



INTERNATIONAL
PARTNERSHIP *for*
MICROBICIDES

ISSUE BRIEF

Microbicide Research & Development



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Why microbicides?

HIV/AIDS ranks among the world's most devastating diseases because it has spread rapidly and mainly afflicts young people in their most productive years. An estimated 33.2 million people worldwide are living with HIV/AIDS; 25 million already have died from AIDS; and, in 2005, more than four million more women, men and children became infected with HIV.^{1,2,3}

Women, particularly those in resource-poor countries, bear an increasing burden of the epidemic as both caregivers for the ill and because of their heightened risk of infection due to greater physiological, economic and social vulnerabilities. In sub-Saharan Africa, almost 61 percent of adults living with HIV are women.¹ In many African countries, women and girls aged 15 to 24 are three times more likely to be HIV-infected than their male counterparts.⁴

Efforts to prevent HIV/AIDS have traditionally focused on the "ABC strategy": **a**bstinence and delaying sexual debut, **b**eing faithful to one sexual partner and the correct and consistent use of **c**ondoms.⁵ However, in many cultures women do not have the power to insist their male partners use condoms during sex or remain sexually faithful. More recently, male circumcision has proven to be associated with significantly reduced HIV

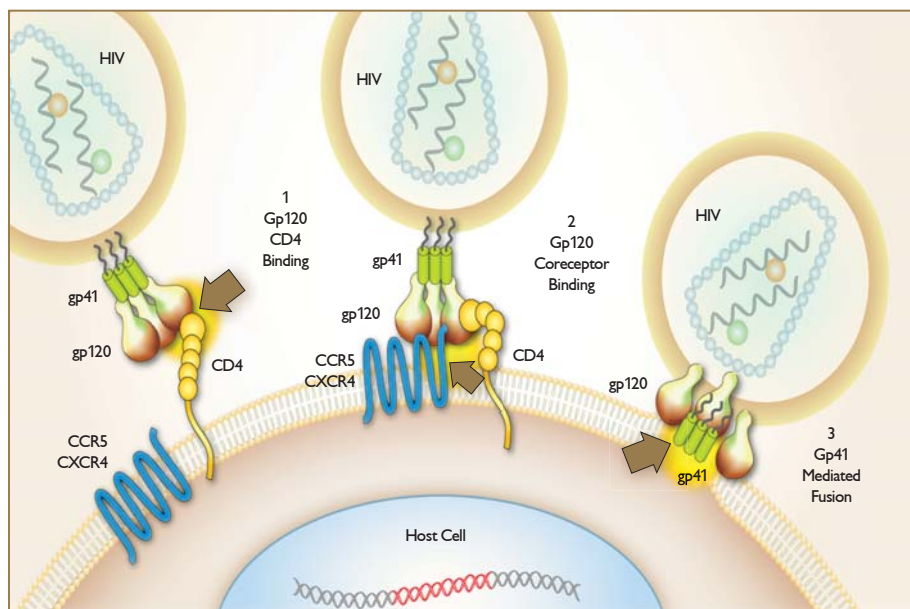
transmission from women to men.^{6,7,8} However, evidence on its impact in reducing infection in women remains inconclusive.⁹

Thus, all currently available HIV-prevention interventions require the cooperation of the male partner, which may or may not be assured. This is why it is essential to develop additional prevention strategies that women can initiate and control. An HIV vaccine could be an effective female-initiated prevention option, and efforts in vaccine development are ongoing, although a marketed product is still at least a decade away according to most experts. Another strategy is to develop microbicides, vaginal products that could prevent HIV transmission to women during sexual intercourse, which would be acceptable to women.

How HIV infects women

A microbicide could prevent HIV infection by interfering at one or more of the various stages in the HIV replication cycle. HIV infection is thought to take place a number of ways including cell to cell transmission and the use of host cell receptors, CCR5 and CXCR4. Presented here is what is thought to be the most likely route of HIV vaginal transmission, the CCR5 co-receptor mediated pathway. First, the virus enters the body through the vaginal and cervical epithelium, the lining of the inner surface of the vagina and cervix, and reaches a host cell

Figure 1: Mechanism of HIV binding and fusion to host cell



called a CD4 lymphocyte (a key immune cell targeted by HIV). In the **attachment stage**, the virus affixes to the host cell. A glycoprotein (gp120) on the surface of the virus binds with CD4 and then, after a binding-dependent change, binds also to a second receptor on the host cell's surface, CCR5. Next, at the **fusion stage**, the binding of HIV to its two receptors allows for the viral glycoprotein gp41 to fuse with the host cell's membrane, and the

IPM's role in microbicide development

The International Partnership for Microbicides (IPM) was established in 2002 to facilitate the development, licensing and distribution of microbicides for women in the developing world. Its mandate is to accelerate this process and maximise the chances of success.

Fundamental to this effort is IPM's Research and Development (R&D) programme. As a product development partnership, IPM has incorporated elements from several organisational models in order to build the most functional approach tailored to microbicide development. Flexibility, the cornerstone of IPM's R&D programme, is only possible because many donors provide funding for the core work plan, allowing IPM to make real-time decisions on resource allocation.

IPM supports microbicide research and development both by directly undertaking projects and by funding efforts originated and executed by third parties. IPM's general approach is to outsource as much as possible and create its own infrastructure only when the benefit to the mission is clear. In this way, IPM functions much like a small pharmaceutical or biotechnology company.

virus releases its contents (viral RNA and enzymes) into the host cell (see Figure 1). This is followed by the **reverse transcription stage**, when the virus uses an enzyme called reverse transcriptase to transcribe the viral RNA (genetic material) into DNA. This viral DNA then crosses into the cell's nucleus and becomes part of the host cell's genome in a process called **integration**. From this point, the viral DNA orchestrates virus production using the cell's own machinery. Each day, in infected untreated people, millions of viral copies are produced.¹⁰ It is also possible for infection to occur via cell to cell mediated transmission, and through an alternative co-receptor (CXCR4).

How microbicides work

The **early generation of microbicide candidates** – two now remain in efficacy trials—work either by electrostatically associating with the virus and blocking it from attaching to target cells in the vagina, or by establishing conditions in the vagina that inhibit infection.

The **next generation of microbicides**, now being developed, use antiretroviral (ARV) compounds that specifically target HIV or its target cells. (For further

discussion on early- and next-generation microbicides, see Table 2 on page 8.) Microbicides that interfere with the virus's life cycle before the integration stage are expected to have a better chance of preventing HIV infection because they act before the permanent insertion of the viral genome into that of the host cell. Classes of microbicides currently under development are generally divided into two main categories: entry inhibitors and reverse transcriptase inhibitors.¹¹

See Table 1 for a summary of potential microbicide candidates that are in various stages of development. Figure 2 presents the various mechanisms of action of several microbicides in development.

Entry inhibitors

The advantage of entry inhibitors is that they seek to act early in the HIV lifecycle by preventing either attachment to target cell surfaces, or entry of target cells after attachment.

Polyanions (electrically charged molecules), which are early-generation microbicides, are nonspecific entry inhibitors. Polyanions carry a negative electrical charge that attracts HIV, which has many positive charges on its surface, hence preventing the virus from attaching

to the host cell. Carraguard® and PRO2000, two early generation products, are both polyanions. The efficacy trial for Carraguard concluded in March 2007 with final results disseminated in February 2008. The trial of PRO2000 is expected to end in 2009.

Vaginal defence enhancers, also early generation microbicides, act by maintaining an acidic environment in the vagina, thus making it inhospitable to HIV. Buffergel is a vaginal defence enhancer currently in efficacy trials. It is also a polyanion. Two other microbicide candidates with this mechanism of action—Acidform and Lactin-V—are in safety trials.

Gp120 inhibitors act by selectively binding to gp120 on the surface of HIV, interfering with HIV binding to the host cell. This group of ARV compounds is specific to HIV. Bristol-Myers Squibb has licensed a gp120 inhibitor (BMS 599793 [DS003]) to IPM that is currently in early pre-clinical studies.

A fourth group of entry inhibitors acts by blocking the host cell's receptors (CCR5 and CXCR4), thus preventing the virus from attaching to the host cell. CCR5 is thought to be significantly more important than CXCR4 in sexual transmission. This group of ARVs are known as **CCR5 blockers**. Merck has licensed a CCR5 blocker (Merck L 860,167 [DS001]) to IPM that is currently in pre-clinical studies. In early 2008, Pfizer agreed to give IPM a royalty-free license to develop another CCR5 blocker, maraviroc, Pfizer's newly-approved HIV treatment, as a microbicide for the prevention of HIV infection.

Finally, **gp41 inhibitors**, such as Trimeris's T1249, act by blocking the viral gp41 protein, thus preventing HIV from productively fusing with the host cell.

Reverse transcriptase inhibitors

There are two main types of reverse transcriptase inhibitors: **non-nucleoside reverse transcriptase inhibitors (NNRTIs)** and **nucleotide reverse transcriptase inhibitors (NtRTIs)**.

NNRTI compounds have an established track record as effective ARVs. They inhibit viral replication by binding to the HIV enzyme reverse transcriptase (an enzyme essential to the virus replication process).⁹ Some NNRTIs bind permanently to reverse transcriptase and are highly potent with long half lives (i.e., they remain stable and active for a long duration once inside the body). 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,¹² suggesting that these compounds could potentially inactivate the virus in the vaginal lumen (cavity) itself. Examples of NNRTIs currently in development as microbicides include IPM's lead candidate, dapivirine (TMC120), the Population Council's MIV 150, CONRAD's UC 781, and Idenix's S-DABO.^{10,13,14}

NtRTI compounds mimic endogenous nucleotides, the building blocks of the viral cDNA. NtRTI compounds can be thought of as a bad link in a chain. Once they are incorporated, the next link can no longer be added. Thus, once they are incorporated into the viral DNA, they prevent the viral DNA from growing any further.¹⁵ CONRAD's and IPM's PMPA is an example of NtRTI-based microbicides currently under development.

Early & next generation microbicides

ARV-based microbicides are sometimes referred to as next-generation microbicides. The differences between earlier iterations of microbicide products and next generation microbicides are summarised in Table 2.

Integrase inhibitors

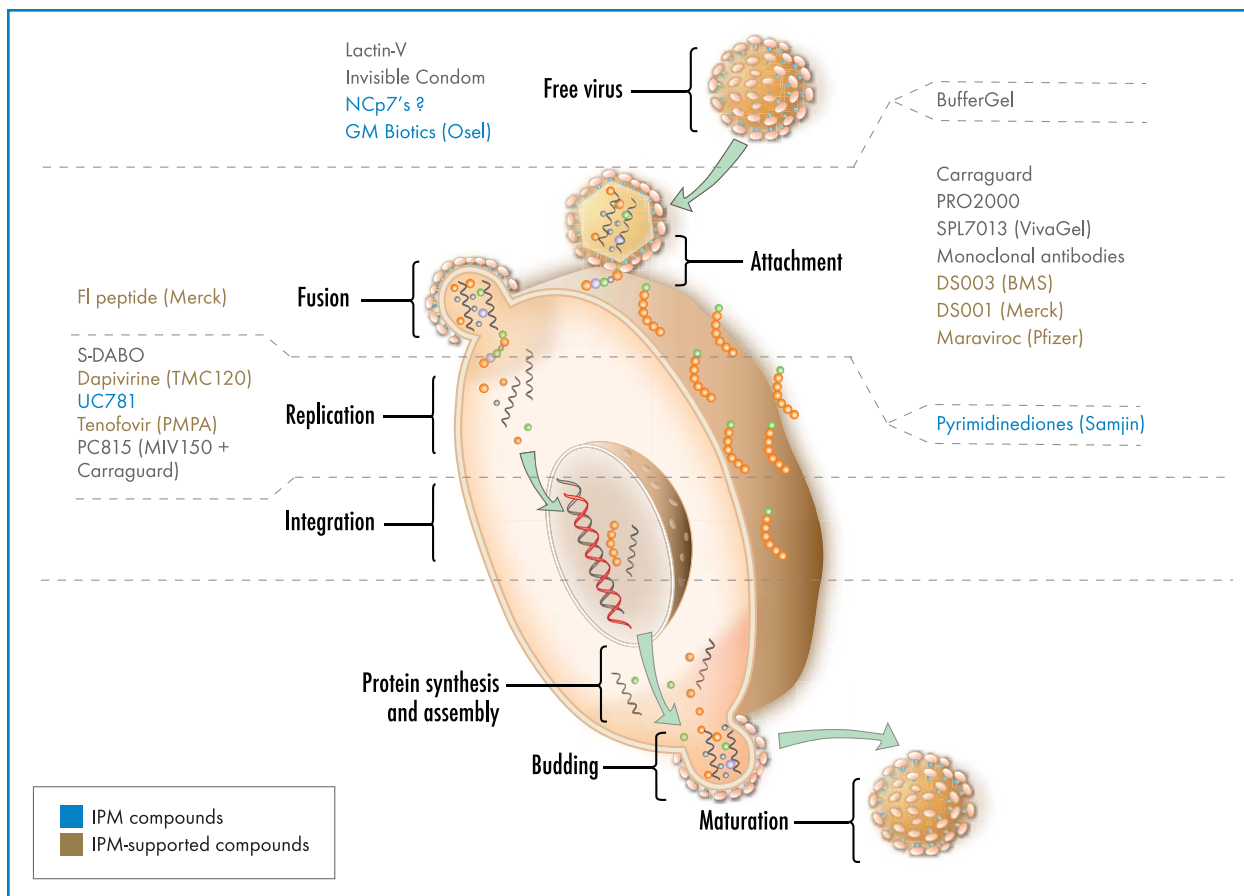
The integration of the viral DNA into the host cell's DNA involves multiple steps that are catalysed by the HIV enzyme "integrase." Integrase inhibitors are a new class of ARVs that prevent this process from occurring, which in turn prevents viral replication. A potential drawback with integrase inhibitors as potential microbicides is that their mechanism of action occurs after transcription of the viral RNA to DNA, which is relatively late in the viral life cycle.

Table 1: Potential microbicide candidates by category, stage of development and developer/sponsor*

Category	Pre-clinical Studies	Developer / Sponsor	Safety Clinical Trial	Developer / Sponsor	Efficacy Clinical Trial	Developer / Sponsor
Entry Inhibitors						
Non-specific:						
Polyanion			Invisible Condom	Laval University / Canadian Government	Carraguard	Population Council/ Gates/ USAID
			SPL7013 (Vivagel)	Starpharma Ltd./ NIH	PRO2000	Indevus Pharmaceuticals Inc./ DFID/ NIH
Vaginal Defence Enhancer			Lactin-V	Osel Technologies, Inc.	Buffer-Gel	ReProtect, Inc. /NIH
			ACIDFORM™ / Amphora™	CONRAD/ Instead, Inc.		
Specific:						
gp120 inhibitor	BMS 599793 (DS003)	IPM				
			Monoclonal Antibodies			
				EMPRO (European Microbicides Project) / European Commission		
gp-41 target	T1249	Trimeris				
	Small molecules	Locus Pharmaceuticals Ltd/IPM				
CCR5 blocker	Merck L 860,167 (DS001)	IPM				
	Merck L 860,872 (DS004)	IPM				
	Merck L 860,882 (DS005)	IPM				
	Merck L 644 (FI Peptide)	IPM				
	RANTES Analogs	University of Geneva/ Mintaka Foundation/ IPM/NIH/USAID				
	Maraviroc (DS006)	Pfizer/IPM				
Reverse Transcriptase Inhibitors						
NNRTIs	S-DABO	Idenix/ European Commission	Dapivirine (TMC120)	IPM		
	Pyrimidinediones (Samjin) (also have entry inhibitor activity)	Imquest /IPM	UC 781	CONRAD/ USAID		
NtRTI			Tenofovir (PMPA)	CONRAD/ IPM	Tenofovir	CONRAD/ South African Government
Combinations						
NNRTI / Polyanion			PC 815 (MIV 150 + Carraguard)	Population Council / USAID		
NtRTI + other compound (s)	Tenofovir in combination	IPM				
NNRTI + CCR5 blocker	Dapivirine + Merck L-860,167 (DS001)	IPM				

*As of February 2008. The microbicide development field is fast-moving and the content of this table will change.

Figure 2: Microbicides in product development, by their site of action in relation to the HIV life cycle (as of February 2008).



Understanding issues of drug resistance

Under certain circumstances, it may be possible for ARV-based microbicides to potentially select for naturally occurring HIV mutations that result in resistance. (See the box on page 10- "How does resistance occur?") The degree to which this may occur, as well as its clinical and epidemiological significance, is currently unknown.

Two issues must be addressed in studies of the potential emergence of resistance to ARV-based microbicides:

- If a woman is exposed to an HIV strain that is resistant to the ARV in the microbicide she is using, will the microbicide be sufficiently efficacious to prevent her from becoming infected?
- If a woman unaware that she was already infected with HIV were to use a microbicide containing an ARV, would this lead to the emergence of a resistant virus? If this happened, would the women be able to benefit from the same ARV as part of her HIV treatment regimen?

Table 2: Comparison between early and next generation microbicides

Early Generation Microbicides
First microbicides developed, currently in efficacy trials.
Nonspecific to HIV.
Gel formulations.
To be applied vaginally within a few hours before sex (coitally dependent).
No concern about potential resistance.
Next Generation Microbicides
Newer products in different stages of preclinical, safety and acceptability clinical trials.
Specific to HIV (ARV-based).
Formulated in different forms: gel, film, vaginal ring and tablet.
Long duration of action (sustained protection) so may be applied once a day. In case of a ring, can be applied once a month or longer (non-coitally dependent).
Resistance is a possible issue that needs to be investigated.

In general, understanding issues of drug resistance requires studies that follow patients who use a certain drug for a period of time. With ARV treatment, drug resistance is studied through long-term follow-up of HIV infected individuals both on and off ARV therapy to examine the virus's susceptibility to the ARV in use.

Questions about the possibility of resistance to ARV-based microbicides can best be addressed during and after an efficacy trial. These clinical trials will provide the basis for follow-up studies investigating the issue of resistance. Women who seroconvert (become infected with HIV) during an efficacy trial will be followed for a period of time after close of the trial to determine the specific HIV strain they have acquired and whether it is susceptible to different ARVs. It is worth mentioning that all volunteers in microbicide clinical trials are counselled before their enrolment regarding protection against HIV infection including the use of condoms.

IPM is committed to providing all study volunteers who become infected with HIV during the course of a trial with appropriate antiretroviral (ARV) treatment. IPM will pay for ARV treatment during and after the clinical trial until national HIV programmes are able to provide this care.

Combination microbicides

The use of combinations of highly active ARV drugs is the gold standard for treating HIV/AIDS¹⁶, because these drugs have proven much more effective than treatment with single drugs as they interfere with HIV at multiple stages in its life cycle. Combination ARVs are also less likely to lead to resistance¹⁷. Similarly, combination microbicides may have greater efficacy than products consisting of only one active component. This hypothesis seems logical, but remains to be proven. A number of combination microbicides are currently under investigation (see Table 1).

How does resistance occur?

Every time an RNA virus such as HIV replicates, an error may occur in the genetic material of the virus. These errors are known as mutations. In animal cells there is a mechanism for correcting errors in DNA replication, so the occurrence of durable mutations in the body is very rare. However, HIV does not have a repair mechanism, and based on the size of the RNA molecule, it is estimated that approximately one mutation occurs every time HIV replicates. This means that each HIV-infected person who is not receiving ARV treatment produces approximately one million mutated viruses every day. Due to the variety of mutations that occur daily, it is not surprising that some mutations may result in viruses that are not susceptible to a given drug (i.e., they are resistant to the drug).

It is important to note that virus mutations take place in HIV-infected individuals whether or not the person is receiving drug therapy. If a resistant virus develops in an HIV-infected person being treated with ARV's, viruses without the resistance mutation would continue to be susceptible to the ARV. The mutated virus would survive and proliferate to become the predominant HIV strain in the infected individual. This is known as "selection."

In some cases, an ARV drug selects for mutated virus that is resistant to other drugs in the same ARV therapeutic class (e.g., NNRTIs).¹⁸ This is known as "cross resistance."

While resistance associated with ARV-based microbicides could be a concern, other HIV-prevention programmes have moved forward despite similar issues. In prevention of mother-to-child transmission programmes, nevirapine, an NNRTI, has been found to select for resistance in some women, yet this has not precluded women from continuing to use it and benefiting from other NNRTIs in the course of their treatment. It is a matter of balancing the potential risks in order to gain the known benefits of using an ARV to prevent HIV transmission.

IPM's Research & Development Programme

IPM's R&D programme focuses on five key areas: (1) microbicide pipeline expansion and development; (2) formulation/delivery; (3) models for animal and tissue testing; (4) production for early clinical trials; and (5) mucosal biology and transmission.

Microbicide pipeline development

For the microbicide field to properly hedge its development efforts, universities, non-profit product development partnerships and biotechnology and pharmaceutical companies working to develop microbicides need to have new candidate microbicides and new ARVs classes in the testing pipeline. This is essential, considering the limited success rate associated with new drug development.¹⁹ (See Figure 3.)

Fortunately, the microbicide field has seen an increase in potential compounds available for evaluation in recent years,²⁰ although many of these new compounds are still in the pre-clinical testing phase.

IPM is concentrating on next-generation ARV-based microbicides and has in-licensed compounds with varying

mechanisms of action from five large pharmaceutical companies: Tibotec Pharmaceuticals, Ltd. (a subsidiary of Johnson & Johnson), Merck & Co., Inc., Bristol-Myers Squibb, Gilead Sciences, Inc., and Pfizer.

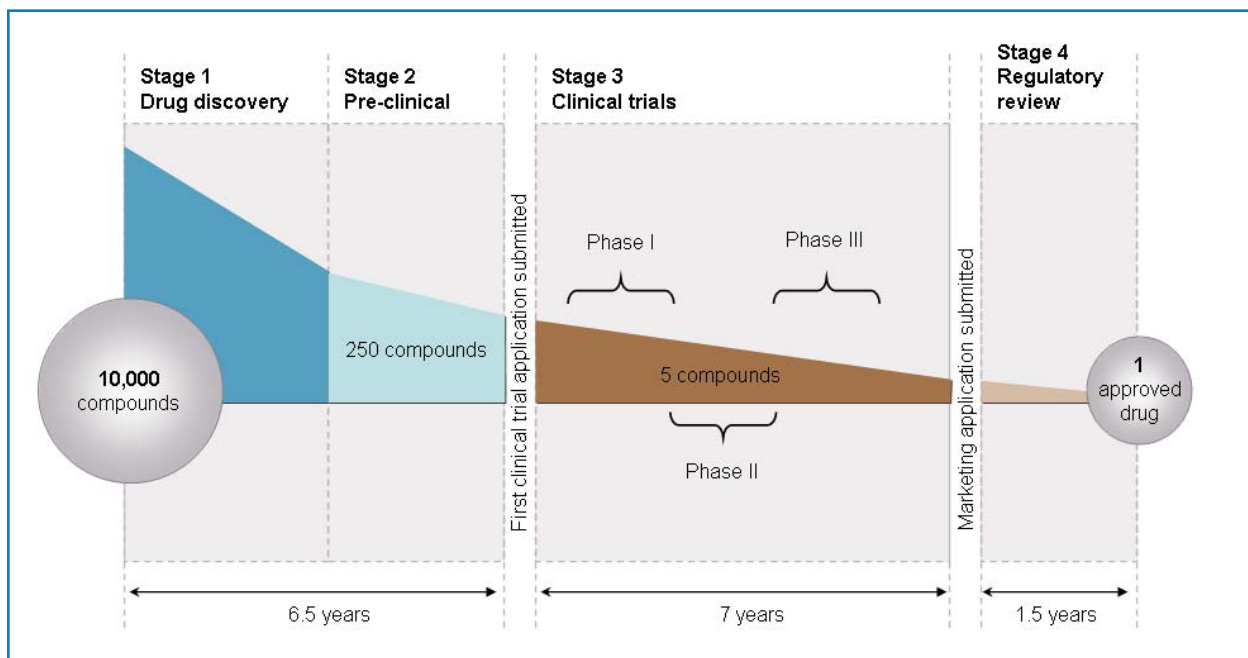
IPM supports a drug screening programme that provides an initial assessment of safety and efficacy in the test tube for microbicide developers and researchers. The screening includes the assessment of activity against various types of HIV, including laboratory strains and viruses that have been isolated from the genital tract. The model can also evaluate the toxicity, the harmful unintended effect on cells, of microbicides. In addition, a model has been developed using human cervical tissue from women undergoing hysterectomies to evaluate whether potential microbicides are effective in preventing HIV infection of the tissue.

Formulation /delivery

A drug's formulation helps determine its efficacy, cost, stability under different climate/storage conditions and acceptability to the user, and hence, is a critical feature of an effective microbicide.

Regional and individual variations in cultural preferences and sexual practices suggest that no single product type will be universally acceptable. For this reason, microbicide developers are investigating different delivery formulations including films,

Figure 3: The Drug Discovery, Development and Review Process



Adapted from: Pharmaceutical Research and Manufacturers of America, 2006

intravaginal devices such as vaginal rings, solid dosage forms such as fast-dissolving vaginal tablets, and novel polymers (biologically triggered drug release).

At this point, all of the microbicide candidates in large-scale efficacy trials are formulated as gels that must be applied shortly before sexual intercourse, known for this reason as being “coitally dependent.” An important advantage of the ARV-based microbicides currently being tested is that they can be formulated in long-acting, “non-coitally dependent,” delivery mechanisms that can be applied once a day, or even less frequently, independent of the time of sexual activity. IPM supports an extensive formulation effort focused on semisolids (gels, creams, lotions). IPM has established a facility with the capability to produce limited quantities of such microbicide formulations, under GMP (Good Manufacturing Practice) conditions, which are sufficient to satisfy the needs of safety clinical trials. IPM has made its facility available to other microbicide developers in order to help lower the cost and speed of the development of microbicides. Dapivirine gels have been tested for safety and pharmacokinetics. Additional trials will evaluate newer gel formulations.

IPM is also supporting the development of vaginal rings that could deliver a drug or combination of drugs for periods of 30 days or longer. Early safety trials with vaginal rings containing dapivirine—IPM’s lead microbicide candidate—have been completed and more are underway. There are plans to move this technology as quickly as possible through additional clinical trials. Looking ahead to large-scale efficacy trials, IPM has recently established its own ring manufacturing capacity, installing a manufacturing ring press in its clinical manufacturing facility in Pennsylvania. This new press will allow IPM to supply thousands of rings each month for its clinical studies.

Finally, for a microbicide product to be effective, it must be acceptable to the women who will use it. IPM has completed the first of several consumer acceptability studies aimed at determining the preferences and opinions of African women and their male partners regarding various types of gel formulations. Results from these and other studies, including gel, vaginal ring, film, tablet and softgel capsule acceptability studies, will enable microbicide developers to better address women’s preferences for different microbicide formulations.

Models for animal & tissue testing

Unfortunately, the microbicide field does not yet have a standardized, validated animal model for the evaluation of microbicides. Microbicide developers have sometimes used animal models for an initial assessment of safety and efficacy.



Photo courtesy of Photoshare, a service of The INFO Project

However, microbicide animal models have several limitations. For example, monkey models test the efficacy of the microbicide on simian immunodeficiency virus (SIV) or SHIV (an HIV-SIV hybrid virus constructed in the laboratory), not on HIV. Moreover, there are histological (cell composition) and other physiological differences between monkey and human vaginas. Because of these limitations, it is not possible at this point to know the predictive value of these animal efficacy models. Also, because of different mechanisms of action of microbicides, a model that is helpful in testing one microbicide may not be relevant to testing another.

Since there is room for improvement in the existing models, IPM has initiated several studies to help refine these models and is funding the development of others.

Production for early clinical trials

It can take several months to arrange production, achieve technical transfers, produce, package and label even modest quantities of microbicide formulations under GMP conditions for early clinical trials. To address this time-constraining factor, IPM has constructed a small GMP production unit capable of producing and packaging semisolids for safety trials. To date, the unit has produced all of the dapivirine gel that has been used in IPM trials since the drug’s acquisition from Tibotec. IPM anticipates a growing need for this production capability among microbicide developers, and offers this service to others.

Efficacy trials, which involve thousands of women, require a higher production capacity. IPM is planning to invest in scale-up production capability, and transfer necessary large scale manufacturing processes under contract to third party manufacturing organisations to fulfill the production needs for its own efficacy trials.

Mucosal biology & transmission

Rational drug design and better model development require a more in-depth understanding of the exact mechanisms by which HIV is transmitted. Despite the recent advances in understanding the HIV life cycle and how the virus invades the host cell, there remain gaps in understanding precisely how HIV is transmitted through sexual intercourse. For example, it is not known how much of the infection is attributed to the free virus itself versus infected cells, such as CD4 lymphocytes, included in the semen.

IPM is supporting research in this area. Using technology based on siRNA (small inhibitory RNA, an RNA construct that blocks the development of the viral RNA), for example, IPM-supported researchers hope to find out precisely which cells are involved in mucosal transmission of HIV. In addition, IPM is supporting research, to be conducted by Johns Hopkins University, to describe the distribution and clearance of CD4 lymphocytes cells administered to the female genital tract.

Challenges in conducting clinical trials

In recent years, substantive progress has been made in the search for a safe and efficacious microbicide. However, several challenges remain. In addition to the bottlenecks in R&D that IPM is addressing, there remain hurdles in conducting clinical trials. They include the following:

Cost: Conducting clinical trials in developing countries is expensive. An efficacy trial necessary to support licensure for a single product requires enrolment of thousands of women and following them for one year so that researchers can compare infection rates among women who use a candidate microbicide with those using a placebo. Depending upon trial design, one efficacy trial can cost an estimated US\$70-120 million.

Specific population criteria for microbicide

trials: Testing preventive strategies, such as microbicides, is difficult because it requires a large population of at-risk individuals in regions with a high incidence of HIV infection. (HIV incidence refers to the number or rate of new infections in a given period.) Measuring incidence accurately can be difficult and efficacy trial locations of some microbicide candidates have been closed in the past due to lower-than-anticipated incidence rates in the populations being tested. IPM is aiming to avoid this problem by completing incidence studies in potential trial

areas. Several HIV incidence studies are underway in Kenya, Mozambique, Nigeria and South Africa. IPM is identifying and helping to build research capacity at up to 20 trial sites in regions of high incidence so they may be able to host future efficacy trials.

Efficacy of microbicides is proven only in expanded efficacy trials:

It is standard practice in developing treatment drugs to evaluate the drug's effect in a small number of patients prior to starting expanded (phase III) efficacy trials, thus determining whether the drug merits further evaluation. But in the case of a preventive drug like a microbicide, the only way to know whether a microbicide candidate will work is to test it in large numbers of uninfected people living in communities with high rates of HIV incidence. There is limited evidence of a microbicide's likelihood of success until this kind of efficacy trial shows significant differences in the numbers of new HIV infections between participants using the microbicide candidate and those using a placebo.

Adherence issues: Adherence is a measure of whether a clinical trial participant is correctly and consistently using the product. In clinical trials, adherence is measured by direct reports from trial participants themselves. But it is well known that the accuracy of participants' reporting cannot be assured, with participants sometimes exaggerating their level of adherence. Even with over-reporting, however, the reported level of gel use in efficacy trials now underway is less than initially anticipated. This has implications for how data from the trials can be interpreted to determine efficacy. New non-coitally-dependent formulations, which can be used independent of sexual activity, such as the vaginal rings



being developed by IPM, may help address some of these adherence issues. In addition, innovative measures, such as direct observation, adapted from “DOTS” (Direct Observation Therapy) for treatment of tuberculosis, can be tested using non-invasive techniques to improve adherence in microbicide trials. Moreover, IPM is attempting to develop “smart applicators” that can be used to apply gels vaginally, and will record the time, date, and environment (vaginal or not) of the gel application.

Setting realistic expectations for the results of clinical trials:

In general, the process of developing an effective new drug compound is long, complex and expensive. In addition, the success rate of establishing sufficient evidence for a new drug compound to merit regulatory approval is very low. As Figure 3 shows, as many as 10,000 compounds undergo consideration and get eliminated before one drug is licensed for use. On average, only one in five compounds entering clinical trials is proven safe and efficacious enough to warrant regulatory approval.²¹

As Figure 4 shows, high rates of attrition are common across several categories of medical compounds. Success rates in developing new compounds in common therapeutic categories range from 8% to 30%.²¹

While the need for developing an effective microbicide is urgent, it is important to realise that microbicides are a new

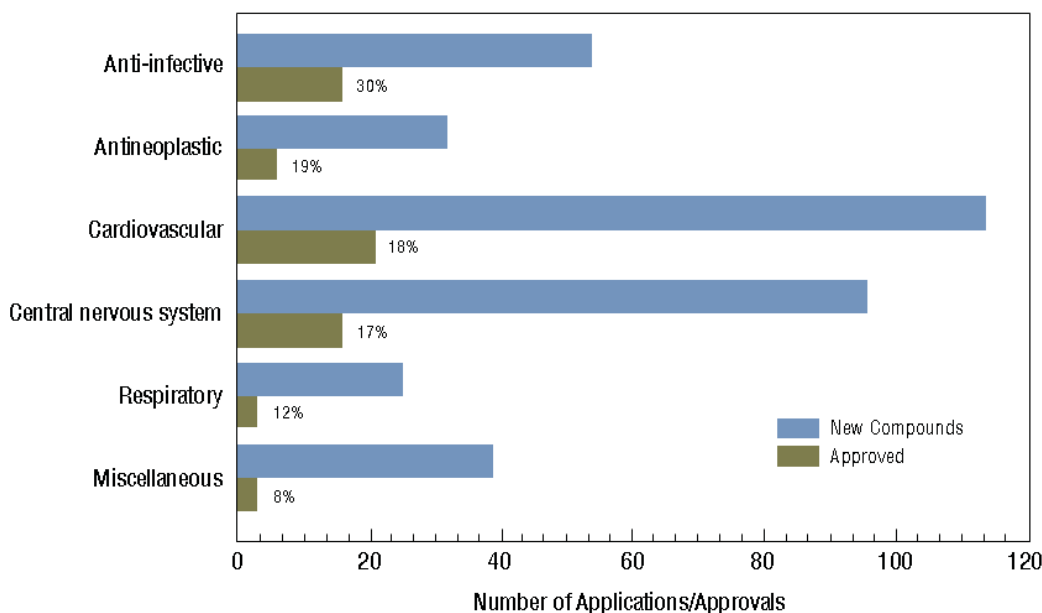
category of medical compound with no established history to help developers predict the success rate for microbicides currently under development. It is important to set realistic expectations regarding the degree of efficacy of early- and next-generation microbicides.

Conclusion

The need for a safe and effective microbicide remains as urgent as ever. More than 15 million women worldwide are infected with HIV, and thousands more become infected every day.²² Prevention, in combination with treatment and care, is the best way to end the HIV epidemic, and a safe and effective microbicide will be a vital prevention tool. But the road to developing a successful microbicide is complex and expensive. Funds and efforts must continue to support research in developing new microbicide candidates and testing them for safety and efficacy. An effective microbicide would finally give women a tool that they can use to reduce the risk of acquiring HIV.

This document will be revised regularly to reflect the latest information about microbicide research and development. For more information, visit us on the web at www.ipm-microbicides.org or contact us by email at info@ipm-microbicides.org.

Figure 4: Success Rate, as of the year 2000, by Therapeutic Class for New Compounds with INDs* First Filed from 1981 to 1992



*IND = investigational new drug application

Source: J.A. DiMasi, "Risks in new drug development: Approval success rates for investigational drugs", *Clinical Pharmacology & Therapeutics* 69, no. 5 (May 2001): 301.

Glossary

Attachment stage (HIV lifecycle): This is the first stage in the HIV lifecycle where the virus attaches to the host cell, typically a lymphocyte. The viral envelope glycoprotein gp120 first binds to CD4 on the cell surface and then binds to one of two co-receptors, CCR5 or CXCR4.

CCR5 and CXCR4: Receptors on the surface of the host cell (lymphocyte) to which the gp120 glycoprotein on the virus surface attaches.

CCR5 blocker (microbicide class): A type of microbicide in the entry inhibitor class that works by preventing virus attachment to the host cell (lymphocyte) by blocking CCR5 receptors on the cell surface.

Coitally dependent: Applied just before the time of sexual intercourse.

Cross resistance: Occurs when resistance to one drug in a therapeutic class results in resistance to all drugs in that class.

Efficacy: Refers to the capacity of a product to achieve a desired effect. In the case of microbicides, efficacy refers to the ability of the product to protect individuals from HIV infection, and perhaps other pathogens.

Fusion stage (HIV lifecycle): This stage in the HIV lifecycle occurs after attachment. The viral envelope fuses with the host cell's (lymphocyte's) membrane and the contents of the virus are released into the cell.

GMP (Good Manufacturing Practice): An international set of guidelines specifying required conditions for the manufacturing of drugs and medical devices. According to GMP, every aspect of the manufacturing process, activities and operations involved with drug manufacture, must be documented.

gp120: Glycoprotein on the surface of HIV that binds to target receptors on the host cell's (lymphocyte's) surface.

gp41: Glycoprotein embedded in the envelope of HIV that facilitates the virus' fusion with the host cell.
Half life: Amount of time taken for half of the amount of drug administered to be eliminated from the bloodstream.

Histological: Type of cells included in a certain organ or tissue.

In vitro: Testing in a laboratory-based biological system (i.e., "in a test tube")

In vivo: Testing in living organisms (animals or humans).
Integration stage (HIV lifecycle): The last stage in the HIV lifecycle when viral cDNA (which is copied from viral RNA during infection) enters the host cell nucleus and becomes incorporated into the host cell's genetic material, permanently "infecting" that cell.

Non-coitally dependent: Applied at regular intervals that are not associated with the time of sexual intercourse.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) (microbicide class): A class of ARV-based compounds that inhibits viral replication by binding to the reverse transcriptase enzyme.

Nucleotide reverse transcriptase inhibitors (NtRTI) (microbicide class): A class of ARV-based compounds that act by mimicking the nucleotides used to copy the viral genetic material, hence blocking the production of viral cDNA.

PMTCT: Prevention of Mother to Child Transmission of HIV infection.

Polyanion (microbicide class): Electrically charged compounds. Polyanion microbicides carry a negative electrical charge that attracts the positively charged HIV, thus preventing it from binding to and entering target cells and causing infection.

Polymers: Compounds typically of high molecular weight that exist as chains of smaller molecules (called monomers).

Replication stage (HIV lifecycle): Refers here to the stage in the HIV lifecycle that occurs after fusion. The genetic material of the virus is copied using the reverse transcriptase enzyme.

Resistance: A drug-resistant HIV strain is one that is less susceptible to the effects of one or more ARV drugs because of its genetic make-up.

Reverse transcriptase inhibitor (microbicide class): A class of microbicides that work by preventing the action of the reverse transcriptase enzyme.

Reverse transcriptase: An enzyme used by HIV to copy its RNA into cDNA, to allow for its incorporation into the host cell DNA.

RNA (Ribonucleic Acid): The type of macromolecule in which HIV stores its genetic material.

siRNA (small inhibitory RNA): An artificially created RNA construct that blocks the translation of naturally occurring RNA into protein.

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IPM MISSION:

The mission of IPM is to prevent HIV transmission by accelerating the development and availability of safe and effective microbicides for use by women in developing countries.

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