that the top two priorities for clinical trials were:

1. Participants agreed that although the top priority was on conducting pivotal phase III studies, the available funds were not sufficient for this
2. In view of the limitations in the funds it was agreed to recommend conducting cooperative projects that will involve phase II clinical trials that will add information that can be pooled together. These should include gathering further information on biomarkers, immunology, impact of sexually transmitted infections, frequency and time of use in relation to the menstrual cycle
3. The clinical trials should be conducted in a cooperative and comparative manner so as to lead to pooling of information in a comprehensive way
4. The studies should incorporate advocacy issues and be linked to future pivotal phase III clinical trials

## 7. Annexes

### *Annex 1: Member state and third party contribution to the stakeholder meeting*

Estimate of all costs covered by hosting country	
Item	Amount
Travel	
Hotel	
Catering	Euro 681 (NOK 5430)
Administration support	
Venue	
Other	
Sum	

Signed by organising Member State:

Name *Karstein Maseride*

Date *17/8-07*

## ***Annex 2: EDCTP Guidelines for Stakeholder meetings***

### **Introduction**

This document aims to describe all aspects related to the aim, organisation and outcome of the EDCTP stakeholder meetings.

EDCTP aims to organise to 2 types of stakeholder meetings: 7 meetings will focus on disease specific topics and one meeting will concentrate on Nodes of Excellence. The disease-specific topics will have a focus on products in the pipeline. These topics are listed below:

- Malaria treatment and malaria in pregnancy (combined meeting)
- Malaria vaccines
- TB treatment
- TB vaccines
- HIV treatment
- HIV vaccines
- HIV microbicides

The Nodes of excellence meeting will focus on the integrated approach of EDCTP towards the establishment of regional nodes of excellence in sub-Saharan Africa with particular focus on reference laboratories and centres specialised in data management encompassing clinical trials design, conduct, and analysis skills, building on sites with existing capacities and competences in these areas.

These guidelines aim to describe the generic approach towards organising both types of meetings. All stakeholder meetings on disease related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP. The expected outcome, communication aspects, timelines and financial issues concerning stakeholder meetings will be clarified. In addition the role of the hosting member state, the organising committee including the independent chair as well as the expected list of participants are described.

To ensure transparency these guidelines are made public and the EDCTP Secretariat will ensure that the implementation will be carried out and documented correctly.

### **Aim and objectives of a stakeholder meeting**

A stakeholder meeting is a one day meeting. It is the start of a process that leads towards EDCTP funding one or more projects through a call or brokering procedure.

The expected outcome of these meetings is:

1. To make recommendations to EDCTP for:
  - The development of cooperative projects and coordination of efforts
  - Priorities for EDCTP:
    - for disease specific topics EDCTP requires priorities in terms of product and sites whereas
    - for nodes of excellence EDCTP needs priorities in terms of sites, location as well as required skills and capacity
2. Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms. These will be followed up by the EDCTP secretariat.
3. Establishment of trust in the EDCTP approach with our stakeholders.

The meetings with a disease-specific topic will have the following objectives:

- Identify products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend priority in terms of product and sites
- Recommend if the funding procedure is a call or brokering or no-go
- Recommend EDCTP timelines concerning the initiation of funding for each topic area

The stakeholder meeting on Nodes of Excellence has similar priorities:

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- Identify potential sites
- Identify needs in terms of skills and capacity
- Recommend priorities in terms of needs and sites
- Recommend if the funding procedure is a call or brokering or no- go
- Recommend EDCTP timelines concerning the initiation of funding

## **Organisational aspects**

All stakeholder meetings on disease-related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP.

All meetings will be organised by an Organising Committee that consists of:

- An independent expert to chair
- A representative of the hosting country. For the European Member States this is the European Networking Officer (ENO) representing the country while for the Nodes of Excellence meeting this role should be fulfilled by the relevant member of the Developing Country Coordinating Committee (DCCC),
- The Partnership Board (PB) and DCCC disease experts
- The Executive Director and Operations Manager from the EDCTP Secretariat

The independent chair will be identified by EDCTP Secretariat, PB and DCCC representatives of the organising committee before the date of the stakeholder meeting is set. The candidate will be approved by the GA in a written procedure. If the hosting country is identified before a chair is selected the representative of the hosting country will also be involved in selecting the chair. The Terms of reference for the Independent chair are the following:

To work with the EDCTP stakeholders' meeting planning group to ensure that the meeting is planned and implemented transparently avoiding or declaring any conflict of interest to give an optimal, independent and objective advice to the EDCTP. This, via the EDCTP Secretariat should take into account the following:

1. The presence of appropriate representation of all significant bodies including industry, private-public partnerships and other stakeholders that are relevant to the topic; ensuring that the representation at the meeting is sufficiently senior to contribute with authority
2. There are appropriate and effective arrangements for conducting the meeting including drafting and approving of the agenda; noting of the attendance; ensuring of adequate participation and deliberation of all the relevant issues
3. Provision in an agreed timescale of a good quality report of the meeting.

Travel and hotels are arranged in close collaboration between the hosting country and the EDCTP Secretariat and the hosting country is expected to play an active role in this. The hosting country should organise location, catering and administrative support as well as assist delegates with their visa requirements. In addition the hosting country is responsible for sending out the invitations to participants. The final list of participants to be invited will be provided by the EDCTP Secretariat in collaboration with the Organising Committee.

## **Participants**

It is a requirement that the following parties are represented at the stakeholder meeting:

- Funders both from the European Member States and if applicable third parties. Each European Member State will be asked to send one representative. It is up to the individual country to accept this invitation or not
- Product developers, Public Private Partnerships and/or industry (disease specific topics only)
- Representatives of African sites that have the capacity to carry out phase II or III trials
- Experts in the field. Each European Member State may bring one expert of their own choosing

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- Independent experts if applicable.

Most participants will be identified by the Organising Committee with the exception of the representatives of the European Member States. Each European Member State is free to send one expert in the field and one representative of their funding body of their own choosing.

It is normally expected that a stakeholder meeting will have no more than around 40 participants.

Invitations to the participants need to go out at least 6 weeks in advance.

## Agenda

The agenda for the stakeholder meeting is set by the Organising Committee using the format developed by the EDCTP Secretariat. The generic format for the meetings on disease specific topics is shown below.

### EDCTP Stakeholder Meeting

**Topic**  
*location, date 2007*  
*Address*  
*Contact*

Agenda items	By	Timelines
<i>Coffee/Tea</i>	<i>All</i>	
1.0 Welcome by host	host	
2.0 Approval of the Agenda	All	
3.0 Science and products 3.1 Scientific overview of the field 3.2 Products in the pipeline: relevant stakeholder (more added if required) More added if required		
Coffee break	All	
4.0 Discussion on products and science	All	
5.0 Sites in Africa 5.1 Relevant stakeholder (more added if required) 5.3 DCCC		
Lunch	All	
6.0 Discussion on sites	all	
7.0 EDCTP procedures	SEC	
8.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	
9.0 Summary of recommendation	Chair	

## Communication

Because EDCTP stakeholder meetings should demonstrate transparency and independence it is important that the meetings are widely advertised and that the hosting country does not have a perceived conflict of interest with the topic. EDCTP will however, not publish a call for participants. The advertisements for the stakeholder meetings will focus on announcement of topics, locations, aims and dates. They should list a contact address and encourage those that would like more information to make contact. If someone contacts EDCTP with a wish to participate, this request will be passed on to the Organising Committee who will make a decision.

Advertising of the stakeholder meetings will be through the following means:

- Internet:
  - EDCTP website
  - Requesting constituency members to publish at their websites
  - Other relevant websites
- Paper advertisement:
  - Publishing of adverts in Lancet as soon as all the dates are set
- Ask EDCTP constituencies to communicate to appropriate parties
- If the opportunity arises mention of EDCTP stakeholder meetings in presentations or meetings

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## **Timelines**

The dates for the various stakeholder meetings will be set as soon as the independent chair and hosting country have been identified and once the chair agrees to the Terms of Reference. It is expected that the stakeholder meetings for TB vaccines, malaria vaccines, HIV vaccines and HIV treatment will take place during the first quarter of 2007. The stakeholder meetings for Nodes of Excellence, malaria treatment/pregnancy, TB treatment and HIV microbicides are scheduled for the second quarter of 2007.

## **Financial issues**

If the stakeholder meeting is hosted by a European country, it is expected that this country will at least as a minimum cover the costs for use of the location, catering during the meeting, administrative support and any other local expenses. If the hosting country is African these costs need to be discussed with the EDCTP Finance Manager. EDCTP will normally pay for travel and hotel for external participants as well as for PB and DCCC members. EDCTP expects that the European Member states will at least pay for travel and hotel of the participants they delegate. EDCTP will pay for travel and hotel of European MS participants and experts only if the European Member State is unable to do so.

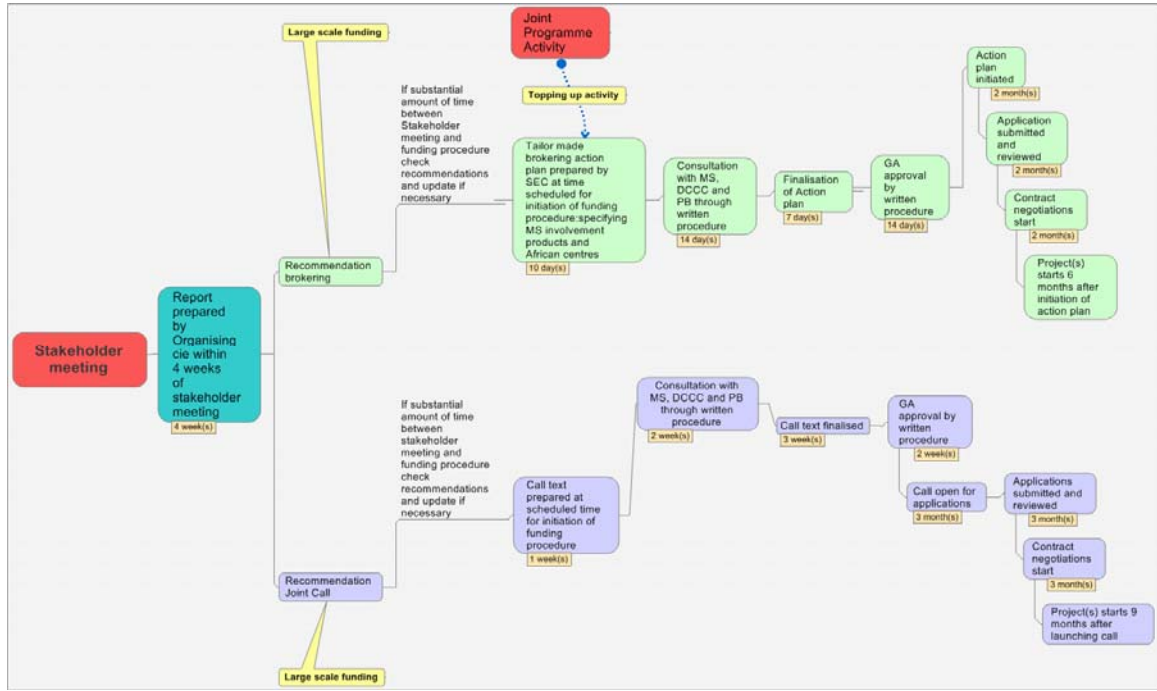
## **Outcome/follow up**

The organising committee will produce a report of the meeting within 4 weeks. The report will be presented to EDCTP. EDCTP will initiate its funding procedures at the appropriate time after considering the report. The timing for launching calls or brokering initiatives can range from 2007-2009 depending on the on the availability of products and sites. A final list of expected dates for initiation of funding procedures will be prepared after all stakeholder meetings have taken place. The diagram below summarises both funding procedures. More information on the EDCTP funding procedures can be found at the website.

A summary of both procedures is described below:

- *Call for proposals*  
A call text is drafted based on the recommendations that came out of the stakeholder meeting. After consultation of the various EDCTP constituencies and approval of the General Assembly the call will be published. An EDCTP call is normally open for applications for a period of 3 months. The applications are then checked against the eligibility criteria as defined in the call text and eligible applications will be reviewed by at least 2 external experts as well as the EDCTP Scientific Review Committee (SRC). The SRC ranks the applications and makes a recommendation for funding. This recommendation is examined by the PB which ensures the quality of the review procedure and also assess if the proposal is in line with the EDCTP strategy. The PB makes the final recommendation for funding to the General Assembly who approves the application.
- *Brokering*  
A brokering action plan is prepared by the EDCTP Secretariat and requires to be approved by the General Assembly after consultation with the EDCTP constituencies. The action plan will be initiated resulting in an application for funding. This application is checked for eligibility as described in the brokering action plan and reviewed by at least two external experts as well as the relevant EDCTP SRC. The SRC make a recommendation for funding or rejection which is examined by the PB which examines both the procedure as well as the alignment of the project with the EDCTP strategy. Upon recommendation of the PB the GA make the decision to fund the project or not.

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## ***Annex 3: Instructions for presentations***

### **Expected outcome of the meeting**

The expected outcome of the EDCTP stakeholder meetings is to make recommendations to EDCTP for:

- The development of cooperative projects and coordination of efforts
- Priorities for EDCTP in terms of product and sites
- Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms.
- Establishment of trust in the EDCTP approach with our stakeholders

The stakeholder meeting is considered the start of a process that leads towards EDCTP funding of one or more projects through an open call or brokering.

### **Audience**

The audience will be a mixture of experts in the field and people who represent funding agencies and may not have a scientific/medical background. Therefore we would like to suggest that your presentation should be aimed at a general audience.

### **Expected contents of your presentation**

Given the expected outcome of the meeting and the composition of the audience EDCTP would like to provide you some points regarding the expected contents of your presentation.

*If you talk about science and products*

- A short introduction on the organisation you are representing
- Without going into too much scientific details basic information about the products in the pipeline:
  - Basic principles of the product
  - Status with respect to clinical testing: what has been done/what is ongoing and what is planned/needed
  - Availability of the product
  - Restrictions with respect to the use of the product: is it only available for persons associated with your organisation/is it for sale?

In addition to the presentation could you provide a short summary document on each product that should enable the participants to the meeting to assess its scientific validity and potential.

*If you talk about sites in Africa*

- A short introduction on the organisation you are representing
- Basic information about the sites you are representing:
  - Capacity and trial experience
  - Commitment to other trials/availability to do the trial
  - Local malaria situation

### **Duration of your presentation**

The time available per presentation is limited to 15 minutes. The presentations will be followed by an initial discussion of 1 hour.

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## **Annex 4: Agenda**

### **Aim of the meeting:**

- Identify and prioritise potential products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend if the funding procedure of EDCTP will be an open call, brokering or whether EDCTP should fund this topic at all
- Recommend EDCTP 's timeline concerning the initiation of funding for this topic

Agenda items	By	Timelines
<i>Coffee/Tea</i>	<i>All</i>	<i>9:00 – 9:15</i>
1.0 Welcome	Charles Mgone, Kårstein Måseide, Johanne Sundby, and Margaret Liu	9:15 –9:30
2.0 Approval of the Agenda	All	9:30-9:40
3.0 EDCTP procedures	Cynthia Naus	9:40-9:50
4.0 Science and products		
4.1 Scientific overview of the field	Janneke van de Wijgert	9:50-10:05
4.2 Products in the pipeline: IPM	Mark Mitchnick	10:05-10:20
4.3 Products in the pipeline: SHIVA	Paolo La Colla	10:20-10:35
4.4 Products in the pipeline: EMPRO	Charles Kelly	10:35-10:50
4.4 Report on trial that was cancelled/stopped: CONRAD	Lut Van Damme	10:50-11:10
<i>Coffee break</i>	<i>All</i>	<i>11:10-11:25</i>
5.0 Discussion on products and science	All	11:25-12:00
6.0 Sites in Africa		
6.1 Capacity Building Needs for the conduct of microbicides clinical trials	Simon Agwale	12:00-12:15
6.2 Field Experience-South Africa	Mitzi Gafos	12:15-12:30
6.3 Role of advocacy in advancing microbicide trials in Africa	Chidi Nweneka	12:30-12:45
<i>Lunch</i>	<i>All</i>	<i>12:45-13:30</i>
7.0 Discussion on sites	all	13:30-14:00
8.0 Member States commitment	Member State representatives	14:00-14:30
9.0 Concluding remarks	Chair	14:30-14:45
10.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	14:45-15:15
11.0 Summary of recommendation	Chair	15:15-15:30
<i>Tea</i>	<i>all</i>	<i>15:30-16:00</i>

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## ***Annex 5: List of participants***

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***Annex 6: Discussion paper***

**EDCTP Background Paper  
Vaginal Microbicides**

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**Introduction**

The need to develop additional HIV prevention tools, especially those that women can use, is urgent (1). After two decades of male condom promotion, the absolute number of male condoms used worldwide has increased dramatically, but consistent condom use in primary partnerships remains rare. Women are often limited in their ability to abstain from sex, or convince their male partners to adopt safer sex behaviors, due to social, cultural and economic gender inequalities. Furthermore, the importance of having children is a major obstacle to condom use for many women and couples. Microbicides are being developed for topical application inside the vagina or rectum to prevent infection with HIV and possibly other sexually transmitted infections (STIs). They could be formulated as gels, creams, suppositories, or vaginal rings; they could be contraceptive or not; and they could be used alone or in combination with a physical barrier. Additional research is investigating ways that microbicides can be formulated for use in the rectum during anal sex.

Remarkable progress has been made in the microbicides field in recent years. According to the Alliance for Microbicide Development, 11 candidate products are currently in clinical development and several others are being investigated preclinically (2). Funding for the field increased significantly (3), and the global movement for microbicides continues to grow, uniting women's health and AIDS advocates, researchers, governments, and institutions. However, an efficacious microbicide has not yet been identified and much work remains to be done.

**Heterosexual transmission of HIV**

After vaginal exposure, HIV is capable of establishing infection through multiple pathways involving a variety of target cells and receptors (4, 5). The relative importance of each pathway is not yet clear. The virus can cross the epithelium by infecting epithelial cells, by transcytosis through epithelial cells, by epithelial transmigration of infected donor cells, via uptake by Langerhans cells, and by direct entry through epithelial disruptions. Crossing the epithelium is likely easier when there are fewer layers of epithelial cells, such as the one layer of columnar epithelium in the cervix as opposed to the multi-layer

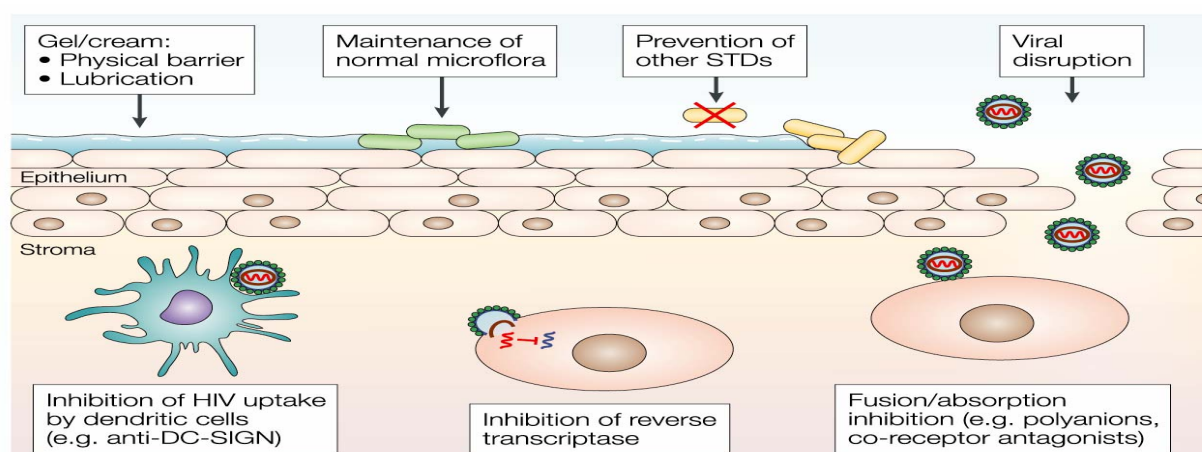
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squamous epithelium in the vagina (6). In the sub-mucosa, the virus can infect CD4+ T-cells, dendritic cells and macrophages. The virus can use the gp120 receptor in conjunction with the CXCR4 or CCR5 co-receptor, but can also attach to mannose-binding C-type lectins such as DC-SIGN. The ideal microbicide should be able to cope with this variety of HIV infection mechanisms, but should also be able to block HIV replication and release once HIV is intracellular; this may require a combination of several active ingredients in one formulation (5). Furthermore, microbicides should not inadvertently increase HIV transmission by disrupting the normal vaginal flora, disrupting the genital epithelium, or activating the immune system in a potentially harmful way.

### Candidate microbicides by mechanism of action

Current microbicide candidates have one mechanism of action (with the exception of one product as described below) and are categorized based on their mechanism of action (figure 1) (5).

**Figure 1: Candidate microbicide mechanisms of action (Shattock and Moore, 2003)**



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These categories include: 1) inhibition of HIV entry or fusion; 2) inhibition of post-fusion activity, such as viral replication; 3) direct killing or inactivation of HIV; and 4) boosting of vaginal defense mechanism. In addition, some microbicide candidates may inactivate or inhibit other sexually transmitted pathogens, which could indirectly reduce HIV acquisition risk. Finally, the mechanism of action of some candidate microbicides is not yet fully understood.

### *Inhibit HIV entry or fusion*

Most of the candidate microbicides that are currently in clinical development inhibit HIV entry or fusion. They include a group of large, negatively charged molecules (polyanions) that are thought to bind to positively charged regions of gp120. These regions are exposed in viruses that use the CXCR4 coreceptor but to a lesser extent in viruses that use the CCR5 coreceptor (7). Data from nonclinical studies only recently suggested that polyanions might have to be present at the site of virus-target cell interaction within mucosal tissue to be effective against CCR5 transmission. This could pose a problem since polyanions were initially selected because of their poor absorption into mucosal tissues (to reduce

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the likelihood of systemic side effects). The degree of tissue penetration required to block viral attachment and fusion is still unknown. Products in this category include Carraguard (Population Council, New York, NY, USA), PRO-2000 (Indevus Pharmaceuticals, Lexington, MA, USA), and cellulose sulfate (Polydex Pharmaceuticals, Scarborough, ON, Canada) (8-10). Two Phase III trials of cellulose sulfate were terminated in January 2007 because more HIV seroconversions occurred in the cellulose sulfate arm than in the placebo arm in one of the two trials (10, 11). The Phase III trial of Carraguard at three sites in South Africa was recently completed and results are expected later this year. A Phase IIB and a Phase III trial of PRO-2000 (0.5% and 2.0%) are ongoing in several African countries and the U.S.; results are expected in 2009.

Several other HIV entry/fusion inhibitors are in development: VivaGel is in early clinical and all others in preclinical development. VivaGel (Starpharma, Melbourne, Australia) is a water-based gel with the polylysine dendrimer SPL7013 as the active ingredient (12).

### *Inhibit post-fusion activity*

The newer generation candidate microbicides, with several candidates currently in early clinical trials, are products containing antiretroviral compounds that specifically block entry of HIV in target cells, inhibit post-fusion events essential for infectivity, or inhibit intracellular replication (13). Five of such products are currently in clinical development: four products containing tight-binding non-nucleoside reverse transcriptase inhibitors (NNRTIs: TMC120 vaginal gel and ring, International Partnership for Microbicides, Silver Spring, MD, USA; UC781 gel, Cellegy Pharmaceuticals, Quakertown, PA, USA; and PC815 gel containing MIV150, Population Council, New York, NY, USA) and one containing a nucleotide-analogue reverse transcriptase inhibitor (NRTI: tenofovir gel, Gilead Sciences, Foster City, CA, USA). PC815 is the only combination product that is currently in clinical development: it combines the polyanion Carraguard with the NNRTI MIV150. The advantages of tight-binding NNRTIs are that they – unlike NRTIs – do not require metabolic activation to achieve antiviral activity (13). They are active against cell-free as well as cell-associated HIV-1, and against both R5 and X4 strains, in semen and in the vaginal environment. The disadvantages of tight-binding NNRTIs are that they are capable of inducing drug resistance, and that they may not be able to prevent infection with HIV-1 isolates containing pre-existing resistance to NNRTIs. An expert meeting, organized by the World Health Organization, the International Partnership for Microbicides, and the US Centers for Disease Control and Prevention in September 2004, concluded that trials of NNRTI-containing microbicides should proceed as quickly as possible, but that emergence of drug resistance in such trials should be closely monitored (14). Meeting participants agreed that study sponsors should ensure that study participants have access to effective antiretroviral therapy, even if they need an antiretroviral regimen that is not available in the national program (for example, due to emergence of drug resistance while participating in a study).

### *Kill or inactivate HIV*

This category could theoretically contain several subgroups including compounds that disrupt lipid cell membranes (surfactants or detergents), increase membrane porosity (peroxidases/peroxides, antimicrobial peptides), cause agglutination (monoclonal antibodies), coat cells (lipids), or inactivate HIV

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by an unknown mechanism. Two surfactants were tested in clinical trials but failed; the best well-known of these is nonoxynol-9 (N-9). When N-9 products were first tested for anti-HIV activity in clinical trials, they had already been used for over 25 years in spermicides and sexual lubricants in the U.S. and elsewhere, they were cheap, and data on anti-HIV activity from *in vitro* and animal models were promising (15). The low-dose N-9 gel COL-1492 was considered safe in early clinical studies, and a Phase 3 trial was launched in 1996. This trial showed no effect against HIV at low frequency of use and an increased risk of HIV when used more than 3-4 times per day (16). Studies that were conducted after the N-9 Phase 3 trial had been completed confirmed that the therapeutic window of N-9 is very narrow (N-9 displays anti-HIV activity at doses that are cytotoxic for epithelial cells and lymphocytes); that N-9 cytotoxicity varies by concentration, duration of exposure, and repeated exposure; and that N-9 induces an inflammatory response (15, 17-19). In the current scientific and regulatory environment, it is highly unlikely that N-9 would have progressed further than preclinical evaluation. The second surfactant that failed to prevent HIV (but did not cause harm) is Savvy (C31G) gel (Cellegy Pharmaceuticals, Quakertown, PA, USA).

The only product in the "HIV inactivation" category that is currently in clinical development is Praneem polyherbal suppository (Talwar Research Foundation, India). Praneem inactivates HIV by an uncharacterized mechanism (20).

### *Boost vaginal defense mechanisms*

The normal vaginal flora of healthy women of childbearing age is dominated by lactobacilli. Lactobacilli produce a number of compounds that inhibit pathogenic microorganisms, including lactic acid, hydrogen peroxide, lactacin, and acidolin. These compounds also maintain a low, acidic pH in the vagina. A few candidate microbicides aim to enhance these natural defense mechanisms of the vagina. BufferGel (ReProtect, Baltimore, MD, USA) and ACIDFORM/Amphora gel (Instead Inc., La Jolla, CA, USA) are formulated to maintain a low vaginal pH by acidifying semen, which otherwise alkalinizes the vagina during and immediately after sex (21). The efficacy of BufferGel in preventing HIV acquisition is being evaluated in a Phase IIB trial in several African countries and the U.S.; ACIDFORM, used together with a diaphragm, is being evaluated for protection against gonorrhea and chlamydia. A few products based on vaginal (re)colonization with healthy lactobacilli are in preclinical development.

### *Scientific challenges in microbicide development*

Several scientific challenges hamper the development of vaginal microbicides (11, 22). First, sexual transmission of HIV is still not fully understood. Second, the human vagina and sexual intercourse physiology have not been fully characterized. And finally, there is a lack of well-established correlations between *in-vitro*, animal model, and clinical data regarding safety and efficacy. For example, repeated exposure of the cervicovaginal mucosa to a candidate microbicide may lead to changes in epithelial integrity and/or permeability, a subclinical inflammatory reaction, and/or local immune dysfunction (increased immune activation or decreased innate immunity). These in turn could facilitate transmission of HIV (and/or other pathogens) instead of preventing it. Some of these changes are invisible to the naked-eye, and may have been missed in past microbicide trials. It is not yet clear how best to monitor them in future trials.

## **Clinical trials of candidate microbicides**

Clinical trials of candidate microbicides are complex (23, 24). The most important challenge is that no validated surrogate endpoints for the biologic activity of microbicides currently exist. Therefore, the primary endpoint of microbicide efficacy trials must be HIV incidence, thus requiring the participation of thousands of women at risk of HIV infection through heterosexual sex. Due to the strong links between poverty, gender inequity and HIV prevalence in the heterosexual population, such communities are mostly found in developing countries, with the exception of some sex worker communities in the industrialized world. For ethical reasons, efficacy trials must measure the incremental effect of the potential microbicide over and above a package of already proven HIV-prevention interventions that include HIV-counseling and testing, condom promotion, and treatment of curable sexually transmitted and vaginal infections. Another microbicide trial challenge is that a perfect placebo does not exist. Even though a placebo typically does not contain the active ingredient of the candidate microbicide, it may nonetheless have some anti-HIV effects *in vivo* (for example, in the case of a gel due to its lubricating and/or physical barrier properties), and local toxicity from long-term use. It may also have a different acceptability and adherence profile than the active microbicide due to small differences in, for example, viscosity. In contrast to vaccines, but like condoms, most (but not all) microbicides would have to be used every time sex takes place, or at regular intervals over time, in order to be protective. Perfect adherence has not been achieved in any long-term microbicide trial to date and high pregnancy rates have resulted in large numbers of women taken off-product. Furthermore, extensive research has shown that there is currently no reliable way to measure sexual behavior, including microbicide and condom use. Many of these microbicide trial complications are likely to result in underestimates of microbicide efficacy.

An in-depth discussion of microbicide trial ethics is beyond the scope of this review and can be found elsewhere (24, 25). The ongoing debate includes important topics such as how best to achieve true informed consent, community participation, and male participation in the microbicide trial context. Medical and psychological care issues are among the most difficult and stressful to handle for microbicide trial teams because the need they encounter is distressingly high, demands placed on them can be overwhelming, and it is often unclear where their responsibilities begin and end. Health care systems in resource-poor communities cannot cope with existing problems, let alone “new” problems that were previously hidden and now uncovered by research. Most agree that researchers should at a minimum provide the local standard of care to participants; the provision of slightly better care than what is available in the community seems to be the norm. For example, many microbicide research clinics provide state-of-the-art HIV and pregnancy prevention programs, state-of-the-art laboratory diagnosis of reproductive tract infections (as opposed to syndromic management), cervical cancer screening, expanded counseling services (such as couple/marriage counseling and domestic violence counseling; often as a result of high participant demand), and active and effective referrals to, for example, HIV and cervical cancer treatment clinics. It should be noted that a tension sometimes exists between local capacity-building needs and the need to develop new prevention technologies as fast as possible.

Candidate microbicides are experimental products that could save many lives if proven safe and effective. Access can only be achieved if successful products are registered with as many drug

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regulatory agencies worldwide as possible. Microbicide trials therefore have to be conducted according to the international regulatory standards set out by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in the Good Clinical and Laboratory Practice (ICH-GCLP) guidelines as well as national drug regulatory and ethical review guidelines (ICH, 1996). Few potential trial communities in developing countries have the required infrastructure or experience to conduct rigorous clinical trials according to such guidelines. Luckily, significantly progress in this area has been made in recent years through capacity-building within international partnerships such as European Developing Countries Clinical Trials Partnership (EDCTP), the Microbicide Trials Network (MTN), the Microbicides Development Programme (MDP), and the International Partnership on Microbicides (IPM). More sites are needed to efficiently test as many candidate microbicides (and other HIV prevention interventions) as possible as they move through the pipeline. Once established, trial sites should be given the opportunity to implement trials continuously so that they maintain skills and retain qualified staff, and to minimize costs.

Future microbicide trial designs may have to be adapted in light of recent prevention successes with male circumcision (26). They may have to be adapted further if recently completed or currently ongoing trials of first generation microbicides show positive results, or other new HIV prevention strategies (such as pre-exposure prophylaxis with antiretroviral drugs) are proven to be effective. Whether such new prevention tools become part of the standard prevention package that is offered to all trial participants, or become the comparator product in equivalence or superiority trials, will most likely depend on the robustness of the new prevention method trial results, whether the results can be extrapolated to other populations and settings, whether providing the new prevention method in addition to currently available methods would increase overall protection, and whether there is strong agreement amongst experts regarding all of the above. Extensive debates on this topic are to be expected in the near future.

### **Conclusions**

What the microbicides field needs most is a wide variety of microbicide candidates in the pipeline, proof of concept, true placebos, and validated safety and surrogate efficacy endpoints. Research on improving the collection of sensitive behavioral and adherence data, and new delivery mechanisms that are less dependent on user-adherence, should continue. The microbicides field has done a good job so far in designing ethical trials and addressing ethical issues. However, trial designs and implementation should continue to be debated and adjusted as the field develops and new efficacious HIV prevention methods become available.

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