



HIV/ADS remains one of the greatest burdens to the future health and well-being of our world. Even with improved access to antiretroviral (ARV) drugs in resource-limited settings, HIV/AIDS is the cause of more deaths annually than nearly any other infectious disease. With 97 percent of new HIV infections occurring in low- and middle-income countries, the epidemic is exacting a particularly high price from the world's most vulnerable societies.

At the United Nations Millennium Summit in 2000, the global community pledged to halt and begin to reverse the HIV/AIDS epidemic by 2015. In 2010, this pledge was reconfirmed and the global community underscored the need for acceleration of further research and development into new tools for prevention, including microbicides and vaccines. Achieving this aim will require markedly greater success in slowing the spread of HIV infection in the low- and middle-income countries that are most heavily affected by the epidemic.

This briefing paper focuses on a promising HIV prevention tool — ARV-based microbicides — to reduce the risk of sexual HIV transmission. Researchers have been working for years toward the goal of developing safe and effective microbicides, and the knowledge they have accumulated has resulted in "proof-of-concept" that an ARV-based vaginal gel can offer women protection against HIV. This paper examines the potential prevention benefits of microbicides, describes the evolving state of microbicide research, and explains why continued, even stronger efforts are needed to accelerate the development of microbicides for HIV prevention.

Safe and Effective Microbicides: A Critical Tool in the HIV/AIDS Response

The world's response to HIV/AIDS has generated tangible benefits, including one of the first-ever widespread introductions of chronic care in resource-limited settings and an unprecedented scaling up of medical services. The epidemic has brought attention to global health inequities, resulted in the establishment of innovative financing mechanisms for health programs, and prompted newfound resolve to strengthen fragile health systems in developing countries.



Yet the HIV/AIDS epidemic continues to overwhelm the world's struggle to slow the pace of new HIV infections. Since the epidemic appeared nearly 30 years ago, more than 60 million people have become infected with HIV and more than 25 million have died.

In 2008 alone, 2.7 million people worldwide became infected with HIV. Although this represents a modest decline in global HIV incidence from 2001, when 3 million new infections occurred, the rate of the epidemic's expansion continues to outpace the response. For every two people placed on ARV therapy in 2007, five more individuals became newly infected with the virus.

In sub-Saharan Africa home to more than onethird of the world's HIV infections — HIV is now endemic at extraordinarily high levels. In Swaziland, survey data released in 2009 indicate that HIV prevalence among pregnant women has increased to an alarming 42 percent since 2006.

What Are Microbicides?

Vaginal microbicides are topical products being developed to prevent heterosexual transmission of HIV.

Microbicides could take many forms, including those that could be used monthly or daily, or at or around the time of intercourse.

Researchers are developing a variety of products that include daily vaginal gels, films and tablets, as well as vaginal rings that would release an ARV drug gradually and provide protection against HIV for as much as a month at a time.

A microbicide would be a significant complement to other HIV prevention measures, including safer-sex education, condoms, voluntary testing and counseling, treatment of sexually transmitted infections, anti-stigma campaigns, safe blood supplies and, one day, a vaccine. Studies have validated an array of effective HIV prevention strategies. These include behavioral interventions, condoms, HIV counseling and testing, services to prevent mother-to-child transmission, access to sterile injecting materials and adult male circumcision for the prevention of female-to-male sexual transmission.

To date, however, these strategies have not succeeded in lowering new infections to a manageable rate, which underscores the urgent need for new biomedical prevention tools to strengthen existing efforts. This is especially apparent in hyper-endemic settings in southern Africa, where infection is so widespread that even very low levels of risky behavior frequently result in HIV transmission.

Promising Results: Proof-of-Concept

Findings from the first clinical trial of an ARV-based microbicide announced in July 2010 offer new cause for optimism. The trial, called CAPRISA 004, demonstrated proof-of-concept that an ARV-based microbicide can prevent women from becoming infected with HIV through sex with an infected male partner. Conducted in South Africa among 889 women, the CAPRISA trial found a 39 percent lower HIV infection rate in women using 1% tenofovir gel as compared to those women using a placebo gel.



Tenofovir gel also prevented transmission of herpes simplex virus type 2, or HSV-2, a lifelong, incurable infection that can increase the risk of HIV infection. The product demonstrated a good safety profile as tested.

Multi-center, confirmatory trials are planned for 2011, and if the results support product licensure, tenofovir gel could be the first microbicide available in some communities as early as 2013. A microbicide to reduce the risk of sexual HIV transmission promises to have a significant impact on the epidemic's future.

Empowering Women to Protect Themselves from HIV

A microbicide would specifically address one of the central weaknesses on the existing continuum of HIV prevention methods: the lack of a discreet prevention method that women can initiate to avoid sexual HIV transmission.

HIV/AIDS has evolved to become one of the greatest of all threats to women's health. Women represent roughly half of all people living with HIV/AIDS worldwide and approximately 60 percent of those infected with HIV/AIDS in sub-Saharan Africa.

A combination of biology and social reality renders women especially vulnerable to HIV. Physiologically, women are more likely than men to become infected during vaginal intercourse. Adolescent girls, whose reproductive systems are not fully developed, are especially vulnerable to acquiring HIV during sex. In some parts of the world, young women (ages 15-24) are three times more likely to be infected than young men of the same age, according to UNAIDS and the World Health Organization.

The physiological vulnerability of women and girls is compounded by social, legal and political disadvantages that impede women's ability to protect themselves from HIV. According to data compiled by the International Center for Research on Women, women in sub-Saharan African own only 1 percent of the land, and laws still exist that make property ownership for women more difficult. Lacking educational or economic opportunities of their own, women and girls are often dependent on men for their livelihood.

With such sharp disparities, many women and girls are often powerless to abstain from sex, or to persuade their husbands or partners to use a condom during intercourse. In the absence of a prevention method they can control on their own, women and girls lack the ability to reduce the risk of infection.

A variety of studies link gender inequality with increased risk of HIV transmission. Women's access to safe, effective, affordable microbicides would help empower them to avoid becoming infected with HIV. Rather than rely solely on men to take action to avert HIV transmission, a microbicide would enable women to take their health into their own



UN Millennium Development Goals

- Goal 1: Eradicate extreme poverty and hunger
- Goal 2: Achieve universal primary education
- Goal 3: Promote gender equality and empower women
- Goal 4: Reduce child mortality
- Goal 5: Improve maternal health
- Goal 6: Combat HIV/AIDS, malaria and other diseases
- Goal 7: Ensure environmental sustainability
- Goal 8: Develop a global partnership for development

hands. While no microbicide on its own will be a panacea, development of a microbicide would expand the range of prevention options and magnify the public health impact of other prevention methods.

Supporting the Broad Development Agenda

Not only could safe and effective microbicides help to reverse the global HIV epidemic, they would also advance broader development goals. The United Nations Millennium Development Goals reflect broad international commitment to a healthier, more just world. Without focused, sustained progress in reducing women's risk of HIV infection, however, these goals are unlikely to be achieved.

The potential for a microbicide to reduce HIV infection in women and girls could play a critical role in breaking the cycle of poverty and hunger, as envisioned in Goal 1. In sub-Saharan Africa, the world's poorest region, HIV/AIDS infection is associated with dramatic declines in household earning. HIV-associated impoverishment has especially dire consequences for women, who are responsible for producing between 60 percent and 80 percent of food supplies in most developing countries.

HIV/AIDS undercuts Goal 2 (universal primary education) by creating teacher shortages and causing



many young girls in HIV/AIDS-affected households to be withdrawn from school. HIV is also a growing cause of morbidity and mortality among women and their children, undermining efforts to achieve Goals 4 (reduce child mortality) and 5 (improve maternal health). And because HIV/AIDS increases the risk of falling ill with tuberculosis — and a growing body of evidence suggests the same is true for malaria — the failure to slow the spread of HIV also impedes progress toward Goal 6 (combat infectious diseases).

The radical gains across the breadth of the development agenda envisioned by the Millennium Development Goals will be difficult, perhaps impossible, to achieve without major progress in cutting rates of new HIV infection. Microbicides represent a potentially powerful tool to promote broad human development by slowing the spread of HIV.

The State of Microbicide Research: Capitalizing on Lessons Learned to Accelerate the Development of Safe and Effective Microbicides

The microbicide field is focused on building upon lessons learned from CAPRISA 004 and other trials to develop microbicides that contain ARV-based compounds similar to those already being used successfully to treat HIV infection and to reduce the rate of mother-to-child HIV transmission.

Advantages of ARV-based Microbicides

These ARV-based microbicides have a number of important advantages over early generation candidates. The ARV compounds selected as the active ingredients in these microbicides have proven to be highly active against and specific to HIV. Not only have ARVs revolutionized HIV/AIDS treatment — radically increasing life expectancy and improving quality of life for people living with the disease — but timely administration of a short course of ARVs also lowers the likelihood of mother-to-child HIV transmission by at least half.



Geoff Oliver Bugbee

Research is well under way to develop microbicides that attack HIV at various points in the virus' life cycle, including those that play an essential role in viral replication. Other potential avenues for microbicide development include using novel compounds that interfere with the virus' ability to attach to and enter a healthy cell.

Because different classes of ARVs interfere with diverse steps in HIV replication, this new frontier also offers the prospect of combination microbicides. Consistent with advances in the therapeutic arena and in the prevention of mother-to-child transmission, microbicides based on a combination of ARVs may maximize their protective effect.

A Rigorous R&D Proccess

Dozens of potential drugs that interrupt HIV transmission or replication are currently being studied as possible microbicide candidates. Each candidate is subjected to rigorous research designed to ensure that only the most promising candidates are prioritized for testing in efficacy trials. The safety of promising microbicides is first assessed in laboratory studies and subsequently in small human trials of low-risk volunteers.

Once a product's safety profile has been investigated, efficacy is evaluated in human trials that typically involve large numbers of women at high risk of infection. Undertaken in settings with elevated rates of new HIV infections, efficacy trials compare infection rates among

Prioritizing Microbicide Candidates

Because it is not feasible to fully develop every possible microbicide candidate or to subject each experimental product to large, expensive clinical trials, it is necessary to prioritize the most promising candidates for further development. High priority should be given to candidates with the following characteristics:

- Mechanism of Action: The optimal candidate should interrupt HIV infection as early as possible prior to viral integration into cellular DNA.
- Potency and Selectivity: The best candidates will exhibit high levels of anti-HIV activity and low cellular toxicity.
- Physical Properties: An ideal candidate will have good stability under diverse conditions and will be compatible with topical application.
- Stage of Development: Compounds that are well-advanced in development have higher priority than entirely new compounds in early development. This criterion responds to the urgent need to buttress HIV prevention efforts as soon as possible with a safe and effective microbicide.
- Human Experience: Compounds that have already been approved for human use as HIV/AIDS therapeutics have already had their safety profile evaluated and are therefore preferable to less well-defined candidates.
- Adherence: Compounds that rely on simpler dosing regimens or that are more acceptable or easier to use have priority over candidates that are more complex or expensive.

study volunteers who have received the microbicide with rates among those who received a placebo or another prevention intervention, with all study participants receiving safe sex counseling, free condoms and treatment for sexually transmitted infections.

International Partnership for Microbicides: A Product Development Partnership to Speed the Availability of Safe and Effective Microbicides for HIV Prevention

Founded in 2002, IPM is a leader in the microbicide field. IPM is a nonprofit product development partnership (PDP) dedicated to developing new HIV prevention technologies and making them available to women in developing countries. By coupling the public sector's commitment to improving international public health with the business approach of the private sector, IPM fills a special niche in the microbicide field.

IPM evaluates promising compounds, designs optimal formulations, conducts clinical trials, identifies appropriate regulatory pathways for microbicide products, and works to establish manufacturing and distribution capacity to ensure ready access to a microbicide as soon as one becomes available. IPM also funds, co-funds or leverages resources to support the drug development projects of other entities.



Through licensing agreements with different pharmaceutical partners, IPM is working to develop a variety of different compounds as microbicides. IPM is developing products in several formulations, including once-daily gels and longacting vaginal rings that would provide up to a month's protection from HIV.

IPM aims to advance products that are the most promising and have the most favorable characteristics (see page 5, "Prioritizing Microbicide Candidates"). To reduce duplication and to ensure added value to the field, IPM accords lower priority to compounds of the same chemical and functional class as those already available or at advanced stages of development in the field.

Taking these considerations into account, IPM is focusing its research efforts on developing and evaluating the following high-priority compounds:

- ▶ Tenofovir. With CAPRISA 004, proof-of-concept was established for tenofovir in HIV prevention and confirmatory trials are planned to support product licensure for a 1% gel formulation. IPM and another product development partnership, known as CONRAD, hold royalty-free agreements to develop tenofovir gel as a microbicide.
- Dapivirine. This highly potent ARV drug is a non-nucleotide reverse transcriptase inhibitor, or NNRTI, that works by preventing HIV from replicating its genetic material after the virus enters a healthy cell. Dapivirine has been tested in 11 oral dosing studies in humans and in one gel trial by Tibotec Pharmaceuticals, which licensed the product to IPM. IPM has studied dapivirine gel in eight safety and pharmacokinetic studies. A vaginal ring containing dapivirine has been shown to be safe as tested in four IPM clinical trials. All the results support moving toward efficacy trials. IPM is preparing to initiate a Phase III program in 2011 to test dapivirine in a long-acting monthly vaginal ring.
- Maraviroc. An approved therapeutic (Selzentry[™], Pfizer) with a large human safety database, maraviroc is a CCR5 blocker that works by blocking a protein on the surface of human cells that is used by HIV to attach to and enter the cell. Licensed to IPM from Pfizer, maraviroc has extensive preclinical and human safety data available as a result of its thorough evaluation in therapeutic clinical trials. Developing a maraviroc-based product, both as a standalone and as a combination product, is a high IPM priority.
- Combination products. IPM is studying a potential combination microbicide composed of dapivirine and maraviroc in various formulations as well as products that combine tenofovir with other ARVs.

IPM is pursuing other products that currently have lower priority than its current high-priority candidates noted above. These products, while promising, are in earlier stages of development and have less extensive safety data available.

Evaluating Promising Microbicide Candidates

To ensure the swiftest possible initiation of clinical trials for candidates that show promise in preclinical studies, IPM has developed partnerships with a global network of trial sites. Because microbicides are being developed to be used in the developing countries where most new HIV infections occur, it is critical to test microbicide candidates in these settings.

Like its other research partners in the microbicide field, IPM is committed to internationally agreed upon, high ethical standards in the conduct of clinical trials. Country-based IPM staff collaborates with community organizations and local representatives to inform and educate communities about trials. Protocols ensure that trial volunteers are fully and regularly informed regarding the risks and benefits of trial participation. Researchers provide prevention counseling to trial participants, and access to condoms and other prevention services. Trial volunteers who test HIV-positive during initial screening or who become infected during trial participation are referred to appropriate medical services and support.

Maximizing Future Access to Microbicides

Historically, it has often taken decades for medical innovations to make their way to low-income countries. This is a tragedy for many, but such delays are potentially catastrophic in the case of HIV/AIDS. IPM has taken two important steps to ensure that the microbicides it develops can actually be used in the developing countries where they are most needed.

Ability to distribute at low cost: First, IPM's royalty-free licensing agreements with pharmaceutical companies enable IPM to distribute its products at low cost to women and their families in resource-limited settings. IPM has made no financial contribution for these licensing agreements.

Products women will use: Second, in addition to evaluating candidate products for their safety and efficacy, IPM conducts extensive studies to gauge their acceptability to consumers. These studies ascertain users' experience with the products and their preferences regarding product characteristics. These studies ask the women who use microbicides to describe their effect on their sexual relationships. Male partners' perceptions are also elicited. By taking into account consumer experience and preferences, IPM's research helps ensure that future microbicides are more than just technically effective but that they are also used in the real world to prevent HIV infection.



Andrew Loxley

Capturing the Promise of Microbicides to Protect Women From HIV Infection

In 2009, total global investment in microbicide research decreased by 3 percent, representing the first year-toyear decline since 2000, according to a report by the HIV Vaccines and Microbicides Resource Tracking Working Group.

Funding levels for microbicide research — \$236 million in 2009 — are well below the annual \$300 million amount recommended by microbicide experts to ensure an optimal research effort, especially in light of new efficacy data showing proof-of-concept that an ARVbased microbicide product can prevent HIV infection in women. As a result of funding shortfalls, promising microbicide research avenues are at risk of moving at a much slower pace than is warranted by the seriousness of the epidemic.

Moreover, as microbicides based on tenofovir and other ARVs progress through large-scale clinical trials required for product licensure, financial needs are likely to grow. Clinical safety trials typically require two years, while efficacy trials often last three years or longer and involve thousands of volunteers. The public sector will remain primarily responsible for ensuring future support for microbicide research.

At least initially, microbicides will be used almost exclusively in countries that have little ability to pay private market prices for health innovations, so individual private companies have little commercial incentive to invest in microbicide research. In 2009, public sector sources provided 94 percent of financing for microbicide research. If the many promising research leads are to be pursued with the needed speed, the US government and other public and philanthropic donors will need to ensure sufficient funding.

In addition, the private sector will need to continue to play an important and unique role, especially by granting royalty-free licenses to ARV drugs for development as prevention tools. These licenses to IPM and others allow for the development, manufacture and distribution of ARV compounds as microbicides in developing countries.

Once an effective microbicide is developed and approved for use, these licensing agreements give PDPs like IPM the full rights to distribute products at little or no cost in developing countries. These agreements serve as a model of public-private partnership in fostering global health solutions.

Lessons learned through years of scientific inquiry have brought the world in 2010 to a milestone in HIV/AIDS research: proof that a topical microbicide can prevent heterosexual transmission of HIV. Continued, even stronger support will be required to capitalize on the promise of safe and effective microbicides to empower women to protect themselves from AIDS.





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