Regulatory issues in microbicide development

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Contents

Abbreviations and acronyms

ACASI audio computer-assisted self-interviewing

ADME absorption, distribution, metabolism and excretion

AIDS acquired immune deficiency syndrome

AMD Alliance for Microbicide Development

API active pharmaceutical ingredient

ARV antiretroviral drug

ASEAN Association of Southeast Asian Nations

AVAC AIDS Vaccine Advocacy Coalition

CAB community advisory board

CPR Center for Policy Research (India)

DSMB data and safety monitoring board (=IDMC)

EMEA European Medicines Agency

EU European Union

GCP good clinical practice

GLP good laboratory practice

GMP good manufacturing practice

gp glycoprotein

GPP good participatory practice

GRAS generally regarded as safe

HIV *Human immunodeficiency virus*

HPTN HIV Prevention Trials Network

HSV-2 Herpes simplex virus 2

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICMR Indian Council for Medical Research

IDMC independent data monitoring committee (=DSMB)

IND investigational new drug

IPM International Partnership for Microbicides

IRB Institutional Review Board

MCC Medicines Control Council (South Africa)

MDP Microbicides Development Programme

MRI magnetic resonance imaging

NCE new chemical entity

NNRTI non-nucleoside reverse transcriptase inhibitor

NRA national regulatory authority

NRTI nucleoside reverse transcriptase inhibitor

OTC over the counter

PrEP pre-exposure prophylaxis

RHRU Reproductive Health Research Unit (Chris Hani Baragwanath Hospital, Johannesburg, South Africa)

RTI reproductive tract infection

SADC Southern African Development Community

SHIV Simian human immunodeficiency virus (a genetically engineered hybrid)

SIV *Simian immunodeficiency virus*

STI sexually transmitted infection

UNAIDS Joint United Nations Programme on HIV/AIDS

USA United States of America

USAID US Agency for International Development

USFDA Food and Drug Administration (USA)

WHO World Health Organization

Acknowledgements

In preparing this document, my aim has been to provide a clear source of reference which, while relatively concise, will be genuinely useful to microbicide researchers, product sponsors, drug regulators and funding agencies. I have drawn on the reports of a series of technical consultations on microbicide science and regulation convened between 2002 and 2008 by the World Health Organization and other leading agencies in the field, and I am most grateful to the authors of those reports (Annex 1) and to the many experts who contributed to the discussions on which they are based (Annex 2). While the present document is based on these consultations and on numerous discussions over more than a decade, within the International Working Group on Microbicides and with many individuals, I have tried to ensure that, as far as possible, it is up to date and reflects current thinking.

I wish to thank the World Health Organization and CONRAD for their support during the course of this work. However, this document does not necessarily represent the views, decisions or policies of the World Health Organization, CONRAD or any other institution.

Alan Stone
London, December 2009

Executive summary

Background

The development of microbicides that individuals can apply vaginally or rectally to protect against infection with HIV and other sexually transmitted pathogens is the aim of intensive research being pursued in many countries. One of the numerous challenges that the microbicide field has had to face is a lack of clarity about regulatory requirements for product development and licensure. In response to this, the World Health Organization (WHO), in collaboration with other leading agencies in the field, and with the support of many international experts, launched a series of technical consultations (Annexes 1 and 2), whose aims were to review microbicide science, identify minimal regulatory requirements and explore ways of strengthening regulatory capacity in low-income countries. The present document draws on the reports of those consultations and other discussions.

Regulatory authorities

For many national regulatory authorities (NRAs), microbicide development is a new area, although several have given considerable thought to microbicide regulation and have engaged in productive debate with the field. While the formal remit of the United States of America (USA) Food and Drug Administration (USFDA) is the protection of USA citizens, the agency's perspectives, and to a lesser extent those of the European Medicines Agency (EMEA), are influential much more widely, and regulators in many countries take account of their position. While it is valuable for NRAs in the developing world to be aware of international processes and recommendations, it is important that they are guided primarily by scientific data considered in the light of local risk–benefit analysis. Their capacity to do so can be enhanced by regional collaboration, resource-sharing and training. WHO and EMEA are prepared to support these processes by providing independent scientific and technical advice.

HIV-prevention technologies

Male condoms, if used correctly and consistently, offer a high degree of protection against human immunodeficiency virus (HIV), but they have had only limited impact on the HIV/AIDS (acquired immune deficiency syndrome) epidemic, largely because they have been insufficiently used in the regions most affected. Some of the newer prevention methods being investigated have so far proved disappointing. These include the use of aciclovir to prevent the acquisition of HIV in people infected with herpes simplex virus type 2 (HSV-2), thought to be a cofactor in HIV transmission; using the diaphragm to protect the cervix; and the development of anti-HIV vaccines, where progress has been slow. On the positive side, trials of male circumcision have demonstrated a 50% or greater reduction in HIV acquisition by circumcised men compared to uncircumcised men. However, the evidence so far indicates that male circumcision does not reduce the risk of HIV transmission to women. Several ongoing studies are evaluating oral pre-exposure prophylaxis (PrEP) with antiretroviral drugs. Microbicide research itself has also suffered some setbacks. It is noteworthy, however, that microbicide science has advanced considerably over the past decade and the field as a whole is far better coordinated than before.

Microbicide candidates

A diversity of microbicide candidates continues to advance through the development pipeline (Annexes 3 and 4). The first generation of products, many of which looked promising in the laboratory and in early human studies, met with little success in large-scale randomized clinical trials to evaluate their protective effectiveness. The surfactant nonoxynol-9 was the first candidate microbicide to be the subject of such a trial. Unfortunately, it turned out that the women receiving nonoxynol-9 gel were at higher risk of HIV than those receiving a placebo gel. Another surfactant-based microbicide, Savvy, also failed to protect, as did BufferGel, an acid-buffered gel intended to reduce the risk

of infection by maintaining the vagina's acidic pH. Several polyanions have been intensively investigated as potential microbicides. In laboratory studies, these compounds work by blocking the attachment of HIV to its cellular receptors. Three of them, carrageenan, cellulose sulphate and PRO 2000, have been the subject of large-scale trials to evaluate their clinical effectiveness. Unfortunately, all failed to demonstrate a protective effect.

Considerable attention is now focused on second-generation products – antiretroviral drugs initially developed for therapeutic use, including inhibitors of HIV reverse transcriptase and HIV-specific entry and fusion blockers. They may be formulated as gels for topical use or, depending on drug chemistry, loaded into intravaginal rings for sustained release. Several such products are in various stages of preclinical and clinical development. Combination microbicides are also being investigated. These could, in principle, exhibit greater potency and a broader spectrum of activity than single-agent microbicides and may also reduce the chances of HIV resistance being a problem.

Non-clinical studies

Table 1 (page 15) summarizes the non-clinical investigations that regulators may require, although it is important to note that not all of these studies may be relevant to a given candidate microbicide. It is strongly recommended that the relevant regulatory authorities are consulted, at an early stage of any microbicide-development programme, about the kinds of investigation they are likely to require.

Chemistry, manufacturing and controls

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has provided guidelines on good manufacturing practice (GMP) and on the characterization of the drug substance and formulated product, their quantitative composition, acceptable limits, and methods for evaluating their identity, strength, quality, purity and stability.

Formulation and delivery systems

A diverse array of microbicide formulations includes gels, tablets, soft-gel capsules, films, and intravaginal rings. Prefilled, single-use, disposable plastic applicators have proved convenient for microbicide clinical trials, where participants insert the gel either daily or a short time before sexual intercourse, but there is also a need for long-acting products. Intravaginal rings could provide sustained release of the active agent for 28 days or longer and may make it easier for users to adhere to product use both in clinical trials and in ongoing use. Microbicide-loaded diaphragms and sponges are also being explored as potential delivery devices. Work on developing formulations and applicators specifically for rectal use is continuing.

Clinical studies

As with many other aspects of microbicide development, clinical testing is evolving rapidly and important lessons are being learned. Table 2 (page 23) summarizes the clinical studies that regulators may require, although it is worth repeating that developers should consult the relevant regulatory authorities as to their specific requirements. With regard to what clinical trial outcomes should constitute an acceptable case for product registration, there needs to be sufficient flexibility to allow account to be taken of the risk–benefit ratio in the particular region concerned.

Ethics, community involvement and institutional review boards

It is important for researchers, trial participants, communities, regulatory authorities and other stakeholders to clearly define and reach agreement on the responsibilities of each party with regard to such matters as informed-consent procedures, confidentiality, participant autonomy,

compensation and the provision of an appropriate standard of reproductive health services and HIV-related care. Institutions directly involved in clinical studies take advice from institutional review boards (IRBs) charged with approving, monitoring and reviewing the research.

Independent data-monitoring committees

The independent committee's task is to consider, in confidence, unblinded trial data at intervals throughout the course of the trial. On each occasion the committee must make a recommendation to either continue the trial, modify it, or stop it on the grounds of adequate evidence of benefit or harm or, in some trials, futility.

Pharmacovigilance

Pharmacovigilance of a new product continues well beyond the phase III trial stage of its development. Once a microbicide has been licensed and is on the market, a systematic programme of surveillance will be put in place. Its purposes are to assess long-term safety with frequent use, satisfy regulatory requirements, control risk and evaluate public health impact. Labelling and package inserts will be monitored to ensure that they present appropriate messages. These activities are among the NRA's responsibilities, and it is also up to the NRA to consider if and when the product should be granted over-the-counter status.

Background

Microbicides are anti-infective preparations formulated for vaginal or rectal use, which individuals will be able to apply to protect themselves and their sexual partners from infection with *Human immunodeficiency virus* (HIV) and other sexually transmitted infections (STIs). Throughout the 1990s, microbicides were increasingly recognized as a potentially important preventive technology, but their development was constrained by political factors, scientific and clinical challenges, and inadequate human and financial resources. Support for microbicide research and development has increased over the past few years, as has the number of private, non-profit and public-sector entities working on microbicides. As a result, more microbicide candidate compounds and products are coming on-stream and advancing from the laboratory into clinical testing. The development of safe, effective, acceptable and affordable microbicides is now the aim of intensive research being pursued in many countries.

As with any new medical approach, one of the many challenges that the microbicide field has had to face is a lack of clarity about what regulatory requirements are applicable at different stages of development, and what data are needed for licensure. This is a complex matter, not least because of the divergent risk–benefit ratios between industrialized countries, where most of the non-clinical development of microbicides is currently taking place, and developing countries, which have the highest incidence of HIV, where large effectiveness trials must be carried out, and where the primary beneficiaries of any successful product reside. These trials must proceed notwithstanding the logistic, social and ethical challenges of enrolling and caring for many thousands of volunteers in low-income countries that are often still in the process of developing adequate capacity to oversee clinical research and license new products. Further regulatory complexity is added by the fact that some microbicides may be contraceptive as well as anti-infective. There are also safety issues related to the possibility that a microbicide designed for vaginal use may find its way into the rectum, inadvertently or otherwise.

In response to this, The World Health Organization (WHO), in collaboration with other leading agencies in the field and with the support of international experts, launched a series of technical consultations in Europe, Africa and Asia (Annexes 1 and 2). The first meeting was held in Villars-sur-Ollon, Switzerland, in March 2002 and sought to identify the minimal regulatory requirements, based on scientific and technical considerations, for the approval of microbicide clinical trials and, eventually, for product licensure. Subsequent consultations were held in regions where HIV/AIDS (acquired immune deficiency syndrome) is a major problem, so that representatives from countries in those regions could play a full part in the discussions: in Gabarone, Republic of Botswana (November 2002), in New Delhi, India (November 2004), in Muldersdrift, Republic of South Africa (June 2005), again in New Delhi, India (November 2007) and in Nanjing, People's Republic of China (November 2008).

The broad goal of these meetings was to promote focused dialogue among concerned international scientists, regulators and policy-makers, in order to anticipate and possibly alleviate constraints to progress in the microbicide field. The specific objectives of successive meetings were marginally different but they had the following aims in common:

- to familiarize representatives of national drug regulatory authorities (NRAs) with the microbicide field through reviewing scientific knowledge, and to provide an opportunity to exchange views, share experiences and address concerns;

- to review regulatory requirements relevant to microbicides in key countries in the different regions, to identify how best to facilitate rigorous regulatory review for clinical trials and product licensure, and to consider mechanisms through which WHO might provide enhanced support to regulatory processes;
- to review and discuss alternative regulatory pathways for microbicides, including WHO's prequalification procedures, Article 58 of the European Medicines Agency (EMEA), and regional regulatory harmonization initiatives;
- to move toward an international consensus on minimal prerequisites for all microbicide research and development phases, from discovery to licensure and post-market monitoring, taking into account country-level variability in burdens of disease, conditions for clinical trials and product use, regulatory structures and ethical principles of justice and beneficence.

Regulatory authorities

NRAs play a vital role in ensuring that the drugs and medical devices on the market are safe and effective and that the claims made for them have been properly substantiated. They are responsible for setting standards and for the oversight of clinical research, product licensure, marketing, labelling and distribution, and for conducting post-marketing pharmacovigilance to ensure that products continue to meet their intended performance. NRAs are also responsible for deciding whether a drug should be available on prescription only or, at some stage, over the counter (OTC). The effective oversight of product development, manufacturing and distribution is leading gradually to mutual recognition between NRAs.

In the microbicide field, the challenge for NRAs has been, and remains, to find an appropriate balance between the urgent need for effective prevention options and the regulators' overriding duty to ensure that products are safe. Naturally, the field fully recognizes the paramount importance of safety. At the same time, there is a need for regulatory requirements to be interpreted with sufficient flexibility to allow progress to be made in the face of the complex logistic realities and ethical imperatives inherent in microbicide clinical trials.

Microbicide development is a relatively new field for many regulatory authorities. Some, however, have given considerable thought to microbicide regulation and have engaged in productive debate with the field. This is true, for example, of the United States of America (USA) Food and Drug Administration (USFDA), South Africa's Medicines Control Council (MCC), EMEA and Thailand's Food and Drug Administration, in whose territories microbicide researchers have been active for many years; it is also true of the Drugs Controller General of India. Moreover, some NRAs have undergone significant reforms to enhance capacity, streamline processes and facilitate review, and several now have mechanisms for fast-tracking review and approval for products related to prevention, diagnosis and treatment of HIV/AIDS, including microbicides.

The USFDA is among those authorities that have established fast-track mechanisms. In the case of a marketing application based on data from a clinical study conducted outside the USA, this is acceptable provided the trial was ethical, well designed and conducted to defined good clinical practice (GCP) standards. The USFDA must be able to validate the data through on-site inspection if deemed necessary. If data from outside the USA are used as the sole basis for a marketing submission, they must be applicable to the US population; bridging studies (safety and tolerability) may be needed. This facility is, of course, critical for microbicides because the USA lacks high-risk communities large enough on their own to sustain an effectiveness trial. Moreover, once a microbicide has been

shown convincingly to be successful in one part of the world, it may be unethical to undertake a similar evaluation subsequently anywhere else. The importance of accepting data from effectiveness trials carried out elsewhere is not unique to the USA. It applies also to NRAs in Europe and in many developing countries.

The formal remit of the USFDA is the protection of USA citizens, but the agency's perspectives on microbicide regulation, and to a lesser extent those of the EMEA, have wider influence, and regulators in many countries, including those that have limited regulatory capacity of their own, are influenced by their position. While this is understandable, the fact remains that the greatest need for microbicides is in high-incidence settings in the developing world. It is therefore important that the deliberations of NRAs in such regions, while taking account of international regulatory processes and recommendations, are guided primarily by the actual data on a product's safety and effectiveness, considered against the scale and nature of the local HIV/AIDS situation, and an analysis of the potential risks, benefits and costs of introducing the product.

In order for NRAs to undertake their task effectively and reliably, many of them will need to be substantially strengthened. This can be achieved through closer regional collaboration, resource-sharing and training, as is indeed happening within the Southern African Development Community (SADC) and the Association of Southeast Asian Nations (ASEAN). WHO and EMEA are prepared to support these processes by providing independent scientific and technical advice.

Sub-Saharan Africa, the epicentre of the AIDS epidemic, is host to numerous HIV-prevention trials, including those for microbicides, and it is salutary to note the procedures and requirements of South Africa's MCC. The regulatory process is driven by scientific considerations and emphasizes relevance to the country's needs and the protection of trial participants' rights and safety. In assessing applications for conducting a microbicide trial, attention is given to the clarity of the trial protocol, details of the informed consent process and plans for community consultation and involvement, and any proposals for enrolling adolescents. Applications must also include data from all previous microbicide trials, whether with positive or negative outcome, giving the reasons why any trials were stopped before completion. Protocols should include clear, specific standards and processes for providing care for participants who become HIV infected during the trial, and for managing practical issues such as the use of the product with tampons or female condoms, during menses, or in multiple acts of sexual intercourse per day. The MCC has the authority to halt a trial, once started, on the grounds of problems with good manufacturing practice (GMP), GCP, ethical issues or other concerns.

The MCC's drug-registration requirements are similar to those of other regulatory authorities and include preclinical and clinical evidence of safety, efficacy and quality. Because of the burden of HIV/AIDS in the region, sponsors may request fast-track status for microbicides and, if it is granted, a decision will be given within nine months. The benefits of a partially effective product are weighed against the burden of disease, other prevention approaches, and the product's safety profile. As with all new chemical entities (NCEs) whose safety profile is incomplete, a new microbicide is likely to be registered with the condition that a risk–benefit plan is put in place to facilitate close monitoring (pharmacovigilance) for a specific period, to detect any safety issues that may not have emerged in the course of the clinical trials.

Alternative regulatory pathways

Clearly, in countries where regulatory capacity is limited, arranging for clinical trial approval and oversight and for product registration poses difficulties. In such cases, the researchers

responsible for international trials, and health-policy officials of the countries concerned, have the option of seeking advice from the USFDA and EMEA. The USFDA will review products under their investigational new drug (IND) procedures even if the trial is conducted solely outside the USA.

The EMEA will only consider new drugs and vaccines for registration if the developer intends to market them in European Union (EU) countries. Notwithstanding this, under Article 58, EMEA, in cooperation with WHO, will provide a scientific opinion on a new medicinal product intended for markets outside the EU and will provide guidance based on a risk–benefit assessment in the countries concerned. This procedure follows the same pattern as for licensure of drugs intended for EU markets and includes a mechanism for ensuring ongoing regulatory oversight. Batches of product will be tested in the same way as drugs intended for marketing in EU countries, and a certificate of quality will be issued. It is important to note that these arrangements apply to drug registration, not to the regulatory aspects of clinical trials.

WHO's prequalification programme involves close cooperation with NRAs and partner organizations in evaluating the quality, safety and efficacy of medicinal products on the basis of information provided by the manufacturers, as well as inspection of the corresponding plant and clinical sites. The programme also engages in staff development for NRAs and with quality-control laboratories and manufacturers, so that priority medicines of high quality can be widely available to those who need them.

HIV-prevention technologies

HIV/AIDS is one of the leading causes of death in many developing countries, especially in sub-Saharan Africa. Several large, populous countries like India, China and Russia are also experiencing the spread of HIV/AIDS on a significant scale and are currently at a critical point where increased prevention could help to avert a full-blown epidemic. Without a cure for HIV infection, there is a pressing need to expand the range of available preventive methods. In 2008 there were three new HIV infections for every one person commencing AIDS treatment *(1)*, highlighting the critical importance of prevention in the context of the AIDS epidemic overall. Male condoms, if used correctly and consistently, offer a high degree of protection against infection during sexual intercourse. In reality, however, they have had limited impact on the global epidemic, partly because of inadequate availability in some settings and partly because they have been insufficiently used in the regions most affected, especially in sexual intercourse between married couples and other long-term partners. Interest in the female condom is being re-energized with the development of new and less expensive products, but the eventual impact of this approach is difficult to predict.

There have been some setbacks in the ongoing quest for new prevention methods. The use of aciclovir to prevent the acquisition of HIV in people infected with Herpes simplex virus (HSV-2), a cofactor in HIV transmission, failed to show a protective effect *(2)*. A trial to find out whether employing a diaphragm to protect the cervix might reduce the risk of HIV infection was also disappointing *(3)*. Progress in the anti-HIV vaccine field has been slow, encouraging researchers to focus afresh on relevant basic science *(4)*. On the positive side, several trials of male circumcision have been markedly successful. For example, in a randomized clinical trial carried out in the Rakai district of Uganda, HIV acquisition by circumcised men was 51% lower than in uncircumcised men *(5)*. Unfortunately, the evidence to date indicates that male circumcision does not prevent HIV transmission to women. Several ongoing studies are evaluating oral pre-exposure prophylaxis (PrEP) using the antiretroviral drugs (ARVs) tenofovir or tenofovir/emtricitabine (Truvada) in different

populations and settings *(6)*. Work in this area has regained momentum since it suffered a setback when several oral tenofovir trials were stopped in 2005.

Microbicide research itself has also suffered some setbacks. Of the handful of effectiveness trials so far terminated or completed, only one, the HIV Prevention Trials Network (HPTN) 035 trial, provided a weak indication that one of the candidate microbicides being evaluated, the polyanion PRO 2000, might confer a measure of protection, but a larger trial of the same product, the Microbicides Development Programme (MDP) 301 trial, showed definitively that it did not.

It is noteworthy, however, that microbicide science has advanced considerably over the past few years. We now have a better, although still incomplete, understanding of the diverse mechanisms by which HIV can be transmitted sexually, including the importance of R5 strains of the virus in sexual transmission, that is, those strains that use as co-receptor the CCR5 chemokine receptor on the surface of the target cell, rather than the CXCR4 chemokine receptor. Novel drugs that intervene at various stages of the virus' life-cycle are being evaluated as vaginal microbicides, including inhibitors of HIV reverse transcriptase and molecules that attach to and block the virus's access to its co-receptors. Ideas about microbicide clinical trial design are evolving and there is a good degree of consensus about handling the contingent ethical issues. The field as a whole is far better coordinated.

Microbicide candidates

A diversity of microbicide candidates continues to enter and advance through the development pipeline (Annexes 3 and 4), although, as in any pharmaceutical endeavour, many of them will be discarded along the way. The list includes molecules intended to prevent mucosal infection by HIV through one or more of a variety of mechanisms of action. These include:

- gels that provide a physical barrier to the virus and/or that, by their lubricating effects, reduce physical trauma to the mucosa during sexual intercourse;
- agents that maintain and enhance normal vaginal defences, including low pH and the presence of lactobacilli (which produce lactic acid and hydrogen peroxide);
- chemicals that cause the disintegration of, or damage to, the viral envelope or the glycoprotein (gp)120 "spikes" needed for attachment to the host cell;
- anti-HIV antibodies;
- agents that block the attachment of gp120 to the virus' receptors and co-receptors on the surface of the target lymphocyte;
- agents that inhibit HIV attachment to, and transportation by, dendritic cells;
- ARVs that prevent intracellular HIV replication;
- agents that may reduce the risk of HIV infection by lowering STI-transmission rates.

The first generation of microbicides to be evaluated in large-scale randomized clinical trials met with little success. Among them was nonoxynol-9, marketed as a vaginal spermicide in many countries for several decades. It is a surfactant that damages the virus' lipid outer envelope. This agent was shown to be very effective against HIV in vitro and there were strong indications of protection in rhesus macaques (*Macaca mulatta*) challenged vaginally with *Simian immunodeficiency virus* (SIV), the simian equivalent of HIV. Unfortunately, a randomized controlled clinical trial to evaluate its protective effect in women showed that those who received the surfactant as a gel were at *higher* risk of HIV than those receiving a placebo gel *(7)*. There were clear indications that this was because

the compound caused lesions in the protective barrier constituted by the mucosa, especially in those women who used the product frequently, allowing the virus easier access to epithelial and subepithelial lymphocytes. It is now accepted that nonoxynol-9 can result in substantial damage to both vaginal and rectal epithelia *(8)*. The clinical evaluation of Savvy, another surfactant-based microbicide, also had a disappointing outcome *(9)*. BufferGel, an acid-buffered gel intended to reduce the risk of infection by maintaining the vagina's acidic pH, similarly failed to show protection in a clinical-effectiveness trial *(10)*.

Several polyanions have been the subject of intensive investigation as potential microbicides. Some of these looked promising on several grounds. In vitro they prevented HIV infection by blocking the attachment of HIV to its cellular receptors and also showed activity against some other STI pathogens. They showed a good level of protection in the macaque-challenge model. They are not cytotoxic, and tests in animals and in the clinic revealed no damage to the genital epithelium. Because they are large molecules, they are not systemically absorbed. They are inexpensive, and some are contraceptive. However, clinical trials of three polyanions: Carraguard (a carrageenan product derived from seaweed) *(11)*, cellulose sulphate *(12)* and PRO 2000 (a synthetic polymer of naphthalene sulphonate) *(13)*, showed they did not offer protection against HIV. PRO 2000 was evaluated in two effectiveness trials, the first, HPTN 035 *(10)*, being a phase IIb trial and the second, MDP 301 *(13)*, being a phase III trial (see Table 2, page 23 for definitions of trial categories). In the smaller trial, the women who had received PRO 2000 showed a 30% reduction in HIV incidence compared to those allocated to placebo. However, the overall numbers of HIV infections were small and the observed reduction in incidence was well outside the conventional level of statistical significance (see page 24). Nine months later, in December 2009, the larger trial concluded definitively that, while PRO 2000 was safe to use, it did not reduce HIV incidence.

Considerable attention is now focused on a new generation of candidate microbicides, particularly certain ARVs initially developed as actual or potential therapeutic agents. Many of these drugs have well-documented safety and efficacy data from extensive testing and from their use in treating HIV-infected patients. As candidate microbicides they are formulated as gels for topical use, and some are suitable for loading into intravaginal rings for sustained release. This class of microbicide includes drugs that block the action of the virus' reverse transcriptase, such tenofovir, a nucleoside reverse transcriptase inhibitor (NRTI), and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) UC781, dapivirine and MIV-150 *(14)*. Applied vaginally, they are absorbed into the genital mucosa and will accumulate in the epithelial lymphocytes that HIV targets. Laboratory studies and therapeutic experience with these agents have provided a wealth of information on the emergence of drug-resistant HIV strains, and before microbicides based on them are widely introduced it will be necessary to determine the degree of drug resistance, if any, that may be anticipated, and also the likelihood of toxicity (to the woman and also to a fetus if she is pregnant). These are fully recognized as challenges to be faced in developing these products, and relevant research is under way. Naturally, specific anti-HIV agents such as these are not active against other STIs.

HIV-specific entry and fusion inhibitors are also being explored. Some act on the virus before it reaches its host cell, for example by binding to gp120 or to gp41. Examples are cyanovirin, FI peptides and DS003, but all of these are peptides and can be difficult and expensive to prepare. Others act on the target cell, specifically blocking the CCR5 chemokine receptor on the lymphocyte's surface, the co-receptor for R5 strains of the virus. This class of drug includes maraviroc, PSC-RANTES

and DS001. As they are specific for CCR5, they do not have activity against X4 strains of HIV, which use a different as co-receptor, CXCR4, so ideally these products will be used in combination with other agents.

Just as drug combinations are preferable to single drugs for HIV therapy, combination microbicides, especially combinations of agents that intervene at different points in the virus' life-cycle, could, in principle, exhibit greater potency and a broader spectrum of activity than single-agent microbicides. They may also reduce the chance of HIV resistance being a problem, because an individual virus is much less likely to develop mutations conferring resistance to two different agents rather than to one agent. Moreover, if, as a result of synergy, it proves possible to use lower concentrations of each active ingredient in comparison to using the agents singly, the likelihood of toxicity would be reduced. There are, however, a number of challenges in developing combination products, including possible difficulties in formulating two or more active pharmaceutical ingredients (APIs) together, the potential for toxicity, complexities in organising agreements among multiple companies and institutions, perhaps higher cost, and an evolving regulatory pathway.

Consultations on regulatory issues in microbicide development

One of the main objectives of the 2002–2008 regulatory consultations was to identify scientific parameters on which microbicide regulation should realistically be founded, and to consider what studies, in the laboratory and in the clinic, could best provide the scientific data required. These issues are discussed below. Recommendations concerning the *non-clinical* development of microbicides were published some years ago by the International Working Group on Microbicides *(15)*, and the USFDA has issued an informal communication covering this topic *(16)*. The International Working Group on Microbicides has also published recommendations concerning the *clinical* stages of microbicide development *(17)*, and other published sources are useful for reference purposes *(18, 19)*. The EMEA has not issued recommendations with respect specifically to microbicides, and developers should refer to that agency's general guidance on the non-clinical *(20)* and clinical *(21)* development of medicinal products for human use.

Non-clinical studies

Within the category of *non-clinical* studies, some, termed *preclinical*, are essential for filing for the approvals needed to proceed to human studies in clinical settings. The remainder may not be needed until the clinical phases of development have begun. Like any drug or vaccine, before a candidate microbicide can proceed to testing in human subjects it is necessary to collect adequate data on the product's safety and activity from in vitro studies and animal models. The core question is how to define adequate; that is, what kinds of data, both qualitative and quantitative, and what degree of precision, should be required by those charged with overseeing the research and by national regulatory authorities. It is recognized that there may be significant differences between the requirements of regulatory authorities, who are primarily concerned with product safety, and additional data that a product sponsor may need to help decide whether to continue to develop a particular entity.

Some non-clinical investigations undertaken by developers are still in the experimental stage; their relevance to product safety and efficacy is unclear and it would be counterproductive at this stage to afford them regulatory significance. One example of this is the non-human primate model for studying microbicide efficacy. It needs to be

better understood, improved, standardized and validated against clinical outcomes before it will be feasible to use the findings to predict how potential microbicides are likely to behave in human sexual transmission.

Another example is work on cytokine-release patterns in response to microbicides. While the presence or increased levels of certain cytokines may be associated with an inflammatory response, others may not, and unusually *low* levels of cytokines may be an indication of cell death. A further example concerns laboratory studies to find out whether a given microbicide prevents a specific route of mucosal transmission, e.g. the dendritic cell (DC-SIGN) HIV attachment and transport mechanism. The existence of this route has been clearly demonstrated in laboratory studies, but until its significance in human sexual transmission is understood it cannot be a regulatory requirement.

It is important to note that not all of the investigations discussed below may be relevant to a given candidate microbicide; the studies actually to be undertaken need to be selected rationally. For example, if a compound is poorly absorbed though the genital epithelium and reaches only very low systemic concentrations, it may not be necessary to undertake a detailed metabolic profile in animals, or drug-interaction and drug-excretion studies.

With regard to local safety, if the results of the rabbit vaginal irritation test are satisfactory, skin-sensitization tests in other species such as guinea-pig or mouse may be superfluous. An existing chemical entity designated by regulators as generally regarded as safe (GRAS) may not need to undergo some of the preclinical studies required for a NCE. Such exceptions should be discussed with regulators on a case-by-case basis. In any case, it is strongly recommended that the relevant regulatory authorities are consulted at an early stage of any microbicide-development programme about the kinds of investigation they are likely to require.

Activity

The fundamental concept underlying microbicides is that they will somehow inactivate viral and/or bacterial pathogens, or prevent them from infecting by some other mechanism. Thus, the first preclinical steps utilize a series of in vitro screening tests to demonstrate the activity of the candidate compound against HIV and other pathogens of interest, and then to explore that activity under a range of relevant conditions. Given that microbicides need to be active at the time of sexual intercourse, their activity in the presence of semen, cervico-vaginal and rectal secretions, and blood, and at different pH levels, needs to be investigated.

Cell-based in vitro assays, and ex vivo human vaginal, cervical, rectal and penile tissue explants can be used to characterize the candidate compound's activity profile, establish dose–response relationships, define a compound's therapeutic index (i.e. the ratio between its activity and its cytotoxicity) and explore its mechanism of action. Some approaches allow the assessment of anti-HIV activity and cytotoxicity simultaneously in vitro, to identify the lowest effective concentration and the highest concentration where the level of cytotoxicity is judged to be still acceptable. A range of HIV clades and strains should be used, including standard laboratory strains and clinical isolates derived from the lower reproductive tract, both R5 and X4 strains. Effects of the compound on both cell-free and cell-associated virus should be investigated. Specific assays may be used to study the effect of the microbicide on viral integrity, on its attachment to cellular receptors and co-receptors, and on its replication. Genetic and biochemical studies can also help to establish the mechanism of action and throw light on the potential for reduced activity due to resistance mutations.

Explant models and reconstituted epithelia are suitable for evaluating both the API and the formulated product. Developers also need to assess the effects that products may have on other microorganisms such as the normal vaginal flora and STI pathogens, and on spermatozoa. A compound's activity against *N. gonorrhoeae* and *C. trachomatis* can be assessed in cultures of these organisms growing, respectively, on agar plates or in suitable human cell cultures. Activity against HSV-2, the virus responsible for genital herpes in humans, can be studied both in vitro and in the mouse vagina and rectum.

Animal models may also be used for studying the potential efficacy of microbicides against HIV infection. The rhesus macaque vagina and rectum are used with SIV or Simian human immunodeficiency virus (SHIV, a genetically engineered hybrid), the mouse vagina and rectum with HSV-2, and the vagina of the Hu-SCID mouse with HIV (that is, an immunocompromised mouse reconstituted with elements of the human immune system).

Until we have a microbicide that is known to be safe and effective in humans, it is not possible to validate these models of microbicide efficacy; at present their significance and predictive value for humans is not known. As a result, there is a continuing debate about the role of such investigations in deciding whether a candidate microbicide should be advanced into clinical studies. The demonstration of efficacy in the macaque model is encouraging, although not necessarily predictive. However, the failure of a product to protect macaques in a well-conducted study may be a sign that the product is unlikely to work in humans *(22)*.

Safety

Toxicological investigations are required to identify any adverse local or systemic effects of the microbicide. Some of the more standard toxicology studies are described in the next section.

General toxicology

The purpose of these studies is to establish the effects of the agent on general health and behaviour. The sequence begins with acute (one-day) oral or parenteral dosing in one rodent and one non-rodent species. This is to identify the no-effect level and the maximum tolerated dose. These studies are followed by longer-term investigations comprising daily dosing for 14 days to 3 months or longer (longer than the proposed duration of a phase I clinical trial). These investigations should test the predetermined no-effect level and maximum tolerated dose, and an intermediate dose, via the proposed route of human administration (in the case of microbicides, vaginal or rectal), using the same formulation that is anticipated for clinical trial use. For a NCE, it is also prudent to fully characterize its toxicity profile over an adequate period using an oral or other parenteral route of administration in order to ensure sufficient systemic exposure. Studies to detect any overt effects on behaviour, or on the nervous, cardiovascular and respiratory systems, are usually conducted in the rat and the dog. An assessment of toxicity related to the reproductive organs, for example the fallopian tubes, should also be carried out. Prior to a phase III trial, longer-term chronic toxicity studies should be conducted, for six months in a rodent species and nine months in a non-rodent species.

Pharmacokinetics

Precise requirements for pharmacokinetic studies of absorption, distribution, metabolism, and excretion (ADME) following vaginal or rectal administration in animals will depend on the specific product being evaluated and the views of particular regulatory authorities. These investigations are especially important for readily absorbed small-molecule compounds, although in some cases they may

also be required for large molecules. They may be carried out in a subset of animals set aside during the general toxicology studies: drug levels in blood, tissues and organs are monitored during and after prolonged and repeated dosing, and metabolic and excretion profiles determined.

Local toxicity

The standard rabbit vaginal irritation test involves daily vaginal administration at several doses for 10 consecutive days. Both the formulated drug and the vehicle on its own need to be assessed. The test products may be compared with nonoxynol-9 as a positive control. Vaginas are examined macroscopically and microscopically for signs of irritation, inflammation and ulceration.

The pig-tailed macaque (*Macaca nemestrina*) can also been used for studying vaginal toxicity, although this should not be regarded as a substitute for the well-established rabbit test. This monkey's similarity to the human in terms of its normal vaginal flora (notably lactobacilli which produce hydrogen peroxide and lactic acid, largely responsible for maintaining the natural acidity of the healthy vagina) provides an opportunity to evaluate the effects of microbicides on these organisms.

Local effects on the rectal mucosa also need to be assessed, using rats or mice. This applies not only to microbicides developed for rectal use but also to those intended for vaginal use, which may find their way into the rectum either inadvertently or otherwise. The local lymph node assay in mice may be used to detect hypersensitivity. The guinea-pig skin-sensitization test may be used to assess cutaneous immunogenicity after repeated administration.

If, in the course of any of the above investigations, an adverse effect is detected, an important question is what level of effect, at what dose of product, should be regarded as a "stop" indication for that product's further development? At present there is no obvious answer to this. There is good in vitro and in vivo evidence that the vaginal mucosa acts as a barrier which, when intact, can make it difficult for HIV to reach its target cells, and that if it is damaged there is an increased chance of infection. Thus it would seem reasonable to regard microbicide A, which shows no such effect on toxicological investigation, as potentially safer than microbicide B, which does. But this raises a second – and very important – question: is it possible that the battery of tests applied to microbicide A failed to reveal more subtle, perhaps submicroscopic, damage to the mucosal barrier that could undermine the ultimate value of the product? The question of whether current methods of assessing safety are sensitive enough, or of sufficient duration, to predict the possibility of harm during repeated use in human sexual intercourse over an extended period has been highlighted by recent clinical trial experience *(23)*. As a result, the search for more reliable biomarkers of safety has been intensified, although it is still too early to judge what their eventual regulatory significance might be. Only when safety studies have been validated against clinical data showing that a microbicide or a particular molecular type or mechanism of action reduces or increases the risk of HIV acquisition will it be possible to know whether they have regulatory value.

Genetic toxicity

To evaluate mutagenicity, the standard battery of tests recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) includes a test for gene mutation in bacteria, e.g. the Ames *Salmonella* assay, an in vitro mammalian gene mutation assay or mouse lymphoma thymidine kinase assay, and an in vivo mammalian chromosomal aberration test.

Effects on sperm and fertility

There are several standard in vitro techniques for evaluating the effects of products on human sperm. For safety reasons, and because it is in any case important to know whether a particular microbicide is likely to be contraceptive or not, the microbicide concentrations chosen should include and exceed those intended in the formulated product. Some agents that are not spermicidal may work as contraceptives by other mechanisms (e.g. by blocking the interaction of the spermatozoa with the ovum). This may be investigated in rabbits during mating, to determine the effects of the product on the number and quality of embryos.

Reproductive toxicology

Microbicides will be used largely by women of child-bearing age, so it is important to rule out adverse effects on the woman's reproductive health or on the developing embryo and fetus. Dose-ranging studies in rats are usually performed prior to the initiation of definitive reproductive toxicity studies, to enable the inclusion in the latter of the maximum no-effect dose and the maximum tolerated dose.

Reproductive toxicology is conducted in three stages, defined by the ICH, in various animal species. *Segment 1* studies to investigate the effects of the agent on fertility and on early embryonic development are usually conducted in rats. *Segment 2* studies examine the effects on embryo-fetal development including organogenesis, and are generally carried out in both rats and rabbits. In view of the close proximity of vaginal products to the reproductive organs and to any developing embryo or fetus, and to spermatozoa during and after sexual intercourse, segment 1 and segment 2 studies should be conducted before clinical studies begin. *Segment 3* studies, required for product registration, identify potential effects on perinatal and postnatal development. They are usually conducted in rats and can be undertaken in parallel with, or subsequent to, clinical-effectiveness trials. However, recent experience has shown that a relatively high frequency of pregnancies can occur during clinical-effectiveness trials (even though actual and planned pregnancies are exclusion criteria). In the absence of segment 3 safety data, such pregnancies require discontinuation of product use on safety grounds. In the light of this, there is a growing view that it would be desirable to complete segment 3 studies before effectiveness trials commence, so that product does not have to be withheld during pregnancy.

Carcinogenicity

The possible carcinogenic effect of chronic exposure to a microbicide needs to be assessed prior to market approval. This is normally carried out while the product is in phase III clinical trials. One approach involves dosing mice and rats for two years. An alternative is a 6-month study of dermal application in Tg.AC transgenic mice. The USFDA recommends evaluation of the highest tolerated dose derived from general toxicology studies, the maximum dose feasible for the product in question, or a dose 25-fold higher than the systemic levels expected from human vaginal exposure.

Effects on physical barrier materials

In addition to toxicity testing, compatibility with physical barriers such as condoms and diaphragms needs to be assured. There are standard condom quality-assurance methods for testing structural integrity after exposure to an API or the formulated product. Table 1 summarizes the non-clinical studies discussed above.

Table 1. Non-clinical studies

Test system	Purpose
Activity	
In vitro cell-based assays, at different pH levels and in the presence and absence of semen, cervico-vaginal secretions and blood; human tissue explant systems (vaginal, cervical, penile)[a]	Activity against HIV (laboratory strains and clinical isolates from lower reproductive tract; various clades; R5 and X4 strains; cell-free and cell-associated virus). Dose–response, therapeutic index, mechanism of action (effect on viral integrity, attachment to cellular receptors/co-receptors, replication). Potential for reduced activity due to resistance mutations. Effects of intended excipients
In vitro systems and animal models	Activity against STIs such as *N. gonorrhoeae*, *C. trachomatis*, HSV-2 etc.
In vitro microbiology	Potential adverse effects on normal vaginal flora, especially lactobacilli
Rhesus macaque vagina and rectum[a]	In vivo activity against SIV/SHIV
Mouse vagina and rectum[a]	In vivo activity against HSV-2
Hu-SCID mouse vagina[a]	In vivo activity against HIV
Safety	
General toxicology: vaginal/rectal administration, and parenteral administration for NCEs, in one rodent and one non-rodent species	Effects on general health and behaviour
Pharmacokinetics: vaginal or rectal administration in subset of animals set aside during general toxicology studies	Absorption, distribution, metabolism, and excretion
Local toxicity: Rabbit vagina; mouse or rat rectum; human rectal tissue explants[a]	Local effects of formulated product and vehicle: macroscopic/microscopic examination for irritation, inflammation and ulceration
Pig-tailed macaque vagina[a]	Microbiology
Mouse lymph node assay[b]	Hypersensitivity
Guinea-pig skin[b]	Cutaneous immunogenicity
Genetic toxicity: Ames *Salmonella* assay; in vitro mammalian gene-mutation assay; mouse lymphoma thymidine kinase assay; in vivo mammalian chromosomal aberration test	Mutagenicity
Effects on spermatozoa and fertility: standard in vitro spermatozoa motility/viability tests	Activity against human spermatozoa
Reproductive toxicology:	
Segment 1: studies in rats	Effects on fertility and early embryonic development
Segment 2: studies in rats and rabbits	Effects on embryo-fetal development including organogenesis
Segment 3: studies in rats[c]	Potential effects on perinatal and postnatal development
Carcinogenicity[c]***:*** vaginal application in mouse and rat, or dermal application in Tg.AC transgenic mouse	Possible carcinogenic effect with chronic exposure
Tests with physical barrier materials: standard condom quality-assurance methods	Effect on integrity of condoms

[a] Not a regulatory requirement.
[b] Not required if no inflammatory potential is identified in rabbit vaginal-irritation assay.
[c] Not required prior to human trials but needed for product registration.

Drug-resistant HIV

Given the anticipated use of microbicides on a large scale over a long period, it is inevitable that some breakthrough infections will occur, and, in addition, product may be used by some already infected women. This could in principle lead to the emergence of HIV strains resistant to the product in question, and/or cross-resistance to related products. This important issue is currently being investigated, particularly in the context of NRTIs and NNRTIs as candidate microbicides. While these are administered at much lower doses than for therapy, sufficient drug must, nevertheless, be absorbed into the genital epithelium and accumulate inside the virus' target cells to prevent viral replication, and drug will also be present systemically at low levels. It remains to be seen whether this could select for drug-resistant HIV and, if so, whether this might be a serious problem. The fact that drug-resistant strains often have reduced fitness for replication could be a mitigating factor. Nevertheless, it may turn out to be prudent to prescribe ARV-based microbicides only to individuals who test HIV negative.

Chemistry, manufacturing and controls

The ICH has developed guidelines on the chemical and pharmaceutical quality assurance of drugs, including recommendations on GMP *(24)*. These provide advice on the characterization of the API and formulated product; their quantitative composition; acceptable limits; methods for evaluating their identity, strength, quality, purity and stability; and batch validation and packaging. Defining and ensuring stability is critical, as microbicides will often be stored and used in settings where fairly high temperatures are normal. For microbicides with active biological components, e.g. genetically engineered lactobacilli, antibodies etc., it is also necessary to carry out checks to confirm the biological activity of each manufactured batch before its release. While GMP is not mandatory for non-clinical investigations, including animal studies, it is often more efficient for developers to keep to GMP standards even at this stage, so that the product may later be suitable for use in clinical trials. Developers should also look ahead to manufacturing scale-up under GMP conditions for both the active product and any placebo to be used in larger trials.

Microbicide products for vaginal use do not have to be sterile, but if sterilization is a component of product manufacture, then sterility and endotoxin tests will need to be performed on the final product. For non-sterile products, microbial limits need to be established and the effectiveness of any preservative tested.

Formulation and delivery systems

The aesthetic qualities and affordability of vaginal prevention products are important factors determining acceptability and ongoing use, so both the formulation and the means of delivering it should meet the needs and preferences of a wide range of users. Developers are working actively on a diverse array of vehicles and delivery systems. These include gels, soft-gel capsules, films, vaginal tablets, intravaginal rings and microbicide-loaded diaphragms and sponges. Some of the newer microbicide gels under development can provide active drug for a day or longer.

Several parameters influence which dosage forms may be possible for a given API. The drug's physicochemical characteristics such as molecular size and charge, pH, solubility and stability need to be factored in, as well as any interactions between the drug and the proposed excipients. Pharmacokinetic parameters will also shape what is possible, as will the desired duration of action, user preferences and cost. At present there is no agreed "gold standard" around microbicide formulation.

Delivery systems for microbicides must consistently apply the correct dose and must be safe and convenient to use. So far, the microbicides that have reached the clinical-effectiveness stage of evaluation have been formulated as aqueous gels administered via prefilled, single-use, disposable plastic applicators. Many users have found these to be satisfactory and, indeed, there are anecdotal findings to suggest that both women and their sexual partners often found the gel's lubricant qualities enhanced sexual pleasure. On the downside, there have been complaints about inconvenience, poor retention, leakage, messiness and the difficulties of storing unused applicators and disposing of used ones. Other kinds of microbicide applicator are under development, including user-filled, reusable ones which would be more economic and would diminish the problem of storage and disposal. Low-cost, disposable paper applicators are also being tested. Work on rectal-specific formulations and applicators is continuing.

Up to now these products have been designed for precoital ("coitally dependent") or daily application, but it is increasingly recognized that there is also a need for longer-acting microbicides that will still be protective if applied less frequently. It is primarily with this in mind that the intravaginal ring is undergoing intensive development as a means of delivering microbicides. Several types of flexible, hormone-releasing rings are currently on the market, designed for contraceptive use or to treat menopausal symptoms. They are inserted into the vagina and left in place, usually for 1–3 months. They are of two kinds: a "matrix" type where the API is diffused throughout the material of the ring, and a "core" type where it is contained within an inner annulus. For microbicides, the ring approach has several positive attributes. It could provide sustained release of the active agent – say a NNRTI or a combination of drugs – for 28 days or longer, could separate insertion of product from sexual intercourse, and may make it easier for users to adhere to product use both in clinical trials and in ongoing use. Several phase I studies have been conducted and so far no safety concerns have emerged. Pharmacokinetic and pharmacodynamic data show that a consistent dose of NNRTI is delivered and that the drug levels built up in the genital epithelium should be sufficient to inhibit HIV replication. Acceptability studies are being conducted in a number of settings. Most women find the ring easy to use and, if mass-produced, it could be relatively low-cost on a per-use basis. A constraint that will need to be overcome is the present limited global capacity to manufacture intravaginal rings.

Diaphragms whose structure includes a reservoir for microbicide are also being explored as delivery devices. They have a number of potentially positive attributes. They combine chemical and physical barrier protection; may offer dual protection against pregnancy and HIV/STIs; can hold the microbicide high in the vagina; and may extend the maximum time recommended between gel insertion and sexual intercourse. Women generally find diaphragms easy to use, but they are not widely available in many parts of the world.

The regulatory pathway for these alternative microbicide-delivery devices is evolving.

Clinical studies

As with many other aspects of microbicide development, clinical testing is evolving rapidly and important lessons are being learned. The standard objectives in the traditional drug-development pathway are the determination of safety in phase I, biological activity in phase II, and efficacy in phase III. However, since there are as yet no validated surrogates of biological activity for microbicides (for example equivalent to immunogenicity in the case of vaccines), developers prefer to consider phase II studies of microbicide products as "expanded safety trials".

Before a regulatory authority is prepared to approve the conduct of a clinical trial within the territory for which it is responsible, it is likely to want to examine a detailed dossier of preclinical investigations on the product in question. Moreover, for the proper conduct of microbicide trials, as indeed any clinical trial, adequate infrastructure is crucial, in terms of laboratory, clinical, and data-management capacity. Both the USFDA and EMEA provide guidance on good laboratory practice (GLP) *(25, 26)*, and there are internationally accepted ICH guidelines that spell out what constitutes good clinical practice (GCP) and how to achieve it *(27)*.

Phase I trials

These represent the first step in assessing in humans a microbicide's local and systemic safety, pharmacokinetics and acceptability. Phase I trials are usually carried out in a small number of healthy women volunteers, perhaps 10–30, sometimes more, at low risk of HIV and other STIs. Such trials typically involve insertion of product into the vagina one or more times a day over a period of 1–2 weeks. A similar, comparison group uses the vehicle only, without the microbicide, or an appropriate placebo. Trial end-points include adverse effects on the vaginal and cervical epithelia and on the normal vaginal flora, and systemic absorption (plasma or serum levels), pharmacokinetics, and liver, kidney and bone marrow function. The demonstration of safety after 14 days of exposure may be regarded as a signal to proceed to phase II. These trials can also provide information about the appropriate dose and formulation of the microbicide. Sociological studies address questions about product attributes, ease of use, effect on sexual pleasure, partner dynamics and other issues.

Until recently it was normal to undertake an initial phase I study in sexually abstinent women and then, if safety is demonstrated, to repeat the study in sexually active women. However, there is no good reason why the process cannot be carried out in sexually active women from the start, provided they are not at significant HIV risk and that effective steps are taken to avoid pregnancy. Safety testing in HIV-infected women can proceed once the data from HIV-negative women have been reviewed and safety established. For ARV-based products, however, because of the potential for selection for drug-resistant virus, safety studies in HIV-infected women may best be delayed until effectiveness trials in non-infected women have demonstrated proof of concept.

For identifying signs of local toxicity in phase I microbicide trials, naked-eye inspection through speculum examination of the vulva, vagina and cervical region can be employed as a means of detecting lesions with or without epithelial disruption and with intact or disrupted blood vessels (for example abrasions, oedema, erythema and ulceration). Such evaluation is complemented by colposcopy, at baseline and after exposure to product. Colposcopy serves to detect not only gross damage but also subepithelial and fine vascular damage leading to petechiae and ecchymoses, and provides a basis for independent review, clarification, validation, and classification of observed lesions through the collection of documentary evidence (photographs and digital images), thereby providing a useful record for review by regulators. There are published resources to encourage the standardization of colposcopic procedures and to reduce interobserver error rates in classifying genital findings *(28, 29)*.

Even colposcopy, however, would not reveal microscopic effects that could in principle enhance the risk of HIV infection. Several potentially more sensitive approaches for evaluating local safety are still in the research stage. Histological examination of vaginal biopsy specimens has been employed to assess genital inflammation in some phase I studies among sexually abstinent women, with the biopsies being taken at baseline and after product use *(30)*. Cervical lavage techniques have been used to detect and quantify micro-haemorrhage

below the threshold of visual detection *(31)*. Changes in the pattern of cytokine secretion may indicate pro-inflammatory responses that could facilitate transepithelial viral penetration and replication *(32, 33)*; some reservations about their interpretation have already been referred to. None of these techniques is yet at the stage where it can replace visual inspection for the assessment of local safety. Nor is any required for a regulatory submission.

Care needs to be taken in interpreting the results of these safety studies, because signs of apparent local toxicity may sometimes be due not to the microbicide or the placebo but to lesions resulting from infections, for example with HSV, or from physical trauma caused by the applicator. In the latter respect, it may sometimes be informative to carry out a comparative study in which participants insert unused, empty applicators.

Ancillary studies, not necessarily an integral part of a phase I trial, may include vaginal lavage to investigate the effects of the product on viral shedding in infected women or in tissue explant models, and the assessment of penile toxicity, and monitoring symptoms, signs, systemic absorption and pharmmacokinetics. There are as yet no standard guidelines for male tolerance studies, but a typical study might involve exposing the penis for 6–10 hours a day for seven successive days; the occurrence of rashes and irritation is a potentially important safety consideration and would also affect product acceptability. Magnetic resonance imaging (MRI) technology has been used to investigate gel distribution in the vagina, with and without intercourse, and the product's retention over time in supine and ambulatory women. However, as yet, the relevance of MRI findings to either microbicide safety or effectiveness is unknown and such studies fall outside the regulatory arena.

It has sometimes been claimed that phase I trials should be carried out in the product's "country of origin". However, this is not necessarily so, provided that the test location has the capacity to carry out the trial to acceptable ethical and scientific standards, in terms of informed-consent procedures, suitable laboratory and clinical infrastructure and skills, and effective data-management practices, and provided that the local regulatory authorities and ethical bodies are in agreement.

Placebo

The placebo for all stages of clinical evaluation should be indistinguishable from the formulation containing the API, in terms of appearance, tactile properties, smell and volume. This is necessary to allow the trials to be double-blinded: to avoid possible bias, neither the investigators nor the participants must know which product has been provided to any given individual while the trial is ongoing. The placebo must be tested in appropriate systems to ensure its safety and its lack of activity on HIV and other STI pathogens. A so-called "universal" placebo based on an aqueous preparation of hydroxymethyl cellulose, lacking both anti-infective potency and buffering capacity, has been developed *(34)*.

Rectal microbicides

It is inevitable that the rectal epithelium will sometimes be exposed to a microbicide developed for vaginal use, so all candidate products need to be tested for rectal safety. Moreover, it is recognized that both men and women may wish to use a microbicide during anal intercourse, whether or not the product is labelled for that purpose. Rectal intercourse is a very efficient route of HIV transmission, with a per-act transmission rate between 10 and 100 times greater than in vaginal intercourse. This is due to several factors, including the fragility of the single-layered columnar epithelium lining the rectum and the high prevalence of HIV-sensitive lymphocytes beneath it.

Work on developing rectal-specific microbicide formulations and applicators, and on approaches to evaluating clinical efficacy, is proceeding *(35)*. However, at present there is no formal regulatory guidance or requirements for rectal safety or efficacy of microbicides. Relevant preclinical safety studies can be conducted in human rectal tissue explants as well as in murine and non-human primate models. New methods are being developed for phase I human rectal-safety studies, and such trials are being planned or conducted with several candidate products to establish baseline values for immunological, virological and histopathological parameters that may be affected by a rectal microbicide.

Phase II trials

Phase II trials of therapeutic drugs are normally designed to provide initial evidence of clinical effectiveness. However, a phase II microbicide trial is unlikely to give even a preliminary indication of anti-HIV effectiveness because the number of infection end-points is likely to be too small to permit meaningful conclusions to be drawn.

Phase II microbicide trials are thus best regarded as expanded safety and acceptability studies. Their main objective is to confirm phase I findings in a larger number of participants, say 100–300, with longer exposure to product (2–6 months) and perhaps comparing different dosing regimes. For microbicides based on ARVs, phase II studies can also provide valuable additional PK data.

Phase II trials can be undertaken in low-risk healthy volunteers, but at some point they should be carried out in different types of population, including communities sharing the chief characteristics of the high-incidence communities in which it is intended to conduct phase III trials. Colposcopic examination to detect adverse local effects is carried out either on all participants, or in a subset, with the remainder subjected to naked-eye inspection with speculum.

Adolescent girls

There is some concern about the safety of microbicides in adolescent girls, particularly with regard to any effects of the product on the extensive area of columnar epithelium exposed as a result of cervical ectopy, a normal state in this age group. It is therefore desirable to include some adolescent females in microbicide trials, provided that to do so is within the law of the country concerned, for example in locations where 16-year-old girls are considered old enough to give consent to receive prescribed contraceptives. This question is of interest to regulators, who may require such data to support approval for product use by adolescent females.

Effectiveness trials (phase III and other approaches)

The outcome of a phase II trial will be an important factor in deciding whether a microbicide should be advanced to the next stage of clinical evaluation, whose principal aim would be to assess its safety and effectiveness in a population at high risk of infection. A *phase III* trial is a full-scale, randomized controlled study, with the prevention of HIV infection the primary end-point. Secondary end-points may include infection with *N. gonorrhoeae*, *C. trachomatis*, HSV-2 and a range of other pathogens. Phase III trials also provide important information on long-term safety, and they allow the application of quantitative methods to assessing product acceptability among more participants over a longer time than in smaller-scale trials. Different doses of the same API may be compared in the same study; for example, the MDP 301 trial was designed to compare the safety and effectiveness of 0.5% and 2% PRO 2000 *(13)*. Phase III trials generally also provide important behavioural data, such as condom use dynamics and changes in sexual practices, variables that significantly impact on the use of the product and hence its ultimate effectiveness.

Safety monitoring for local adverse effects of the product is based on reported genital symptoms and gross examination; given the large numbers, it is neither necessary nor practical to employ colposcopy widely during effectiveness trials. Recent experience with phase III trials has highlighted a different, and very important, indicator of potential harm: that is, when an interim analysis of the data reveals a higher HIV incidence in the microbicide arm than in the comparison arm. The difference may be small and not "statistically significant" in the conventional sense, and the basis of it may be obscure *(12)*. Responsibility falls to the trial's independent data monitoring committee (IDMC) to consider the data in context and to decide whether or not to recommend closing the trial (or the relevant part of it in a multi-arm trial).

The basic design of a phase III microbicide trial, in its simplest terms, involves the randomization of a calculated number of HIV-negative women between two arms. Women in one arm are provided with the microbicide, and women in the other a matched placebo. It is sometimes practicable to compare more than one microbicide against a single placebo, and such a multi-arm trial can result in economies of cost, time and human resources. Typically, a phase III microbicide trial may involve 1000–3000 volunteers per arm, followed up on treatment for nine months to two years. Throughout the trial, all women are examined on a regular basis and tested for HIV infection to find out whether those receiving the microbicide are better protected than those receiving the placebo.

Because it is not known whether the microbicide will offer protection, all participants, in all arms of the trial, are given intensive counselling not only on product use but also on HIV risk-reduction. They are provided with condoms and encouraged to use them, and they also receive treatment for STIs (STIs can increase HIV risk). Clearly, any protective benefits of the microbicide will only be observed if, in practice, the consistency of condom use in the trial population is considerably less than 100% which, despite all efforts to the contrary by those responsible for counselling, is often the case.

As the aim of the trial is to demonstrate a statistically significant reduction in the number of new infections, a great number of women need to be enrolled, and this generally involves enrolling participants across several sites. Calculations to estimate the number required will need to take account of factors such as the HIV incidence in the populations concerned, the planned duration of follow-up, the minimum level of product effectiveness[1] to be demonstrated, and the strength of evidence required. Allowances need to be made for an expected drop in incidence as the trial proceeds, for example as a result of safer-sex counselling, the provision of condoms and treatment of STIs. Allowances are also made to compensate for losses to follow-up for whatever reason, and for withdrawals from the study product, for example in the case of adverse events or if a woman becomes pregnant.

It follows that sites for phase III microbicide trials must meet certain criteria, and it is prudent to conduct a feasibility study in each prospective site before the main trial is initiated there. These preliminary studies can assess HIV prevalence and incidence, the pattern of other STIs, women's and men's attitudes to the proposed trial, expectations regarding condom use, the likelihood of enrolling and retaining the required numbers of participants

[1] By convention, a microbicide's *effectiveness* denotes the per cent reduction in incidence actually observed in the circumstances of a particular clinical trial, irrespective of how inconsistently or incorrectly the product is used or other factors that might affect the result. The term *efficacy* denotes the per cent reduction in incidence if the product is used under ideal circumstances, and used correctly in every sexual act. Since full compliance with microbicide use cannot be assured in a phase III trial and self-reported product and condom use is not 100% reliable, phase III trials are not able to measure the *efficacy* of a product.

for the duration of the trial, rates of anal sex and intravenous drug use (potential infection routes that would not be protected by a microbicide in the vagina) and a variety of logistic and infrastructural factors. Because these trials must be conducted in communities with rates of heterosexually transmitted HIV that are high enough to mount a study of feasible size, most suitable sites are located in developing countries. This raises issues about the generalizability of the findings to other settings. The EMEA has recently published its views on extrapolating the results of clinical trials of medicinal products conducted outside Europe to the EU population *(36)*.

A phase III trial may be conducted quite separately from phase II, after the conclusion of the latter and analysis of the data. However, in the interests of speed, efficiency and cost-effectiveness, it may be desirable to make the transition by using the so-called *"run-in"* or *phase II/III* approach. In this, those women recruited in the early part of a phase III trial, say the first 10% of the planned final number, are followed up intensively with frequent and rigorous safety evaluations as for a phase II trial. The findings are reviewed by the trial's IDMC and, subject to the latter's approval, the early participants are incorporated into the larger trial alongside new enrollees.

On financial and logistic grounds, it is not realistic to hope to mount *phase III* trials to test every microbicide candidate that looks promising. *Phase IIb* trials, typically involving 500–800 participants per arm, are powered to obtain *preliminary* evidence of clinical effectiveness and safety and may be employed to compare several microbicides head-to-head against a placebo. Poorly effective products are discarded and sufficiently promising ones may be further evaluated in a subsequent phase III trial powered to meet the strength of evidence required for licensure. If a particular microbicide turns out to be very effective, a phase IIb trial of adequate size may provide sufficient HIV end-points to furnish convincing evidence for a licensure submission without the need for a two-trial scenario. However, it is possible that the phase IIb approach could lead to the elimination of an effective product in error, or to taking a poorly effective product into phase III, and trials need to be designed to minimize these risks. At the time of writing (December 2009), one phase IIb trial, HPTN 035, which evaluated PRO 2000 and BufferGel, had been completed *(10)*, and a second, CAPRISA 004, evaluating tenofovir gel, was in progress *(37)*.

A disadvantage of the phase IIb approach is that the need for a subsequent phase III trial could add to the overall cost and could delay the development of a product by several years. Moreover, an ethical dilemma could arise in moving a product into a further trial if it had already shown fairly clear evidence of effectiveness in phase IIb although not sufficient for licensure. (This could also be an issue even for phase III trials if a second study is needed to provide the strength of evidence required for product registration.)

A further approach is the *"adaptive design"* trial which aims to increase efficiency by eliminating poorer products from a multi-arm study at an early stage and retaining the more successful ones. Such a trial may take one of several forms, of which the following is an example. The trial begins with multiple candidates and their matched placebos. As it progresses, a series of interim reviews of safety and effectiveness identifies less promising candidates, and they and their placebos are dropped according to predetermined rules defined in the trial protocol. The surviving candidates continue to be evaluated, with additional enrolment to increase the trial's power. Again, inferior candidates are dropped and only the best candidate and its placebo are advanced into the

final stage (or the best in each class of product if that is the nature of the trial).

The above studies are all of the blinded, randomized controlled trial design. Once one of these trials has succeeded in proving the microbicide concept and a safe and effective product has been identified, community-based trials and participant-preference studies will be of great value. At present it is not known how these types of trial would be regarded by regulatory authorities.

Table 2 summarizes the clinical studies discussed above. Developers are well advised to consult relevant regulatory authorities about what they would regard as a suitable portfolio of clinical data to serve as a basis for product licensure.

Table 2. Clinical studies

Study	Purpose	Typical study
Phase I trial	Local and systemic safety: adverse effects on the vaginal/cervical epithelia and on normal vaginal flora; pharmacokinetics; dose-ranging studies; acceptability studies	Healthy women (*n*=10–30, sometimes more), sexually abstinent and/or sexually active, neither pregnant nor planning pregnancy, at low risk of HIV and other STIs Comparison group: placebo Product inserted once or several times per day for 1–2 weeks; naked-eye (speculum) and colposcopic examination of the lower genital tract; microbiology; local and systemic absorption, pharmacokinetics, and liver/kidney/bone marrow function; a similar trial in HIV+ women once safety (and also effectiveness in the case of ARV-based products) has been demonstrated
Ancillary studies	Effects of product on vaginal viral load and inflammatory response	Virological and immunological examination of vaginal lavage samples
	Product distribution and retention in vagina/rectum, with and without sexual intercourse	MRI studies
	Penile and rectal toxicity	Symptoms, signs, systemic absorption and pharmacokinetics
Phase II trial	Expanded study of safety and acceptability, perhaps comparing different dosing regimes; adverse effects on genital epithelia; acceptability studies; pharmacokinetics (especially with ARV-based microbicides)	Women (*n*=100–300), neither pregnant nor planning pregnancy, randomized between product and placebo: double-blind; condom promotion and safer-sex counselling for all participants Product inserted once or several times per day for 2–6 months; colposcopy in all participants, or in a subset, with naked-eye (speculum) examination of the remainder

Continued on next page

Study	Purpose	Typical study
Phase III trial	Primary end-point: effectiveness against HIV infection; secondary end-points (not for ARV-based microbicides): effectiveness against infection with *N. gonorrhoeae*, *C. trachomatis* and HSV-2. Long-term safety; long-term acceptability; effects on behaviour	Women (*n*=1000–3000 per trial arm), at high risk of HIV infection, neither pregnant nor planning pregnancy, randomized between product and placebo, double-blind, regular follow-up on treatment for nine months to two years; condom promotion and safer-sex counselling for all participants Local adverse effects based on reported genital symptoms and gross examination in subset; other adverse events; markers of viral and bacterial infections Assess adherence to protocol (e.g. focus groups, questionnaires, sexual diaries, in-depth interviews, used applicator counts)
Phase II/III ("run-in") trial	Saves time and cost of mounting separate phase II and phase III trials, and makes more efficient use of infrastructure	Women recruited to early part of phase III trial (e.g. first 10% of planned final number) followed up intensively with frequent and rigorous safety evaluations, interim analyses by IDMC, then incorporated into phase III trial alongside new enrollees
Phase IIb trial	Powered to give preliminary evidence (definitive evidence if product is very effective) of safety and effectiveness, comparing one or several products head-to-head against placebo. Identifies product(s) that are sufficiently promising to justify evaluation in a subsequent phase III trial powered to meet licensure requirements	Typically 500–800 participants per arm; other aspects as for phase III trial (see above)
"Adaptive design" trial	Starting with multiple candidates and matched placebos, interim reviews for safety and effectiveness allow progressive exclusion of less promising candidates and their placebos; best in each class and its placebo are retained in the trial, with additional enrolment to meet the desired power	Inclusion criteria as for phase III trial (see above)

Level of effectiveness

It is highly unlikely that any clinical trial will show a microbicide to be 100% protective (see footnote on page 21 regarding effectiveness and efficacy), and the products now in the late stages of development may be less effective than some of those developed in the future. This raises the question as to what might be an acceptable lower limit of effectiveness in terms of recommending a particular microbicide for large-scale manufacture and distribution. The answer to this will ultimately depend on several factors, including the scale and dynamics of the HIV epidemic in regions where the product may be deployed, the availability and uptake of other preventive measures in those regions, and economic considerations. It could, however, be

argued that an effectiveness of anything much below 25–30% would be of dubious practical value in most circumstances. This is one reason why most phase IIb and III trials to date have been powered to detect a lower effectiveness level of not less than around 30%.

Mathematical modelling has shown that even at relatively low levels of effectiveness, microbicides could have a major impact on the HIV epidemic *(38)*. It needs to be recognized, however, that if a microbicide is only partially effective, no matter at what level, there will always be a dilemma in reconciling its public health benefit, which may be substantial, with its incomplete protective value to the individual user. At the same time, it should be borne in mind that the level of effectiveness demonstrated in a microbicide trial is likely to underestimate the product's innate efficacy, given that its consistent use for every sexual act by all women in the trial is unlikely.

Strength of evidence

Before approving a product for licensure, the USFDA usually requires evidence from at least two independent pivotal trials, each convincing on its own, traditionally interpreted as each with a two-sided *P* value less than 0.05.[2] The majority of evidence will come from the pivotal trials, but will take into account information from other studies and trials. Furthermore, trials with strong internal consistency would increase confidence in the result, whereas lack of consistency would reduce confidence. Conducting two independent trials more or less at the same time may be feasible, but conducting the trials one after the other may pose insurmountable practical and ethical difficulties, particularly if the first trial showed evidence of protection with a *P* value well below 0.05. Since evidence from two independent trials may not be possible, the question arises as to when a single trial might provide sufficient strength of evidence. Formally, two independent trials each statistically significant at the 0.05 level would provide the equivalent strength of evidence as a single trial that is statistically significant at the 0.001 level.[3] However, requiring a single study to achieve that strength of evidence for a microbicide may be impracticable considering the nature of the end-point: reduction in the incidence of HIV infection. Regulatory authorities might consider licensure based on a single pivotal trial with a *P* value greater than 0.001, but there must be strong internal consistency and good supporting evidence from other sources. The final decision on licensure will take account of the totality of evidence and will not be driven solely by *P* values.

Duration of follow-up

Depending on the trial's design and relevant epidemiological factors, a follow-up period of 12 months may be sufficient to detect a significant protective effect in the trial population. However, to demonstrate long-term safety, and also to demonstrate the durability of the protective effect, regulators may require a more extended follow-up, perhaps two years. Unfortunately, there is often a tendency in these trials for product use and clinic attendance to decline gradually over a lengthy period, leading to a loss of power and possibly to biases between the trial arms. To overcome this difficulty, it may be sufficient to collect long-term safety data in a subset of participants, perhaps those in just one site in a multicentre trial, and to complete follow-up earlier in the majority.

[2] *P* represents the probability that the result could have arisen purely by chance under the assumption that the product has no effect. Thus, a *P* value of 0.05 means that there is a 1 in 20 (5%) probability that a result similar to or more extreme than the one found arose by chance alone (known as a type I error). A *P* value of 0.05 or less is, by convention, regarded as being "statistically significant", and, provided the observed difference is in the direction of protection, is regarded as a statistically significant protective effect.

[3] The chance of making a type I error and falsely concluding effectiveness in two separate trials is $0.025^2 = 0.000625$, corresponding to a two-sided type I error in a single trial of $2 \times 0.025^2 = 0.00125$.

Withdrawals and losses to follow-up

For a variety of reasons, some trial participants will contribute less data than expected. Women may lose interest or may move to a different location and fail to appear for follow-up clinic visits. Some may be withdrawn from product in response to adverse events or pregnancy. All of these will reduce the trial's power. This can be compensated by planned over-recruitment at the outset.

But there is another concern: the loss of woman-years on study may differ between the two arms of the trial, for example if there are subtle differences between the microbicide and the placebo in terms of aesthetic qualities, adverse effects and/or contraceptive efficacy. A significant bias of this kind could lead to difficulties in interpreting the trial's outcome. For this reason, for registration purposes regulators will be looking for a high rate of participant retention throughout the trial and will wish to know the HIV status of participants who leave the trial prematurely. Experience has shown that in a well-run microbicide trial, it is certainly possible to sustain retention rates of over 85%.

Comparison arm

The usual comparison arm in these trials involves an "inactive" placebo that matches the formulated microbicide, and in a multi-arm trial economies can be gained by comparing more than one microbicide against a single placebo, provided it is suitable for "blinding" purposes across all arms.

Some years ago the USFDA raised concerns about the use of placebo as a sole comparator in trials of microbicide gels. First, a placebo gel may not be totally inactive. On the one hand, it may have some direct activity against HIV and other STI pathogens, or it may be a good lubricant during sex, thereby reducing trauma and decreasing the risk of HIV infection. Such a placebo could mask the potential benefits of the microbicide. On the other hand, the placebo might increase HIV risk, giving a false impression that the microbicide is protective. A further concern was that, even if a trial succeeded in demonstrating fewer infections in the microbicide arm than the placebo arm, this might reflect a differential *increase* in HIV rates in both arms, compared to the background rate, as a result of biological and/or behavioural factors associated with the use of either product.

In the light of these concerns, the USFDA indicated that it would like to see at least one microbicide trial that included a "no-gel" comparison arm as well as a placebo arm. The HPTN 035 trial *(10)* included a no-gel arm. The procedure for the no-gel arm was the same as for the other arms, including risk-reduction counselling and condom provision, except that the women were not provided with either the microbicide or the placebo gel. The USFDA argued that this group would provide a baseline HIV rate for comparison purposes. The outcome, in the case of the HPTN 035 trial, was that the numbers of infections in the no-gel and placebo arms were very similar, but had they been significantly different the interpretation of the trial data would have been complicated and might possibly have given rise to misleading conclusions. The no-gel arm is, by its very nature, unblinded, so this design infringes the well-tested concept of the double-blind controlled trial as a means of avoiding observation bias, bias resulting from differences in follow-up and drop-out rates, and bias resulting from diverse behaviours. The latter is particularly significant for microbicide trials, where behaviours around sexual intercourse (for example frequency of sexual acts, number and type [regular or casual] of sexual partners, condom use, microbicide/placebo use, vaginal washing procedures, "dry sex" practices, anal intercourse etc.) have a pivotal influence on the risk of HIV acquisition and are at the same time difficult to monitor. So it would be difficult to judge whether a higher or lower HIV rate in the no-gel arm was related to a biological effect of the gels or to different risk behaviours.

As to future effectiveness trials, once a proven microbicide is available, on ethical grounds it may no longer be reasonable to include a placebo arm or a no-gel arm. Trials then may have to be of the superiority or non-inferiority kind, designed to assess the superiority or equivalence of the new microbicide (or microbicide combination) in comparison with the proven one. If these trials are to demonstrate this with adequate statistical power, they will require a substantially greater number of participants than placebo-controlled trials, and this will pose major challenges in terms of time, cost and logistics.

Combination microbicides

The potential benefits of microbicides that contain two or more APIs have already been mentioned. The USFDA has issued general guidelines for the non-clinical evaluation of drug combinations *(39)*. For a combination that involves one or more NCEs, the USFDA recommends the full safety evaluation of the NCE(s) and may request a general toxicology study of the combination for up to 90 days in an appropriate animal species. They may also wish to see chemical, toxicological, pharmacokinetic and pharmacodynamic data on the combination, to assess the potential for adverse interactions between the drugs. Where the combination includes only previously marketed drugs, if existing non-clinical and clinical safety data on the individual APIs are sufficient to support the safety of the combination and there is no evidence to suggest adverse drug interactions, additional non-clinical studies, including direct assessment of the combination by testing in animals, may not be needed.

The regulatory aspects of clinical trials to evaluate the effectiveness of microbicide combinations are still evolving. They merit detailed consideration and, given the range of possible combinations, a flexible approach. The EMEA has stated in a recent document that clinical trials to evaluate the effectiveness of fixed-combination medicinal products should *preferably* compare the combination with its individual components and, where feasible, also with a placebo (i.e. a four-arm trial) *(40)*. In terms of the logistics involved, to request such a trial may be reasonable for comparing therapeutic drugs, but for evaluating microbicides to prevent HIV infection a trial of this design would be very large, complex and costly. Moreover, if there is reason to believe that one of the APIs may be less effective than the other as a single agent, it would be as questionable on ethical grounds to allocate a group of participants to use it as it would be to use a placebo. It can be argued that, provided there is a robust scientific rationale behind the choice of a particular combination, a two-arm trial would be sufficient to determine whether the combination is superior to the more effective of the component APIs.

Monitoring sexual behaviour during trials

Estimates of safety and effectiveness in microbicide trials are critically affected by the extent to which participants use the product, particularly in acts not protected by condoms, so monitoring relevant aspects of sexual behaviour is an important part of the trial. Unfortunately, it is difficult to obtain reliable data on such sensitive matters as frequency of sexual intercourse, numbers and types of partners, sexual practices, condom use and product use, and investigators generally use a combination of different approaches. "Self-reporting" approaches can include focus groups, questionnaires, in-depth interviews, sexual diaries, and, to provide privacy, audio computer-assisted self-interviewing (ACASI).

A less subjective approach involves counting returned used applicators. Applicators can be immersed in an appropriate stain to detect the presence of vaginal mucus to provide evidence of use. Biological markers (for example prostate-specific antigen in the vagina as an indicator of unprotected sex), and "smart" applicators or intravaginal rings that use temperature sensors,

microprocessors or other technologies to measure product use and sexual activity, are under development. Ensuring high rates of product use is especially challenging with gels intended for coitally dependent insertion, but may be less problematic when the product is delivered by means of once-a-day gels or intravaginal rings.

Ethics, community involvement and institutional review boards

Microbicide trials are guided by a series of ethical considerations and conducted under a variety of ethical, community and regulatory oversights. This poses numerous challenges. For example, informed consent must be sought from potential enrollees who often have only limited understanding of research and randomized trials. The appropriate level of sexual partner and community involvement must be achieved to foster trust and transparency, while at the same time participants' confidentiality and autonomy must be protected. An appropriate standard of care must be provided. Such issues need to be considered in the context of particular settings, populations and individuals.

Practical experience, together with discussions involving a variety of stakeholders, has given rise to effective approaches for addressing these challenges *(41)*. By definition, participants in microbicide-effectiveness trials are considered to be at risk of HIV infection, and most will have a range of other health-care needs. Those conducting the trials must provide a sufficient standard of care, and this may include reproductive health services (treating STIs and urinary tract infections, providing contraception, and offering examinations to identify any gynaecological abnormalities) and HIV-related care (voluntary counselling and testing, safer-sex counselling, condom provision, referral for treatment of HIV and opportunistic infections, partner referral and treatment).

Consideration needs to be given to mechanisms through which the results of the trial, whether positive or negative, will eventually be communicated to the trial community and other stakeholders, and to issues around making the microbicide available to the community at the conclusion of the trial should it prove to be a successful product. Investigators and their sponsors should regard clinical trials as opportunities to improve local services and standards of care in ways that will be sustainable after the trials have been completed. At the same time, the package of benefits offered to trial participants must not constitute undue inducement to participate in the trial: it should not be so tempting that volunteers might agree to take part even though the possible risks of doing so may otherwise have deterred them.

It is important for researchers, trial participants, communities, regulatory authorities and other stakeholders to clearly define and reach agreement on the responsibilities of each party on the above issues. Interaction between site-based community advisory boards (CABs), scientists and microbicide advocates is one of a range of approaches for implementing ethically and scientifically rigorous trials with meaningful community involvement. The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the AIDS Vaccine Advocacy Coalition (AVAC) have jointly developed good participatory practice (GPP) guidelines, which lay out core principles, key issues, and recommended activities in this regard *(42)*.

From a researcher's perspective, such involvement can help articulate research needs and priorities, determine the best ways to translate and explain complex research terms and concepts, and facilitate agreement on appropriate care and compensation for trial participants. From the community's point of view, active participation in research design and implementation can increase the relevance, transparency and accountability of the research enterprise; provide skills training and experience; and ensure that research investments

benefit communities over the longer term. Such engagement can help to reduce power disparities between researchers and the community, and more generally between North and South.

The role of institutional review boards (IRBs) is to approve, monitor and review the research, with the aim of protecting the rights and welfare of the individuals under study and ensuring that the responsibilities of clinical investigators are being fulfilled. IRBs provide advice and feedback to the organizations directly involved in clinical studies. Their primary concerns include the appropriate standard of care, informed consent, therapeutic misconceptions, stigma, issues around participant compensation, incentives and trial-related injury, as well as intellectual property matters. These are important responsibilities, but in many developing countries there is insufficient capacity to establish the necessary structures. One way forward is for a group of countries in a particular region to share resources and organize effective training measures; WHO is prepared to assist in such processes.

Independent data-monitoring committees

As for any other drug, the task of reviewing progress while a clinical trial is under way belongs to an appropriately constituted IDMC, sometimes referred to as a data and safety monitoring board (DSMB). The IDMC must be truly independent from those directly involved in the trial and must operate with integrity, maintaining strict confidentiality. Its membership must have appropriate expertise to make informed judgments in the face of uncertainty. In performing its role, the IDMC considers data from the trial at all its study sites, the trial's context, and data from other sources. It has confidential access to unblinded trial data. At each review it must make a recommendation from among four possible options: stopping the trial for evidence of benefit; stopping for evidence of harm; changing procedures to minimize risks; or continuing the trial. In some trials the IDMC may additionally recommend stopping for futility if their review indicates that the chance of demonstrating a significant benefit is remote.

Pharmacovigilance

Pharmacovigilance of a new product continues well beyond the phase III trial stage of its development. Once a microbicide has been licensed for use and is on the market, a systematic programme of surveillance will be put in place to satisfy regulatory requirements, to assess long-term safety, to control risk and to evaluate public health impact. The regulator may require the applicant to present a comprehensive pharmacovigilance plan to be agreed before approval, implementation of which will be the obligation of the applicant. In this case the applicant is required also to report at regular intervals about implementation of the pharmacovigilance plan. In addition to direct safety concerns, biomedical and behavioural benefits and problems will need to be monitored and systems introduced to combat negative trends such as undesirable changes in sexual behaviour – for example, a decrease in condom use, or problems related to drug-resistant HIV strains. In the case of this particular group of products, it is possible that relying on traditional spontaneous reporting of adverse events may not be satisfactory. This might require setting up specific mechanisms to record adverse events (cohort event monitoring) in selected populations of users. Although more costly, such cohorts might be more appropriate to safeguard users and reassure health-care providers and policy-makers that the products are being used safely and as intended.

Labelling and package inserts

Labelling and package inserts for microbicides will need to be subject to proper regulatory scrutiny before approval and be monitored after marketing to ensure that they present appropriate messages to the provider and the user. It could be advisable to test the clarity of the user information

in potential user target groups. The package inserts will need to cover partial effectiveness for HIV prevention, effectiveness against other STIs, contraceptive effects, potential for drug resistance (especially relevant for microbicides based on ARVs) and contraindications, for example cervical abnormalities diagnosed by Pap smear. The impact of microbicides on disease incidence will be largely realized, in practice, in settings where condom use is low or erratic; however, in settings where condom use is high, condom substitution with microbicides could be counterproductive from a public-health and disease-prevention perspective *(43)*. Labelling and package inserts, as well as education around microbicide introduction, will need to find a balance that will not promote a substitution effect while, at the same time, avoiding giving the impression that microbicides are intended for use only with condoms.

Over-the-counter microbicides

From a public-health perspective, it would be advantageous for licensed microbicides to be available OTC. This is particularly the case for settings in developing countries with an urgent need for microbicides and where prescription mechanisms may be fairly rudimentary in rural areas. However, this should not happen before enough information has been gathered about the safety of these products in settings of more controlled use. Only when regulators have sufficient evidence on their safety and are satisfied that any specific concerns have been addressed, including the matters of drug resistance and access to safer-sex advice, should consideration be given to moving the product from prescription-only status (e.g. through health and family planning facilities) to OTC status.

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Annex 1: The six consultations

1. International Regulatory Issues in Microbicide Development, Villars-sur-Ollon, Switzerland, March 2002

Supporting agencies: World Health Organization, with support from the US Agency for International Development

Organizing committee: Tim Farley (WHO), Henry Gabelnick (CONRAD, Arlington, VA, USA), Polly Harrison (Alliance for Microbicide Development [AMD], Silver Spring, MD, USA), Isaac Malonza (WHO)

Rapporteur: Polly Harrison (AMD)

2. Scientific Guidance for Regulation of Research and Development of Microbicides and HIV Vaccines: Southern African Regional Workshop, Gabarone, Republic of Botswana, November 2002

Supporting agencies: World Health Organization

Organizing committee: Salim Abdool Karim (University of Natal, Durban, South Africa), Tim Farley (WHO), Polly Harrison (AMD), Ismael Joseph (Ministry of Health, Botswana), Ivana Knezevic (WHO), Isaac Malonza (WHO), Saladin Osmanov (WHO), Helen Rees-Randera (Reproductive Health Research Unit [RHRU], Chris Hani Baragwanath Hospital, Johannesburg, South Africa), Lut Van Damme (CONRAD)

Rapporteur: Polly Harrison (AMD)

3. Regional Meeting on Regulatory Pathways for Microbicides in Asia, New Delhi, India, November 2004

Supporting agencies: WHO and the Indian Council for Medical Research (ICMR)

Organizing committee: Nomita Chandhiok (ICMR), Lee Claypool (US Agency for International Development [USAID]), Paul Coplan (IPM), Tim Farley (WHO), Henry Gabelnick (CONRAD), Megan Gottemoeller (Global Campaign for Microbicides), Polly Harrison (AMD), Judy Manning (USAID), Elizabeth McGrory (WHO Consultant), Badri Saxena (Center for Policy Research [CPR] New Delhi, India),

Rapporteur: Elizabeth McGrory, WHO Consultant.

4. Regulatory Review of Microbicides in the Southern African Development Community (SADC) Region, Muldersdrift, Republic of South Africa, June 2005

Supporting agencies: WHO in collaboration with International Partnership for Microbicides (IPM)

Organizing committee: Lahouari Belgharbi (WHO), Paul Coplan (IPM), Liliana Chocarro (WHO), Tim Farley (WHO), Polly Harrison (AMD), Isaac Malonza (WHO), Julie Milstien (WHO Consultant), Elizabeth McGrory (WHO Consultant), R.N. Misra (Department of Health Medicine Regulatory Authority, Clinical Evaluating Trials, Pretoria, South Africa), S. Munbodh (Department of Health Medicine Regulatory Affairs, Pretoria, South Africa), Lulu Oguda (IPM), I. Opfou (Department of Health, Pretoria, South Africa), Helen Rees-Randera (RHRU, Chris Hani Baragwanath Hospital, Johannesburg, South Africa), Jeremy Nuttall (IPM), Sydney West (IPM),

Rapporteur: Alan Stone, International Working Group on Microbicides, London, United Kingdom.

5. Regional Meeting on Regulatory Issues for Microbicides in Asia, New Delhi, India, November 2007

Supporting agencies: WHO in collaboration with ICMR and CONRAD

Organizing committee: Tim Farley (WHO), Henry Gabelnick (CONRAD), Badri Saxena (CPR)

Rapporteur: Elizabeth McGrory, WHO Consultant.

6. Scientific, Regulatory and Public Health Aspects of Microbicide Research and Development, Nanjing, People's Republic of China, November 2008

Supporting agencies: World Health Organization

Organizing committee: Chen Zhiwei (AIDS Institute, University of Hong Kong, Special Administration Region of China), Tim Farley (WHO, Geneva, Switzerland), Henry Gabelnick (CONRAD), Judy Manning (USAID), Wiwat Rojanapithayakorn (WHO, Beijing, China), Badri Saxena (CPR, New Delhi, India), Alan Stone (MEDSA Ltd, London, UK), Wu Allen Zhiwei (Center for Public Health Research, Nanjing University, Nanjing, China), Zhang Linqi (Comprehensive AIDS Research Center, Tsinghua University, Beijing, China)

Rapporteur: Alan Stone, MEDSA Ltd, London, United Kingdom.

Annex 2: Participants in the consultations

1. Villars-sur-Ollon, Switzerland, March 2002

Invited experts

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Zvavahera Chirenje (University of Zimbabwe School of Medicine, Dept. of Obstetrics and Gynaecology, Harare, Zimbabwe)

Janet Darbyshire (Clinical Trials Unit, Medical Research Council, London, United Kingdom of Great Britain and Northern Ireland)

Virginie Ettiègne-Traoré (Project RETRO-CI, Abidjan, Côte d'Ivoire)

Salim Abdool Karim (University of Kwa-Zulu Natal, Durban, South Africa)

Dwip Kitayaporn (Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand)

Sheena McCormack (Clinical Trials Unit, Medical Research Council, London, United Kingdom)

Sanjay Mehendale (National AIDS Research Institute/ NARI, Pune, India)

Margaret Muganwa (Institute of Public Health, Makerere University, Mulago Medical School Complex, Kampala, Uganda)

N.M. Samuel (AIDS Society of India, TNDR MGR Medical University, Chennai, India)

Badri N. Saxena (Centre for Policy Research, New Delhi, India)

Regulatory agencies

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Suchart Chongprasert (Investigational New Drug Subdivision, Food and Drug Administration, Nontaburi, Thailand)

Ishmael Joseph (Ministry of Health, Gaborone, Botswana)

Sheryl Lard-Whiteford (Center for Biologics Evaluation and Research, US Food and Drug Administration, Rockville Maryland, United States of America)

O.N. Mainasara (Central Laboratory, National Agency for Food and Drug Administration and Control, Lagos, Nigeria)

Helen Rees-Randera (Medicines Control Council, Chris Hani Baragwanath Hospital, University of Witwatersrand, Bertsham, South Africa)

Frances Rotblat (Medicines Control Agency, London, United Kingdom of Great Britain and Northern Ireland)

Beatriz Tess (Department of Science and Technology and Health, Ministry of Health, Brasilia, Brazil)

Sang Guo Wei (State Drug Administration, Beijing, China)

Collaborating agencies

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Lori Heise (Global Campaign for Microbicides, Program for Appropriate Technology in Health, Washington, DC, United States of America)

Michael Isbell (International AIDS Vaccine Initiative, New York, NY, United States of America)

Elof Johansson (Center for Biomedical Research, Population Council, New York, NY, United States of America)

Christine Mauck (CONRAD, Eastern Virginia Medical School, Arlington, Virginia, United States of America)

Elizabeth McGrory (The Population Council, New York, NY, United States of America)

Patricia Reichelderfer (National Institute of Child Health and Human Development, National Institutes of Health, Rockville, Maryland, United States of America)

Zeda Rosenberg (Family Health International, Arlington, Virginia, United States of America)

Alan Stone (International Working Group on Microbicides, London, United Kingdom of Great Britain and Northern Ireland)

Janneke van de Wijgert (The Population Council, New York, NY, United States of America)

Observers

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Lorna Clisby (ML Laboratories PLC, Surrey, United Kingdom of Great Britain and Northern Ireland)

Anne-Marie Corner (Biosyn, Inc., Huntington Valley, Pennsylvania, United States of America)

Ryoko Krause (International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland)

Jens Van Roey (Tibotec-Virco, Mechelen, Belgium)

Sandeep Shah (SSL International plc, Cambridge, United Kingdom of Great Britain and Northern Ireland)

Meeting secretariat

Philip A. Corfman (working group rapporteur, Bethesda, Maryland, United States of America)

WHO secretariat

TimFarley (Department of Reproductive Health and Research, WHO, Geneva, Switzerland)

Isaac Malonza (Department of Reproductive Health and Research, WHO, Geneva, Switzerland)

2. Gabarone, Republic of Botswana, November 2002

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Shabir Banoo (Medicines Control Council of South Africa, Department of Health, Pretoria, South Africa)

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3. New Delhi, India, November 2004

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4. Muldersdrift, Republic of South Africa, June 2005

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Julie Milstien (WHO Consultant, Geneva, Switzerland)

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T. Malangu (Ministry of Health, Department of Pharmacy, Gombe, Democratic Republic of Congo)

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5. New Delhi, India, November 2007

Rashmi Bagga (Department of Obstetrics and Gynaecology, Post Graduate Institute of Medical Education and Research, Chandigarh, India)

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P.S. Chauhan (Emeritus, Cell Biology Division, BARC, Mumbai, India)

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6. Nanjing, People's Republic of China, November 2008

International and national delegates

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Annex 3: Microbicide candidates in preclinical development as of October 2009*

ADVANCED PRECLINICAL†

Candidate	Mechanism of Action	Developer/Researcher/ Sponsor	Additional information+
Cyanovirin-N (CV-N)	Entry/fusion inhibitor, vaginal defense enhancer	NIH, Osel Inc., U. Pittsburgh	Also known as MucoCept, in NHP Mode.
D-peptides	Entry/fusion inhibitor	NIH, U. Utah School of Medicine (M Kay)	D-peptides have broad antiviral activity (clades A-G) using PBMC target cells. Pharmacokinetic studies underway. Undergoing preclinical evaluation in NIAID's Topical Microbicide Screening Algorithm.
5P12- RANTES	Entry/fusion inhibitor	Mintaka Foundation for Medical Research	Fully recombinant analogue of PSC-RANTES with equivalent potency *in vitro* and equivalent efficacy in macaque vaginal challenge model. Lower product costs and better safety profile (no CCR5 signaling) than PSC-RANTES.
mapp66	Combination of antibodies, neutralization	Mapp Biopharmaceutical, Inc.	mAbs produced in Nicotiana; one mAb blocks HIV binding to CCR5 receptor, one mAb binds to gpD on HSV.
Nisin	Combination	Nat'l Institute for Research on Reproductive Health (KVR Reddy)	No anti-HIV activity but effective against various sexually transmitted pathogens. Advanced preclinical studies in rabbits suggest is safe and effective as a spermicide.
Octylglycerol Gel	Surfactant	NY State Institute for Basic Research, Magee-Women's Research Institute, U. Pittsburgh (CE Isaacs, L Rohan, S Hillier)	Monkey efficacy and toxicity studies underway at U. Washington (D Patton).
Opuntia spp (Osp)	Entry/fusion inhibitor, Replication inhibitor	CIDEPLAN, SELADIS (R Carvajal, K Terrazas, S Zambrana, P Terceros)	
PEHMB	Entry/fusion inhibitor	Drexel U. College of Medicine, Novaflux Biosciences, Inc.	Working to further define 1–2 additional mechanisms of antiviral activity.
Polycarboxylated aryl oligomer, poly[1,4-phenylene-(1-carboxyl) methylene] (PPCM)	Entry/fusion inhibitor	Albert Einstein College of Medicine (AECOM), TOPCAD/ Rush U., YASO	*In vitro* and mechanistic studies completed, formulation fully protective in murine herpes model; contraceptive.
Retrocyclins	Entry/fusion inhibitor	NIH, UCLA, U. Central Florida, U. Pittsburgh, U. Washington (A Cole and collaborators, including R Lehrer, A Waring; P Gupta, L Rohan, D Patton)	
SJ-3991	Multiple mechanisms	ImQuest, IPM	

DISCOVERY/EARLY PRECLINICAL±

Candidate	Mechanism of Action	Developer/Researcher/ Sponsor	Additional information+
BASANT		A Singh for GP Talwar	Against *Chlamydia trachomatis*.
C5A	Vaginal defense enhancer	NIH, Scripps Research Institute, Viriome (F Chisari, P Gallay)	Mechanism ruptures integrity of both viral membrane and mature core. Currently testing C5A in HIV vaginal transmission mouse model. Plans to test in HIV vaginal transmission macaque model.
CADA (Cyclotriazadisul fonamides)	Entry/fusion inhibitor, Uncharacterized mechanism(s)	Rega Institute, U. Nevada, EMPRO (D Schols, TW Bell)	First and only chemical compound described to down-modulate specifically the human cellular CD4 receptor.
Combinations	Entry inhibitors, Replication inhibitors	IPM	CCR5 blockers.
Diterpene	Combination	FAP, FIOCRUZ, UFF (C Cirne-Santos, L Castello-Branco, P de Palmer Paixao, I Frugulhetti, V Teixeira)	Dolabelladienetriol blocks integration of HIV-1 provirus and ablates HIV-1 replication in PBMCs. Noncompetitive inhibitor of reverse transcriptase: additive effect with AZT; synergistic effect with Atazanavir.
DS003/BMS-599793	Entry/fusion inhibitor	IPM	gp120 binder.
DS004/L-860,872	Entry/fusion inhibitor	IPM	CCR5 blocker, will only be developed as combination microbicide with compounds with other mechanisms of action.
DS005/L-860,882	Entry/fusion inhibitor	IPM	CCR5 blocker, will only be developed as combination microbicide with compounds with other mechanisms of action.
EBd peptides	Entry/fusion inhibitor	NIH, U. Wisconsin School of Medicine	Funding in process to begin preclinical research.
Flavonoids (EGCG)	Entry/fusion inhibitor	NIAID, NY State Institute for Basic Research, U. Pittsburgh (S Hillier, C Isaacs)	EGCG: Epigallocatechin Gallate.
Glycerol monolaurate (GML)	Uncharacterized mechanism(s)	NIAID, U. Minnesota (A Haase, P Schlievert)	
HHA, KRV2110, T20 Combinations	Combination	ANRS Multi Micro Project (L Belec, MA Jenabian, H Saidi, G Vanham)	*In vitro* synergistic activities of drug combinations: HHV+KRV2110, HHA+T20, KRV2110+T20).
ISIS 5320	Entry/fusion inhibitor	ImQuest	
K5-N, OS(H), K50SH	Entry/fusion inhibitor	San Raffaele Scientific Institute, Glycores 2000, EMPRO	Completing toxicity studies in cervical explants and macrophages; manuscripts being compiled.
KP1, KP17	Replication inhibitor, Combination	CONRAD (K Parang, GF Doncel, HK Agarwal)	
L'644 peptide	Entry/fusion inhibitor	IPM	gp41 inhibitor.
Maraviroc	Entry/fusion inhibitor	IPM	CCR5 blocker.
MIV-150 Vaginal Ring	Entry/fusion inhibitor	Population Council	Preclinical testing of MIV-150 (NNRTI) in vaginal ring.
Nanobodies™	Entry/fusion inhibitor	U. College London, U. Utrecht, Ablynx NV, EMPRO	Nanobodies/Llama VHH.
NCp7 Thioesters (SAMTs)	Replication inhibitor	ImQuest	
Novasomes	Combination, entry/ fusion inhibitor, uncharacterized mechanism(s)	Novavax (A DeVico)	

Continued on next page

Candidate	Mechanism of Action	Developer/Researcher/ Sponsor	Additional information+
Optimised dendrimers	Combination, entry/ fusion inhibitor	NIH (DAIDS), Reprotect, Starpharma Pty Ltd (J Paull)	Combination of technology of VivaGel™ containing a dendrimer as active ingredient (entry/fusion inhibitor) and BufferGel™-related formulation in a combination product.
PC-710	?	Population Council	Zinc salt in Carraguard gel; appears highly effective against HSV-2.
PSC-RANTES	Entry/fusion inhibitor	La Jolla Foundation for Microbicide Research, Mintaka Foundation, NIAID, NIH, Scripps Research Institute, University of Geneva (M Lederman, D Mosier, R Offord, O Hartley, and collaborators)	CCR5 inhibitor.
Pyrimidindiones	Multiple mechanisms	ImQuest	Funding through Small Business Innovation Research (SBIR) program.
Pyrimidindiones and ISIS 5320	Combination (2 products)	ImQuest	Funding through Microbicide Innovation Program (MIP).
RANTES peptides	Entry inhibitor	San Raffaele Scientific Institute, Osel, Inc. (L Vangelista, M Secchi, X Liu, Q Xu, P Lusso)	Development of live microbicide based on lactobacilli-producing RANTES derivatives.
Recombinant lactobacillus (LAB)	Entry/fusion inhibitor	Aaron Diamond AIDS Research Center, NIH (D Boden)	Live microbial anti-HIV microbicide.
REP 9C, REP 9AC	Entry inhibitor	REPLICor Inc., NIH/NIAID (A Vaillant and collaborators)	Amphipathic DNA polymers attach to viral glycoproteins and neutralize their entry activity, preventing viral infection. Technology shown to be well tolerated in rodent, avian, and non-human primates species and demonstrated potent, well-tolerated *in vivo* antiviral activity in representative viruses from 7 different viral families including HCV, HBV (DHBV), influenza, respiratory syncytial virus, HSV-2, cytomegalovirus, and Ebola virus.
sCD4–17b	Entry/fusion inhibitor	NIH (E Berger)	
Single-chain ICAM	Entry inhibitor	Osel, Inc.	Inhibits cell-associated viral entry.
siRNA	Combination, entry/ fusion inhibitor	Immune Disease Institute, Harvard Medical School, NIH, IPM (J Lieberman)	siRNA-based microbicide.
Sodium Rutin Sulfate (SRS)	Entry/fusion inhibitor	Zhejiang CONBA Pharmaceutics Company	
Soluble DC-SIGN	Entry/fusion inhibitor	Scripps Research Institute	
Syndecan	Combination	Scripps Research Institute (P Gallay)	Compounds that neutralize either the mucosal syndecans or syndecan-binding of HIV-1, gp120; compounds that block gp120-syndecan interactions also block gp120-CCR5 interactions. Shows protective effect against HSV and *N. gonorrhoeae*.
Talactoferrin	Entry/fusion inhibitor, uncharacterized mechanism	Aggenix, Inc. (D Cho, I McGowan, P Anton)	Preliminary research on human recombinant lactoferrin (talactoferrin) focused on investigating *in vitro* efficacy of this naturally occurring glycoprotein against HIV target cells. Studies suggest inhibition of binding of HIV to target receptors. Low potential for toxicity and adverse effects.
TATC-D peptides	Entry/fusion inhibitor	NIH, U. Wisconsin School of Medicine	Funding in process to begin preclinical research.

Candidate	Mechanism of Action	Developer/Researcher/ Sponsor	Additional information[+]
Unipron	Vaginal defense enhancer	Institute of Primate Research, Dept. of Reproductive Health (PG Mwethera)	Formulated, developed and patented in collaboration with Universal Pharmaceutical Cooperation Ltd, which is currently manufacturing Unipron for preclinical/ clinical trials. Vaginal lubricant.
x-REPLAB	Vaginal defense enhancer, combination	Makerere College of Health Sciences, Restrizymes Canada Corp., Restrizymes Biotherapeutics LTD (W Misaki, B Wilson, K Henry)	Modifies native vaginal lactobacilli strains to enhance antimicrobial properties. Combination properties expressed through a "search and destroy" strategy.
ZCM (PC-1005)	Combination	Population Council	Zinc salt and MIV-150 in Carraguard gel.
Zinc tetra-ascorbo-camphorate derivative "C14"	Combination	MGB Pharma (L Belec, MA Jenabian, H Saidi B Gombert, A Mannarini)	Possible entry and pre-integration inhibitor.

NB: This table should be considered a draft summary of preclinical candidates rather than a vetted list of viable products.

[*] This list of preclinical microbicide candidates includes those reported by the Alliance *Mapping Exercise* respondents and those in published literature and/or recent conference abstracts; all were subsequently confirmed by the Researcher/Developer. Many other products are in preclinical development but lack verification responses from Researcher/Developers and are therefore not included in this table.

[†] "Advanced Preclinical" reflects candidate's success in discovery and initial tests and some likelihood that the product could advance to human trials.

[+] All products with plans to file an Investigational New Drug (IND) number application by the fall of 2009 are so indicated by "IND" in the "Additional Information" column.

[±] "Discovery/Early Preclinical" indicates that the candidate is in the very early stages of discovery and testing.

Annex 4: Microbicide and pre-exposure prophylaxis (PrEP) candidates in clinical development as of December 2009

Ongoing clinical trials

Phase	Candidate Name	Mechanism of Action	Study Title	Sponsor*	Sites by Country
3	Truvada®: Oral	RI	Chemoprophylaxis for HIV prevention in men (iPrEx)	BMGF, NIH	Brazil, Ecuador, Peru, South Africa, Thailand, United States
	Truvada®: Oral	RI	Safety and efficacy of daily and oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults (TDF2)	CDC	Botswana
	Truvada®: Oral, Viread®: Oral	RI	Parallel comparison of tenofovir and emtricitabine/ tenofovir PrEP to prevent HIV-1 acquisition in HIV-1 discordant couples (Partners PrEP)	BMGF, U. Washington	Kenya, Uganda
	Truvada®: Oral	RI	Study to assess the role of Truvada® (a tenofovir-FTC drug combination) in preventing HIV acquisition in women (FEM-PrEP)	BMGF, FHI, USAID	Kenya, Malawi, Tanzania, Zambia
2/3	Viread®: Oral	RI	Safety and efficacy of daily tenofovir to prevent HIV infection (BTS)	CDC	Thailand
2B	Tenofovir: Gel	RI	Safety and effectiveness of vaginal 1% tenofovir gel to prevent HIV infection in women in South Africa (CAPRISA 004)	CAPRISA, CONRAD, FHI, Gilead, LIFElab, USAID	South Africa
	Tenofovir: Gel	RI	Safety and effectiveness of tenofovir 1% gel (PMPA) with two oral HIV prevention approaches: tenofovir and Truvada™ (MTN-003 – VOICE)§	CONRAD, DAIDS/NIAID, Gilead, MTN, NICHD, NIMH	Malawi, South Africa, Uganda, Zambia, Zimbabwe
2	Tenofovir: Gel, Viread®: Oral	RI	Adherence and pharmacokinetics study of oral and vaginal preparations of tenofovir (MTN-001)	CONRAD, DAIDS/NIAID, Gilead, MTN	South Africa, Uganda, United States
	Viread®: Oral	RI	Extended safety trial	CDC	United States
1/2	Dapivirine: Gel	RI	Safety and acceptability of dapivirine gel, conducted using daily monitored adherence in healthy HIV-negative women (IPM 014A)	IPM	Kenya, Malawi, Rwanda, South Africa, Tanzania
	Dapivirine: Gel	RI	Safety and acceptability of dapivirine gel, conducted using daily monitored adherence in healthy HIV-negative women (IPM014B)	IPM	Kenya, Malawi, Rwanda, South Africa, Tanzania
	Dapivirine: Gel	RI	Dapivirine gel expanded safety study (IPM 020)	IPM	United States
	VivaGel®: Gel (SPL7013)‡	EFI	Assessment of local retention and duration of activity of SPL7013 following vaginal application of 3% SPL70 13 Gel (VivaGel®) in healthy volunteers	NIAID, NIH, Starpharma	Australia

Phase	Candidate Name	Mechanism of Action	Study Title	Sponsor*	Sites by Country
1	Acidform: Gel	VDE	Safety of Acidform lubricant (Amphora) in women at low risk for HIV-1 infection (AF 020)	AECOM, NIAID/ DAIDS	United States
	Dapivirine: Ring	RI	Safety and pharmacokinetic trial to assess delivery of dapivirine from the matrix vaginal ring (IPM 024)	IPM	Belgium
	Device	N/A	Acceptability and performance of a device for vaginal drug delivery	FHI	South Africa
	HEC/CS/N-9: Gels†	N/A	Assessment of markers of inflammation after vaginal product use	CONRAD/ USAID	USA
	PRO 2000: Gel‡	EFI	Postcoital anti-viral activity of cervicovaginal secretions following intravaginal application of 0.5% PRO 2000/5 Gel (P) (MSPRO 030)	AECOM, Indevus, NIH	United States
	Tenofovir: Gel‡	RI	Pharmacokinetic study of the vaginal microbicide agent 1% tenofovir gel (A04–095)	CONRAD, IPM/ USAID	Dominican Republic, United States
	Tenofovir: Gel	RI	Maternal pharmacokinetics and placental perfusion of tenofovir/PMPA gel (MTN-002)	CONRAD, DAIDS/NIAID, MTN, NICHD	United States
	Tenofovir: Gel	RI	Safety, acceptability, and pharmacokinetic trial of topical, vaginally-formulated tenofovir 1% gel applied rectally compared with oral TDF (RMP-02/MTN-006)	CONRAD, Gilead, MTN, NIAID/DAIDS	United States
	Tenofovir: Gel	RI	Effect of repeated applications of tenofovir gel on mucosal mediators of immunity and intrinsic antimicrobial activity of cervicovaginal secretions	NIAID	United States
	UC-781: Gel‡	RI	Safety and persistence of 0.1% UC-781 vaginal gel in HIV-1 seronegative women	NIAID, CONRAD	United States
	UC-781: Gel‡	RI	Safety and acceptability of 0.1% and 0.25% UC-781 topical vaginal microbicide in women and acceptability in their male partners	CDC, CONRAD, Thailand Ministry of Health	Thailand
	UC-781: Gel‡	RI	Male tolerance study (A06–104)	CONRAD	United States
	UC-781: Gel‡	RI	Safety and acceptability of UC-781 topical vaginal microbicide in heterosexual women and male partners (HC 101)	CDC, CONRAD, Emory U.	United States
	VivaGel®: Gel (SPL7013)**	EFI	Safety and acceptability of 3% w/w SPL7013 Gel (VivaGel®) applied vaginally in sexually active young women (MTN-004)	DAIDS/NIAID, MTN, NICHD, Starpharma	Puerto Rico, United States
N/A	No Product	N/A	Observational cohort study of women following HIV-1 seroconversion in microbicide trials (MTN-015)	DAIDS/NIAID, MTN	Malawi, South Africa, Uganda, Zambia, Zimbabwe
	Placebo ring‡	Placebo	Safety and acceptability of a placebo vaginal ring microbicide delivery method for the prevention of HIV infection in women (IPM 011)	IPM	South Africa, Tanzania (ongoing); Kenya (site closure)

Acronyms used in this table: Entry/Fusion Inhibitor (EFI), Replication Inhibitor (RI), Vaginal Defense Enhancer (VDE), and Surfactant (S)

* The Alliance uses the term "sponsor" as defined by the International Conference on Harmonisation *(Guideline for Good Clinical Practice, 1996)* as follows: "An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial."

† HEC, CS, and N-9 are not in development as microbicides. Rather, this trial's objective is to characterize inflammation and genital epithelial changes in healthy, sexually abstinent women before, during, and after 13½ days of twice-daily applications of one of three products: a hydroxyethylcellulose (HEC)-based "universal" placebo, 6% cellulose sulfate, or 4% nonoxynol-9 (Conceptrol®) gel; to determine the degree ofcorrelation between different methods of clinical assessment; and to determine the degree of correlation between the results of this clinical study and the results of the preclinical assessment of the same compounds. This trial is currently in data analysis.

§ This study includes an observational cohort study (MTN 003B), entitled Bone Mineral Density Substudy, which will explore the effects of oral study products on bone mineral density.

‡ These trials have completed clinical studies, but data analysis is ongoing.

** ATN 062, "Tell Juliana," is an ancillary observational study taking place in parallel with MTN 004.

± This device is intended for use with a microbicide.

Continued on next page

Planned and funded clinical trials

Phase	Candidate Name	Mechanism of Action	Study Title	Sponsor*	Sites by Country
3	BufferGel®: Barrier Method and Gel	VDE	Trial of a diaphragm with a candidate microbicide to prevent sexually transmitted infections (MIARADIA)†	CDC, CONRAD, NIAID/ NIH, UNC, UNC-MD, USAID	Madagascar
	Dapivirine: Gel and Ring	c	Dapivirine efficacy study (IPM 009)	IPM	Various
	Tenofovir: Gel	RI	Daily or pericoital tenofovir gel for prevention of vaginally acquired HIV (MDP 302)	MRC/UVRI	Mozambique, South Africa, Tanzania, Uganda, Zambia
2/3	Invisible Condom®: Gel	RI	Effectiveness of Invisible Condom® in high-risk women‡		
1/2	Dapivirine: Ring	RI	Safety of an intravaginal matrix ring with dapivirine for prevention of HIV infection in healthy HIV-negative women (IPM 015)	IPM	Kenya, Malawi, Rwanda, South Africa, Tanzania, Zambia
	Dapivirine: Ring	RI	Dapivirine vaginal ring expanded safety study (IPM 021) – Status TBD	IPM	Denmark, Germany, Netherlands, United Kingdom
1	Dapivirine: Gel	RI	Dapivirine gel male tolerance study (IPM 010)	IPM	TBD
	Dapivirine: Ring	RI	PK and safety study in healthy HIV negative women to assess delivery of dapivirine from matrix vaginal rings (IPM 013)	IPM	Belgium
	MIV-150 + gel: Gel	C	Study protocol under review	Population Council	TBD
	MIV-150: Ring	RI	Study protocol under review	Population Council	TBD
	Tenofovir: Gel	RI	Rectal safety and acceptability study of 1% tenofovir gel (MTN-007)	CONRAD, MTN/NIAID/ DAIDS	United States
N/A	No product	N/A	Seroconverter protocol (IPM 007)	IPM	
	Placebo: Ring	Placebo	Expanded safety and acceptability study of a non-medicated intravaginal ring (MTN-005)	DAIDS/NIAID, MTN	India, United States
	No product	N/A	EMBRACE (Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure) (MTN-016)	DAIDS/NIAID/ NICHD/ NIH	Malawi, South Africa, Uganda, Zambia, Zimbabwe
	Placebo: Gel and Ring	Placebo	Simulated microbicide clinical trial to explore methods for improving adherence and reporting of product adherence among women	Population Council	Zambia
	Placebo: Gel	Placebo	Simulated microbicide clinical trial to explore willingness to participate and methods for improving reporting of adherence in a sex-worker cohort	Population Council	India

Definition of acronyms used in this table: Entry/Fusion Inhibitor (EFI), Replication Inhibitor (RI), and Vaginal Defense Enhancer (VDE), Combination (C)

* The Alliance uses the term "sponsor" as defined by the International Conference on Harmonisation (Guideline for Good Clinical Practice, 1996) as follows: "An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial."For definitions of acronyms, please visit the Alliance website.

† Because of recent political events in Madagascar, plans for MIARADIA have been revised.

‡ Currently un-funded.

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