

## The Future of HIV Prevention: Prospects for an Effective Anti-HIV Microbicide

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As the devastation of the HIV-AIDS epidemic continues, women are increasingly bearing the greatest impact, particularly in developing countries [1]. In many of these countries, nearly 60% of people living with HIV-AIDS are women [2], and in several African countries, women 15 to 24 years of age are more than three times more likely to be infected than men the same age [3]. In South Africa, one in four women is infected by 22 years of age [4]. Globally, more than 17.5 million women are now living with HIV-AIDS [5], and there are an estimated 13.2 million infected women in sub-Saharan Africa [6].

Although effective prevention technologies and strategies do already exist, these are clearly insufficient to address the problems of the epidemic, especially in developing countries. The “ABC” approach (Abstinence, Be faithful, and use Condoms) has been used with some success in a number of African countries [5,7]. However, in a survey among young women in

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Harare (Zimbabwe), and Durban and Soweto (South Africa), 66% reported having one lifetime partner and 79% had abstained from sex until at least 17 years of age, yet 40% of the women were HIV-positive [8]. Clearly, abstinence is not a viable option for married women or for those who are victims of sexual violence. In addition, being faithful in a monogamous relationship will not protect women whose partners are unfaithful. In reality, in many countries being a married and monogamous woman is one of the highest risk factors for infection [9]. The consistent use of male and female condoms has been shown to be highly effective in preventing infection [10–12], but in many developing countries women have little or no say in their sexual practices, and their male partners are often not amenable to the use of condoms [13]. In addition, the ability of a woman to bear children is often critical to her status within her marriage and within society [14], and neither abstinence nor condoms are practical options for women who want to have children. These factors are reflected in the United Nations Population Division estimate that, globally, only 4.8% of married women of reproductive age use condoms regularly [15].

In view of these statistics, there clearly is an urgent need for female-initiated HIV-prevention options and, in the absence of an effective vaccine, microbicides present one of the most promising strategies for combating the epidemic. In fact, mathematical models predict that even a microbicide that is only partially effective could prevent millions of new HIV infections [16].

### **What is a microbicide?**

Microbicides are self-administered prophylactic agents that impede transmission of HIV or other sexually transmitted pathogens. In the broadest sense of the term, microbicides include products that can be used by any route or mode of administration to prevent infection. For example, a number of studies have been conducted to evaluate the effectiveness of oral drugs when taken before transmission of a pathogen (pre-exposure prophylaxis, or PrEP) or shortly after transmission (post-exposure prophylaxis) [17–19]. However, the focus of this article is on products that can be applied vaginally to impede sexual transmission of HIV. These include a variety of formulations, such as gels, creams, films, suppositories, sponges, and intravaginal rings. A summary of the status of topical microbicides that are actively being developed is presented in Table 1.

For a microbicide to be successful there are a number of criteria that must be met. Aside from efficacy, of utmost importance is safety. This was made clear during clinical trials investigating the use of the spermicide nonoxynol-9 as an HIV microbicide, in which the incidence of seroconversions was higher in women who used nonoxynol-9 multiple times each day when compared with those receiving placebo [20]. Possible explanations for this finding include inflammatory cell recruitment to the genital tract and

Table 1  
Status of microbicides currently in development

Class	Compound	Status
<i>Membrane disruptive agents</i>		
Surfactants	Sodium lauryl sulfate Sodium dodecyl sulfate	Phase I/II Preclinical development
<i>Entry inhibitors</i>		
Polyanions	Carageenan poly(styrene-4-sulfonate) (Carraguard) Carbopol (Buffergel) Dextrin-2-sulfate (Emmelle) Naphthalene sulfonate polymers (PRO 2000/5) Acetyl phthaloyl cellulose (cellulose acetate phthalate-CAP; Aquateric) Acid buffering gel (Acidform) Polystyrene sulfonate Dextran sulfate	Phase III  Phase III Phase III Phase III  Phase I  Phase I Phase I Preclinical development
Dendrimers	Vivagel (SPL7013)	Phase I
CCR5 blockers	L-860,167  RANTES analogs	Preclinical development Preclinical development
gp120 inhibitors	BMS-599793  Cyanovirin-N	Preclinical development Preclinical development
<i>Reverse transcriptase inhibitors</i>		
Nonnucleoside reverse transcriptase inhibitors	MIV-150 TMC120 (Dapivirine) UC781 S-DABO	Phase I Phase I Phase I Preclinical development
Nucleotide reverse transcriptase inhibitors	PMPA (Tenofovir)	Phase I/II

epithelial damage resulting from the local toxicity of nonoxynol-9 [20,21]. Secondly, it is crucial that a microbicide is used correctly, so it must be easy to use, acceptable to the user, should not interfere with sexual intercourse, and should have an appropriate duration of action [22]. Thirdly, a microbicide should be stable at the high temperatures typically encountered in developing countries, because refrigerated storage is not feasible in those regions most in need of these products. In addition, there are properties that although not crucial for a microbicide, would be very beneficial, including activity against other sexually transmitted diseases and availability

without prescription. Products should also be available with and without contraceptive properties, depending on the target population [23].

**How microbicides work**

The life cycle of HIV provides a number of points at which a microbicide could prevent infection. For this to be achieved, it is believed that the product should attack the virus at a point before integration (ie, before insertion of the proviral DNA into the host cell's DNA) [24]. Classes of microbicide drugs now under development are generally divided into four categories: (1) membrane disruptive agents [25], (2) entry inhibitors [26], (3) reverse transcriptase inhibitors [27], and (4) dendritic cell uptake inhibitors (Fig. 1) [24].

The first microbicide candidates developed are nonspecific compounds that work either by disrupting the viral envelope (membrane disruptive agents or surfactants) or electrostatically binding the virus and preventing it from interacting with its target cells in the vagina (entry inhibitors [eg, polyanions]) [24,28]. Three of these first-generation microbicides are now in large-scale efficacy trials. Of these, Carraguard and PRO 2000 are polyanions. BufferGel

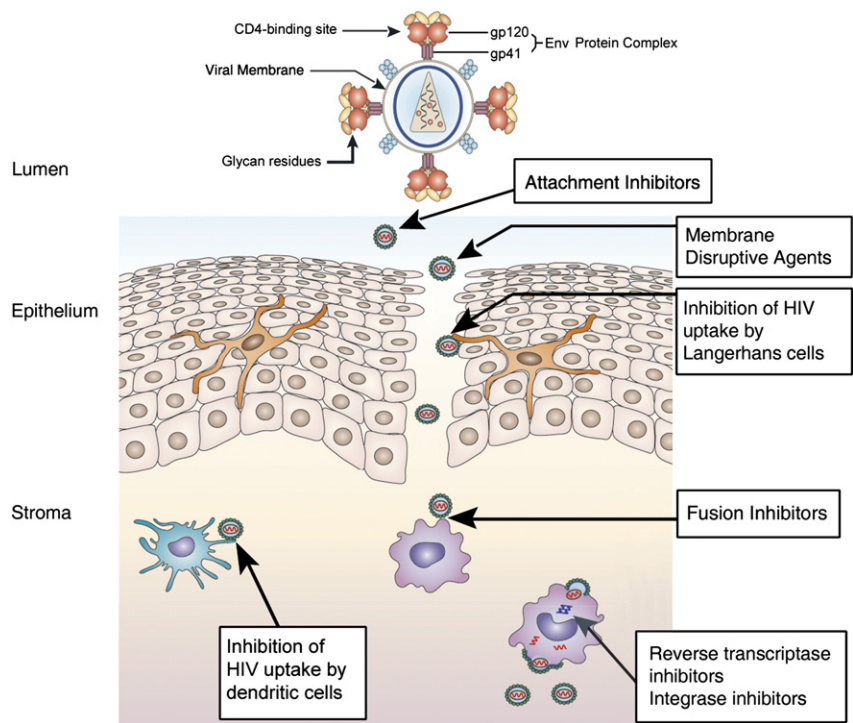


Fig. 1. Routes of infection by HIV and opportunities for microbicides for prevention of infection.

is also a polyanion but is designed also to maintain the low pH of the vagina, making it inhospitable to HIV [24]. Savvy is a surfactant that was also being evaluated for efficacy, until the trials were terminated because of the combination of an unexpectedly low HIV incidence and low protection seen at interim analysis, making it unlikely that the trial could provide convincing evidence that Savvy protects against HIV [29]. Dendrimers, such as VivaGel, are highly branched macromolecules that also prevent HIV from attaching to the target cells [30]. VivaGel is currently in safety studies. All of these compounds are formulated in clear gels and are intended to be applied vaginally just before sex (ie, coitally dependent).

A new generation of microbicides is now in development, consisting primarily of products based on antiretroviral (ARV) drugs that specifically target HIV, or the cells it infects. These include nucleotide reverse transcriptase inhibitors (NtRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and entry inhibitors. New classes of drugs that may also have use as microbicides but are not yet under investigation include nucleotide-competing reverse transcriptase inhibitors and integrase inhibitors. These classes, along with their advantages and disadvantages, are described below.

### *Entry inhibitors*

For HIV to infect a cell, it must bind to the CD4 receptor of the target cell. Binding occurs by gp120, a glycoprotein expressed on the viral coat [31]. Compounds that interfere with this process have been shown to prevent infection *in vitro*. For example, cyanovirin-N is a protein that targets gp120, potentially inhibiting its interaction with CD4 [31].

When gp120 binds to CD4, it undergoes a conformational change, revealing another glycoprotein known as “gp41,” which is involved in fusing the viral and cell membranes [32]. This process can also be inhibited by drugs such as enfuvirtide, which is marketed as Fuzeon for the treatment of HIV-AIDS [33]. Work is ongoing to develop small molecule drugs with similar activity for use as microbicides [34,35], which would reduce cost and production challenges frequently associated with peptides and recombinant proteins.

The great advantage of entry inhibitors is that they act very early in the HIV lifecycle, long before integration occurs. However, compounds that target the viral envelope may have differential activities against different clades of HIV, and as has been learned from attempts to develop vaccines against HIV, there is rapid evolution of diversity in the envelope resulting in resistance [36–39].

### *Nonnucleoside reverse transcriptase inhibitors*

These compounds inhibit viral replication by binding to the HIV-1 reverse transcriptase, which is the enzyme responsible for the transcription

of viral RNA to proviral DNA [27]. Within this class is a subgroup of tight-binding NNRTIs that bind irreversibly to reverse transcriptase, and consequently they are highly potent with long half-lives. In addition, they have an established track record as therapeutic drugs. There is also some evidence that in addition to inhibiting the replication of HIV within the host cell, NNRTIs may also inhibit infection by acting on cell-free virus [40], suggesting that these compounds could potentially inactivate the virus in the vaginal lumen. However, the mechanism of this cell-free inhibition has yet to be determined, and its relevance in vivo is unknown [41]. NNRTI compounds currently in development as microbicides include dapivirine (TMC120), MIV-150, UC 781, and S-DABO [27,42,43].

#### *Nucleotide reverse transcriptase inhibitors*

NtRTIs are closely related to another class of antiviral drugs used in the treatment of HIV-AIDS: the nucleoside reverse transcriptase inhibitors (NRTIs). Both classes exert their activity by mimicking endogenous nucleotides; once they are incorporated into the proviral DNA the chain cannot be extended any further [44]. For this reason these drugs are also known as “chain terminators.” To be active, NtRTIs and NRTIs require phosphorylation, and here lies the difference between them. NRTIs require three phosphorylations, and this process is influenced by a number of cellular factors including cell type, cell cycle, and the activation and infection status of the cell in which they occur [45]. In particular, the initial phosphorylation by nucleoside kinases is believed to be rate-limiting [46]. In contrast, NtRTIs undergo only two phosphorylation steps and it is the initial rate-limiting step of the NRTI activation process that is not required [46]. Consequently, NtRTIs are more suitable for development as microbicides than the NRTIs.

Tenofovir is currently the only drug in the NtRTI class, and the prodrug tenofovir disoproxil fumarate is marketed as Viread [47]. Therefore, there is extensive information available on the safety of tenofovir. Clinical studies are in progress, with tenofovir formulated as a microbicide gel [48].

#### *Nucleotide-competing reverse transcriptase inhibitors*

This is a novel class of inhibitors that act by competing with endogenous nucleotides for the binding site of reverse transcriptase [49]. Very little is known currently about the potential of this class as microbicides or therapeutics because it is so new.

#### *Integrase inhibitors*

The integration of the proviral DNA into host cell DNA involves multiple steps that are catalyzed by the HIV-1 enzyme integrase. This involves a series of DNA cutting and joining reactions in which the proviral and host DNA is prepared for “strand transfer,” the process by which the

processed ends of the two DNA strands are joined together [50]. Integrase inhibitors are a new class of ARVs that prevent this process from occurring, which in turn prevents viral replication. The drawback with integrase inhibitors as microbicides is that their mechanism of action occurs after transcription of the viral RNA, which is relatively late in the life cycle. Theoretically, it would only take one strand of proviral DNA to evade the inhibitor for infection to occur. They are most likely to have use in a microbicide when used in combination with drugs with other modes of action.

### *CCR5 and CXCR4 antagonists and dendritic cell uptake inhibitors*

There is a third group of compounds that differ from the ARVs described previously in that, rather than targeting the virus itself, they target the cells associated with infection. Included in this group are the CCR5 and CXCR4 antagonists and dendritic cell uptake inhibitors.

#### *CCR5 and CXCR4 antagonists*

In addition to binding with CD4, HIV must also bind with a coreceptor expressed on the cell membrane to enter a T cell. These are the chemokine receptors CCR5 and CXCR4 [51], and blockade of these receptors has been shown to be effective in clinical trials in HIV-AIDS patients [52]. Because most sexual transmission of HIV is believed to occur by CCR5-tropic strains [51], it is CCR5-blockers that have greater potential as microbicides, and a number of these compounds are under investigation for this purpose [53].

One of the concerns about use of these compounds is that the effects of long-term blockade of the CCR5 receptor on T-cell functionality have yet to be determined. Approximately 1% of Caucasians is highly resistant to HIV infection because they are homozygous for a 32-base pair deletion of the CCR5 receptor gene and do not express the CCR5 receptor, but these individuals maintain a normal inflammatory response [52]. It is not known, however, what effect CCR5-blockade has in individuals that do express this receptor. Secondly, in approximately 50% of HIV-AIDS patients, CXCR4-tropic viruses appear late in infection and often precede a rapid deterioration in clinical condition. It is possible that the suppression of CCR5-tropic virus could allow CXCR4-virus to predominate, resulting in accelerated disease progression [52]. However, these are currently only theoretical concerns, and ongoing clinical studies with CCR5-blockers in development as therapeutics should provide some insight into the actual risk associated with these compounds.

#### *Dendritic cell uptake inhibitors*

Dendritic cells are immune cells that transport captured antigens and disseminate them to T cells in the lymph nodes [24]. When an HIV virion crosses the epithelial barrier and is taken up and transported by dendritic cells, it can result in recruitment of additional susceptible cells to the site

of infection. Dendritic cells express the CD4 surface marker, and most of these cells also carry CXCR4 and CCR5, and a molecule known as DC-SIGN that is capable of binding HIV. Compounds, such as mannan, that inhibit the association of HIV with DC-SIGN may have potential as microbicides, but because they do not prevent direct infection of dendritic cells and lymphocytes by CD4 and CXCR4 or CCR5 [54], they would have to be used in combination with drugs with other modes of action.

Given the ability of HIV to develop resistance to drugs with a single viral inhibition target, and the fact that sexual transmission may occur by more than one mechanism [55], it is very likely that future generations of microbicides will comprise multiple active ingredients. For many years, the use of combinations of highly active antiviral drugs has been the gold standard for the treatment of HIV-AIDS [56]. This is because it has been proved to be much more effective than monotherapy [57]. Similarly, it is expected that combination microbicides would have greater efficacy compared with those consisting of only one active component.

### Challenges for product development

A critical step in microbicide development is the design of the formulation in which the drug is delivered. The composition and physicochemical properties of a formulation can influence a product's efficacy, systemic absorption, and toxicity, and it can also determine its cost and acceptability to the user. All current microbicide candidates in large-scale efficacy (Phase III) trials are formulated as coitally dependent gels and must be applied shortly before sex [2]. One of the advantages of the next generation of ARV-based microbicides is that they can be formulated in ways that allow them to be used independently of sex (eg, once-a-day). It is anticipated that, like contraception, consumer compliance would be higher with coitally independent use, and this could be crucial for HIV prevention during unanticipated or forced sex. Future gel development will include technologies designed to accommodate combinations of active components. Other delivery mechanisms are also under investigation. Vaginal rings, for instance, may be able to deliver a drug or combinations of drugs for periods of 1 month or more [58]. The feasibility of a vaginal ring to deliver the NNRTI dapivirine has recently been demonstrated *in vivo* [59].

To avoid the possibility of systemic toxicity, the absorption of microbicides into blood should be very low. Formulation technologies are available that allow for the sustained release of drugs over prolonged periods of time [60], and these technologies may have use in altering the pharmacokinetic properties of microbicides that would otherwise be systemically absorbed. However, local toxicity or irritation to the vaginal or cervical mucosa, is a concern for all topically applied microbicides. Severe local toxicity could result in breaches in the mucosal epithelium, providing HIV with a free passage to the systemic circulation and its targets for infection [61]. More subtle

inflammatory reactions are also a concern because the cells involved in the inflammatory response are also the target cells for HIV, so recruitment of these cells to the vagina and cervix may increase the risk of infection [62]. For this reason, rabbit vaginal irritation studies must be performed before initiation of clinical trials [63].

The normal vaginal flora plays an important role in protecting against infection. For example, the *Lactobacillus* species naturally present in the vagina produce hydrogen peroxide, which has properties that help protect against infection by HIV and other mucosal pathogens [64]. It is important that microbicide products do not disturb the vaginal ecology in a way that might compromise this natural barrier to infection.

Acceptability is crucial to ensuring that a microbicide is used correctly. Data from safety and acceptability studies of microbicide gels in many developing countries point to the need for microbicides that do not interfere with sexual intercourse and may be used discreetly [65]. Regional variations in cultural preferences and sexual practices suggest that no single product-type is universally acceptable, so microbicide developers are investigating other alternative delivery formulations including lotions, films, intravaginal devices, and solid dosage forms, such as foaming pills, and novel polymers and biologically triggered drug-release approaches.

One of the key challenges for product development is determining the optimal dose level of a microbicide. It is standard practice during drug development that before starting large-scale Phase III trials, a drug is first evaluated in a Phase II dose range-finding study using a small number of patients to obtain a proof of concept and determine what the appropriate dosage might be for the Phase III study [66]. However, because correlating dose with efficacy in HIV-prevention trials requires thousands of participants, a Phase II study in the traditional sense is not possible. At present, there are no well-characterized animal models of efficacy, so dose levels for Phase III microbicide studies are selected based primarily on in vitro antiviral activity assessments, pharmacokinetic data in women, and on the physicochemical characteristics of the product, such as its rheologic and drug-release properties. Therefore, the first definitive measure of whether a microbicide works is the large-scale efficacy trial.

### Challenges for clinical trials

There are no validated surrogate end points for microbicide efficacy; therefore, the primary end point of microbicide effectiveness trials must be HIV incidence [67]. Ethical requirements for the conduct of efficacy trials for microbicides require that participants are provided with, and counseled to use, condoms [68]. Trials must be designed in such a way that they can determine the effectiveness of a microbicide in preventing infection on those occasions when condoms are not used but the microbicide is used. Since

these instances are likely to be relatively infrequent, the trials require thousands of subjects at high risk of infection to be monitored for at least 1 year. The complexity of conducting such large trials is complicated by the limited number of clinical trial sites in suitable locations that are capable of working to the rigorous standards of Good Clinical Practice that are required of studies to support licensure of pharmaceutical products [68]. The demands of the study size, duration, and location mean that efficacy studies for microbicides are very expensive. The cost of conducting pivotal efficacy studies to support licensure for a single product is estimated at up to \$100 million [69].

One challenge specific to microbicide gel efficacy trials is the design of the placebo control arm. To maintain study blinding, an ideal placebo gel would be identical to the gel vehicle in the active arm. However, some vehicles are designed to have bioadhesive, lubricating, and pH-buffering properties, all of which might contribute to the protective effect of the active gel. To address this issue, a universal placebo gel has been constructed and is currently being used in most of the ongoing trials [70]. Since the effect of the universal placebo on HIV incidence is unknown, one current trial, HPTN 035, has included a second no-gel control (condom only) arm to address concerns that placebo gels may themselves reduce or enhance HIV infection, and that the use of microbicides could decrease condom use, resulting in a net increase in HIV infection rates [71]. Critics of this design have highlighted the fact that the inclusion of a condom-only arm means the study is no longer blinded, which may influence behavior and preclude a true “like-with-like” comparison between arms [68,72,73]. Since including a third arm requires a 50% increase in the size of the study, with consequential increases in time, cost, and strain on the limited capacity of clinical sites [72], it is hoped that the data from HPTN 035 will eliminate the need for further no-gel control arms.

Sample sizes for Phase III efficacy trials are based on predicted HIV seroconversions. If actual HIV incidence in the placebo arm is lower than expected, there will not be sufficient statistical power to determine efficacy. For example, the Phase III study for Savvy was terminated at the Ghana site in November 2005 and at the Nigeria site in August 2006 because of lower than expected incidence rates [74]. The anticipated annual rate of new HIV infections at trial initiation was 3.7%, but almost 2 years into the study, the annual HIV incidence was less than 2%. Prospective cohort studies under trial conditions are necessary to measure HIV seroconversions and to ensure appropriate trial design.

Another issue is compliance, which is the frequency at which the participants use the product correctly. The first generation of microbicides in efficacy trials is intended for use with every sex act. In some of these trials, compliance, measured by direct reports from the trial participants themselves, ranges from 40% to 80% [75]. A low level of compliance in the current efficacy trials will reduce the likelihood of observing efficacy. Therefore, consideration needs to be given to ways of improving levels, and measures, of compliance in studies.

Women enrolled in Phase III efficacy trials are required to use at least one form of contraception during the study [68]. However, despite this prerequisite, high chemical pregnancy rates of up to 70% have been observed in the current efficacy trials [76,77]. Women who become pregnant must discontinue product use, so high pregnancy rates can complicate data interpretation and result in a study that is underpowered to demonstrate whether a microbicide is effective. Improved access to contraception could reduce the extent of the predicament. The possibility of maintaining pregnant women on product throughout pregnancy has been proposed, providing the preclinical safety program has been completed, including the full package of reproductive toxicity studies and carcinogenicity studies [77]. However, this would mean substantial delays to the start of the Phase III studies, and despite the availability of preclinical data, there remains an element of risk to the developing fetus.

With the conduct of clinical trials in developing countries, there is a moral obligation to safeguard the welfare of volunteers, and most believe this has implications for the provision of diagnostic and treatment services to the persons who are participating in the trials [68,78]. These may include diagnosis and treatment for sexually transmitted infections and vaginal infections, family planning services and care for those who become pregnant, and Pap smears for the detection of cervical carcinoma. The recent increased availability and lower cost of ARVs, and the establishment of national treatment programs, have resulted in commitments to provide ARV treatment to persons who become HIV infected during the course of their participation in a trial. In most cases, those who become infected with HIV during a trial are now able to be referred to local HIV treatment centers or are provided treatment by the study sponsor, although there is concern that these centers will soon be overloaded with newly diagnosed HIV-infected persons.

Informed consent in developing countries is a challenge because of lower education and literacy rates of trial participants, the use of research concepts unfamiliar in the local cultural context, the potential that trial benefits may be an undue enticement, and that the risks may not be fully understood [68]. To help overcome these potential problems, the “informed consent” should not only be a form that is signed, but also a process that is continuously reinforced throughout the trial to ensure that participants are fully aware of the risks and benefits. Some trials have used such measures as a “test of understanding” to ensure that participants truly understand the nature of the trial and its risks before enrollment. In addition, it is crucial that the local ethical review committee and community advisory board guide the investigators to ensure that trial benefits or incentives are appropriate and do not entice or pressure the participant to engage in a research study.

It is important that the community in which the trial takes place fully understands and supports the trial, otherwise false perceptions may lead to misleading information, discrimination of trial participants, high drop out rates, or even closure of the trial [68]. Early in the preparations in advance

of the trial, investigators should meet with community advisory boards, key opinion leaders, and the media to explain the purpose and procedures of the trial and to receive their feedback and support. In addition, it is important to maintain channels of communication by means of newsletters or meetings throughout the trial to keep the community and its leaders informed of the progress of the trial and the final results.

It is increasingly evident that anal sex is practiced more than previously thought in developing countries and in developed countries among gay men and heterosexuals [79]. It is very likely that microbicides intended for vaginal use may also be used rectally, particularly after a proven effective microbicide is licensed and available for widespread use. This is a concern because the anal/rectal epithelium and other factors for anal sex are very different from the vaginal/cervical mucosa. It is unknown at present whether the safety and efficacy profiles are different for these two modes of HIV transmission. Research and trials of microbicides appropriate for anal sex are currently underway. In the meantime, in trials of vaginal microbicides, it is very important to stress to trial participants that they do not engage in anal sex or use the microbicide rectally during the trial.

## **Drug resistance**

The use of ARVs as microbicides has theoretical implications regarding the development of drug-resistant HIV. One issue is the potential for transmission of drug-resistant strains that may overcome an ARV-based microbicide [41]. It is important to remember, however, that resistance represents a reduced susceptibility of HIV rather than a total invulnerability to a drug [80], so a resistant strain will only overcome a microbicide if it is unsusceptible to the concentration of drug to which it is exposed in the vaginal lumen or target tissues.

A second concern is the potential for microbicides that are systemically absorbed to select for resistance in HIV-positive women who are unaware of their HIV status and are using a microbicide. This also has implications for the subsequent treatment options that would be available to infected women in this circumstance [41]. However, the importance of this is not yet understood, and it is possible that systemic concentrations of drug will be inadequate to select for resistance. The development of ARV-containing microbicides should include resistance studies to gain a better understanding of the relevance of these concerns.

## **Regulatory hurdles**

As with any pharmaceutical product, once a microbicide has been demonstrated to be safe and effective it must be approved and registered by the appropriate regulatory authorities in those countries in which it is

intended to be distributed. Understanding the route by which a product is to be licensed is important well in advance of the registration procedure, because there are implications for the product development pathway.

Microbicides represent a new class of pharmaceutical products, and reviewing regulatory applications for first-in-class products requires a level of expertise and resources that authorities in developing countries generally do not have [72]. In fact, new pharmaceutical products in developing countries are often approved on the basis that they have been licensed and widely used in the United States or Europe [81]. Licensure applications could be reviewed by authorities that do have the necessary expertise and resources, such as the US Food and Drug Administration or the European Medical Evaluation Agency (EMA); however, the mandate of these authorities is only for their own populations. Since drug approvals are based on an assessment of benefit versus risk to the target population, a decision made by the Food and Drug Administration or EMA is unlikely to have relevance for a developing country because the risk of HIV infection in the United States and Europe is relatively low and treatment is readily available for HIV-AIDS patients. A microbicide of even modest efficacy is more likely to be acceptable in developing countries where the risk of infection is high.

In recent years, some progress has been made in addressing these issues. The capacity of developing country agencies to make licensing decisions for vaccines has been strengthened [81], although resources remain inadequate. In 2004, the EMA issued Article 58 of Regulation (EC) No 726/2004, which established a mechanism whereby the EMA, in cooperation with the World Health Organization, is able to give a scientific opinion on certain medicinal products intended exclusively for markets outside the European Union [82]. The authorities in the developing countries can then use the scientific opinion as the basis on which they decide whether a drug should be approved. However, the Article 58 procedure has only been used three times, and in all cases this was for ARV products that are duplicates of products that were already approved and used in the European Union [83–85]. The procedure has yet to be used for products that have not been licensed elsewhere.

The EMA has also established a procedure under Regulation (EC) No 726/2004 for a Conditional Marketing Authorization for drugs that will address unmet medical needs and are in the interest of public health [86]. This includes drugs that are for treatment, prevention, or diagnosis of seriously debilitating or life-threatening diseases, or drugs to be used in emergency situations in response to public health threats recognized by the World Health Organization or by the European Community. The mechanism grants marketing authorizations on the basis of less complete clinical data than is normally required, providing that the risk-benefit balance is positive and the benefits to public health of making the medicinal product immediately available outweigh the risk inherent in the fact that

additional data are still required. The holder of the Conditional Marketing Authorization is obligated to fulfill certain requirements, including the completion or initiation of studies to confirm that the risk-benefit balance is positive. The authorization is renewed annually until the data package is complete, at which point a normal marketing authorization may be granted [86].

The Canadian authority, Health Canada, has developed a similar process for what is called a Notification of Compliance with Conditions (NOC/c) [87]. The NOC/c policy can be applied to products related to a serious, life-threatening, or severely debilitating disease or condition for which there is promising evidence of clinical effectiveness. This evidence is based on the available data that show the drug has the potential to provide effective treatment, prevention, or diagnosis of a disease or condition for which no drug is presently marketed in Canada, or a significant increase in efficacy or significant decrease in risk such that the overall benefit-risk profile is improved over existing therapies, preventatives, or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada. Clinical data from only one study that demonstrate a favorable benefit-risk balance may be sufficient for a NOC/c application, whereas data from two studies are usually required for registration. In addition, clinical evidence may be established in a variety of ways including by literature review, expert opinions, panels, or pharmacokinetic/pharmacodynamic studies. However, a prerequisite for a Notification of Compliance qualifying under the NOC/c policy is the sponsor's written commitment to pursue confirmatory studies acceptable to Health Canada and to adhere to the pharmacovigilance and restricted use conditions.

Another regulatory hurdle is the lack of guidance on the requirements for registration of products that contain combinations of two or more active ingredients. Although not documented in any guidelines, regulatory authorities have expressed an expectation that products containing more than one active ingredient must show clinical superiority of the combination over the individual components [88]. This has implications for development timelines, the size of the clinical trials and, consequently, the costs, particularly if clinical superiority must be proved in the Phase III studies. For example, for a microbicide with 50% efficacy to demonstrate superior efficacy relative to a placebo group, about 5600 volunteers would be needed. Whereas, for a two-agent microbicide with 70% efficacy to demonstrate superiority over a single-component product with 50% efficacy, about 19,000 women would be needed [72]. Given the recent success of combination ARV therapies, a strong preclinical rationale for combination microbicides may be sufficient for testing of the active ingredients alone.

Although there has been some progress in addressing the regulatory hurdles for microbicides, more work is required to establish proven processes for registration and to clarify and expedite the pathways for combination products.

## **Introduction, use, and future access**

Once licensed, the HIV-prevention potential of microbicides will only be realized if they can be successfully and appropriately introduced into HIV-prevention programs and used by women and their partners. Epidemiologic modeling can help guide decisions on where and how most effectively to introduce microbicides as part of a broader HIV-prevention mix. This should include scenario planning for the launch of microbicides with different product characteristics. Epidemiologic modeling should be complemented by studies to understand the factors that influence the adoption and continued use of microbicides by women with their sexual partners. Building knowledge of and demand for future microbicides among women and support within communities is essential to supporting their future use.

With over 97% of HIV-infected people living in low-income countries and 77% in sub-Saharan Africa [5], microbicides have their greatest potential for women living in the developing world. However, it is estimated that only one in five people living in developing countries currently has access to existing HIV-prevention services [89]. Early planning and timely mobilization of partners and resources are needed to ensure that microbicides reach and can be used by women most in need of them. Microbicides need to be available in sufficient quantities to meet demand, geographically accessible at appropriate distribution points, acceptable to women (and to policy makers and health professionals), and affordable (for individuals and for others financing their use).

To address these components, access must be integrated into microbicide development from the early stages. Candidate products must be designed to meet the needs of women in developing countries. They must be capable of manufacture at large scale and at low unit cost. Intellectual property agreements should allow flexibility in manufacturing and pricing strategies, thereby supporting affordability and sufficient and secure supply.

As promising candidates progress through clinical testing, studies to estimate potential microbicide demand are required to inform the scaling of manufacturing and to mobilize necessary financing. Strategies and programs need to be developed, costed, and implemented to build demand, distribute microbicides, and provide the necessary supporting services and education. A range of policy and advocacy resources is needed to make the case for and to inform decisions on microbicide introduction by developing countries' policy makers and to mobilize the support of local and international communities.

With three candidates currently in Phase III trials and next-generation candidates already in safety trials, the microbicide field is progressing work in many of these areas [90]. These efforts need to continue and iteratively build an evidence base that can mobilize partners, support successful introduction, and provide maximum health benefit.

## Summary

Microbicides present one of the most promising strategies for combating the HIV-AIDS epidemic. However, the development of a microbicide is a long and complicated process, with many hurdles that are unique to this class of product. These include challenges in product design, in the conduct and design of clinical trials, and in obtaining licensure of a new class of products intended for use almost exclusively in developing countries. Once they have been registered, there are additional challenges to the marketing and distribution of microbicides.

Successfully overcoming these obstacles requires close collaboration among many parties including scientists, regulatory authorities, policy makers, funding organizations, community members, and activists. In addition to the critical funding provided by governments and the private sector, support from policy makers and global leaders is required to bring microbicides successfully to women who need them most. Microbicides must be firmly situated within the broader contexts of comprehensive responses to HIV-AIDS, gender, health, and development policies, and evolving commitments to support research and development for the health needs of developing countries.

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