Tools, Trends and New Technologies in HIV Prevention

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Introduction

At the end of 2007, the Joint United Nations Programme on HIV/AIDS (UNAIDS) announced that over 33 million people were living with HIV worldwide. Over 2 million people died of AIDS-related illnesses in 2007, and 2.5 million people were newly infected with the virus in 2007. [i] There continues to be an urgent need to scale up prevention efforts using both existing means and through new tools and approaches.

In the period 2005-2007, prevention moved to the top of the global HIV and AIDS agenda. This was particularly true at the 2006 International AIDS Conference in Toronto, where there was much discussion and media attention focussed on prevention, especially new prevention technologies.

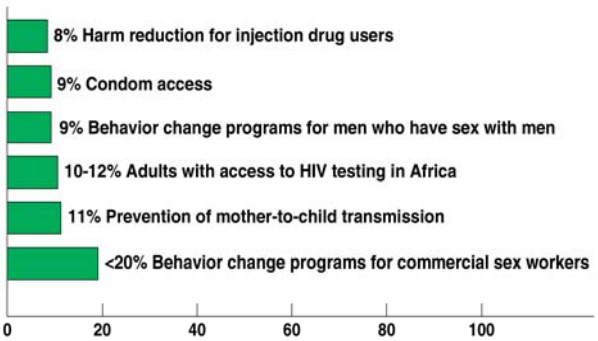
As part of a comprehensive approach to addressing HIV and AIDS, the international community has been calling for increased efforts towards universal access to prevention, care, treatment and support. This includes significantly improving access to existing proven means of preventing HIV transmission.

> *"The steady growth of HIV prevalence throughout the world stems not from the deficiencies of available prevention strategies and tools but rather from the failure to use them."* UNAIDS, 2007 [ii]

At the same time, the world desperately needs new prevention tools in the fight against HIV/AIDS – tools and new technologies that will work with and complement existing prevention methods.

Until male circumcision trial results were released in late 2006, there had been no significant new biomedical HIV prevention strategy in more than a decade. The US Food and Drug Administration approved the female condom for sale in the US in 1993; in 1994 AZT was identified as an effective means of preventing mother-to-child transmission of HIV. These prevention methods were added to those that had already been identified – male condoms, clean needles, blood bank screening, post-exposure prophylaxis and universal precautions for health care workers.

Percentage of Individuals at Risk with Access to HIV Prevention



Source: Global HIV Prevention Working Group, 2007; WHO/UNAIDS/UNICEF, 2007

There are a number of global efforts underway to develop new technologies to prevent HIV. Currently, there is research being conducted on diaphragms and cervical barriers, treatment of genital herpes, vaginal and rectal microbicides, vaccines, and pre-exposure prophylaxis (PrEP).

Potential Prevention Tools

The following section provides a brief definition of each of these potential prevention tools and gives an overview of the state of research.

• DIAPHRAGMS AND CERVICAL BARRIERS

Diaphragms and cervical barriers provide partial contraceptive protection. Since they cover the cervix, which contains some of the cells most

vulnerable to HIV infection in the vagina, they are also being tested as a potential HIV prevention option for women.

Unlike most of the vagina's surface, which consists of several layers of flat, sturdy cells, parts of the surface of the cervix are made up of a single layer of fragile cells, which are more easily damaged. In younger women, these cervical cells are even more exposed than in adult women, increasing the risk for adolescent girls. In addition, several target cells for HIV are found more frequently on the cervix than throughout the rest of the vagina. The passage of infectious fluids into the upper genital tract (also highly susceptible) via the cervix may be another factor in women's HIV acquisition.

In July, 2007, results were announced from the MIRA (Methods for Improving Reproductive Health in Africa) diaphragm study, which took place in South Africa and Zimbabwe. The trial found that there is no added benefit from the use of a diaphragm and lubricant in the context of a comprehensive HIV prevention package (condoms, counselling, STI screening and treatment). Other cervical barriers could still be explored, perhaps in combination with other emerging strategies like microbicides.

• HSV-2 TREATMENT

The presence of genital ulcers caused by herpes simplex virus type 2, or HSV-2, has been suggested as a possible risk factor for HIV infection. Suppressing herpes with the inexpensive, off-patent drug acyclovir may lower HIV risk—both the risk of acquiring HIV infection and the risk of transmitting it to others.

Two large-scale efficacy trials are underway in Africa, Latin America, and the United States to test the effectiveness of herpes suppression for HIV prevention, one of which focuses on whether one's likelihood of acquiring HIV is reduced, and the other of which focuses on the likelihood of reducing transmission through HSV-2 treatment. One small study of HSV-2 treatment in HIV-negative people did not show a substantial risk reduction; however, this may be explained by low rates of adherence to the daily dosing schedule. Additional research results will be available in 2008.

• MALE CIRCUMCISION

The male foreskin contains a concentration of immune cells that are targeted by HIV during the earliest stages of infection. In particular, the inner side of the foreskin of the penis is highly susceptible to HIV infection; the skin that remains after circumcision is thought to be less so. It is possible that circumcision helps protect men from HIV infection by removing these targets for HIV.

Since the 1980s, observational studies have found that countries with higher rates of male circumcision have lower rates of HIV infection. In 2006, the first randomized efficacy trial of male circumcision for HIV prevention, conducted in South Africa, showed that circumcision reduced the men's risk of becoming infected by 60% in settings in which transmission risk is largely between men and women. This result was confirmed in two subsequent trials in Kenya and Uganda. Overall, the three studies suggest that safe, sterile male circumcision performed by a trained professional can reduce HIV-negative men's risk of acquiring HIV through vaginal sex by approximately 50%. There are no conclusive data about male circumcision in HIV positive men. There is also no conclusive data on the impact on transmission to female partners. One study found an insignificant trend towards increased risk of male-to-female transmission; this could be related to incomplete wound healing and more research is needed. There is no randomized clinical trial data on the impact of male circumcision on HIV infection rates through anal intercourse.

Based on the data from the trials in HIV-negative men, there is a strong case for making male circumcision available as a complement to current effective HIV-prevention strategies like condoms, clean needles, and behaviour modification. These programs must stress what is known and what is not known about male circumcision.

"Two decades have elapsed since HIV/AIDS first came to light in the early 1980s. It is completely unacceptable that for over 20 years we have failed to provide women with the means to protect themselves against HIV infection. I see no pursuit more worthwhile that the search for an effective microbicide." – Graça Machel, Opening Address, Microbicides 2006, Cape Town, South Africa

• MICROBICIDES

Microbicides are substances that can be applied topically to prevent the sexual transmission of HIV. Microbicides could take the form of a gel, film or sponge, be contained in a vaginal ring that releases the active ingredient gradually, or in a rectal enema.

In sub-Saharan Africa, the epi-centre of the pandemic, women are disproportionately infected with HIV. A combination of biological, social, cultural and economic factors contribute to women's increased vulnerability to HIV infection. Gender inequalities prevent women from being able to control the circumstances that increase their vulnerability to infection, particularly in the context of sexual relationships. Also, women are physiologically more susceptible to becoming infected with HIV than men. There is an increasing recognition that women need access to safe, effective and female-initiated HIV-prevention options. Hence, the global effort to develop an effective microbicide.

There is research and development being conducted on both vaginal and rectal microbicides, though research into rectal microbicides is several years behind vaginal microbicides, with the first phase I trial starting in the US in 2007.

Phase III trials of three (vaginal) microbicide candidates, nonoxynol-9, Savvy and cellulose sulfate, have concluded and the products were found to be ineffective for HIV prevention.

A fourth phase III trial has been completed with the vaginal microbicide candidate Carraguard, and results of the data analysis are expected in early 2008. Two products are still in Phase IIb/III trials: BufferGel and PRO2000. Results from these trials are expected in 2009. A number of next generation candidates, based on antiretroviral (ARV) drugs, are in earlier stages of clinical trials.

• PRE-EXPOSURE PROPHYLAXIS

Pre-exposure Prophylaxis or "PrEP" refers to an experimental HIV prevention strategy that would use antiretrovirals to protect HIV-uninfected people from HIV infection. In the strategies that are currently being tested, HIV-uninfected people would take a daily dose of a single drug or a combination of drugs. PrEP can be compared to birth control pills: whereas a contraceptive pill is taken once daily to prevent pregnancy, a PrEP pill could be taken once daily to prevent HIV infection in case of exposure.

As of December 2007, there were five human clinical trials of PrEP: in Ghana (women), Thailand (men and women), Botswana (men and women), the United States (men who have sex with men), and Peru (men who have sex with men). These studies are testing a PrEP strategy using either tenofovir (Viread) or Truvada™ (tenofovir with emitricitabine), two antiretroviral drugs currently used as treatment for HIV infection. In addition to these ongoing trials, there were trials stopped or cancelled for different reasons in Malawi, Nigeria, Cameroon and Cambodia.

• VACCINES

A vaccine is a substance that teaches the body to recognize and defend itself against bacteria and viruses that cause disease. A vaccine causes a response from the immune system—the body's defense system—preparing it to fight, and also to remember how to fight, if exposed to a specific infection. A vaccine is not a cure, but prevents infection or slows disease progression.

Currently, there are close to 30 clinical trials of experimental HIV vaccines underway in over 20 different countries around the world. The majority of these trials are small Phase I and II safety and immunogenicity studies. There is one large-scale Phase III efficacy trial underway in Thailand. This prime-boost trial is testing a combination of two

vaccines called ALVAC and AIDSVAX. A large-scale Phase IIB proof of efficacy trial is expected to begin in 2008.

Vaccinations in two large-scale Phase IIB proof of efficacy trials (the STEP study) were halted in late 2007 after a planned initial analysis showed lack of efficacy. Participants were unblinded in both trials after further data analysis indicated the possibility that the study vaccine, developed by the Merck Research Laboratories, may have increased the likelihood of HIV infection among a certain subgroup of vaccine recipients. The study vaccine does not cause HIV infection. HIV prevention counselling was offered throughout the trial, and is continuing. Data analysis is ongoing, and results are being made public as they are announced.

There have been two previous efficacy trials of an HIV vaccine candidate, called AIDSVAX. Both of these studies found that the candidate did not protect against infection.

Existing Prevention Tools: Male and Female Condoms

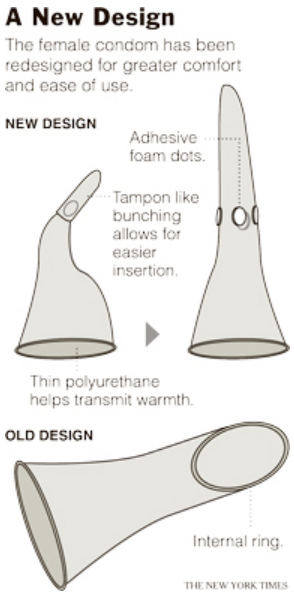
Male and female condoms are prevention technologies that are available now to enable couples to reduce their risks. When used properly, they can both reduce risk of transmission of HIV by more than 90%. However, global access to male condoms is extremely low, and female condom access is even worse.

In both cases, the global community needs to substantially increase distribution, promotion and access efforts.

In the case of female condoms, initial forecasts of uptake and impact were too optimistic, given the challenges of introducing a new product. These challenges include negative perceptions of barrier methods, provider bias, and lack of support for large-scale programs. One of the biggest drawbacks for women in developing countries in terms of using a female condom is the cost. Where female condoms are available, they are dramatically more expensive than a male condom.

Investigations in more than 40 countries have found good initial acceptability of the female condom among individuals of varied age, social and economic status, and sexual history. Many women like the female condom because it provides protection from HIV and other STIs, is easy to use, increases sexual pleasure, and is a good option for men who do not like to use male condoms.

New female condom designs are being developed by PATH (Partnership for Appropriate Technologies in Health), a non-profit health research organization.



Efforts to increase male and female condom promotion, distribution, access and use play a crucial role in stemming the HIV pandemic.

Several studies have shown that while barrier methods are an important component of prevention efforts in the context of sex with casual partners, they are almost universally discarded in the context of more stable, ongoing relationships. This may be due to several factors, including the desire to conceive, and the feeling that barrier methods are effective barriers to intimacy, not just to HIV, STIs and pregnancy.

However effective male and female condoms are at preventing HIV transmission, non-barrier methods such a microbicides and vaccines are desperately needed.

How Research is Done

It takes more than a decade to develop and test a new product. Before any new drug candidate can be tested in human beings, the developers have to show that (a) it's not likely to be harmful to humans and (b) it may be beneficial. The research is done in laboratory testing and in animals and can take anywhere from 2 to 6 years.

If a product is approved for human trials, it goes first through a series of Phase I safety trials, where small numbers of people who are at low risk of infection use the product and are carefully monitored for signs of problems. Next come one or more Phase II trials to gather extended safety data and establish safety among different groups of people -- for example, those who may already be HIV positive or have another sexually transmitted infection.

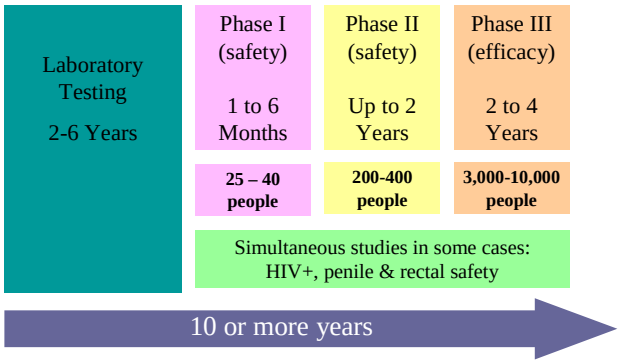
If a product is shown to be safe in these first two phases, it can then be tested for effectiveness. Generally, the next step is to conduct Phase III trials which can take several years because they need to enroll thousands of participants who use the product for many months up to several years to see if it reduces their risk of HIV infection. More than one Phase III trial may be needed before a product can be licensed for use.

Traditional research designs can take years before a product is available for licensure with no guarantees of a successful product. In some cases, a non-traditional approach could be used with an adaptive trial design that integrates the Phase II and Phase III. This approach could allow for the fastest transition from a "successful proof-of-concept" to a pivotal, licensure trial.

There are many mechanisms in place to protect participants in clinical trials, including ethics committee reviews, the informed consent process and access to care and treatment for participants who become HIV-positive during the trials.

Before a trial can proceed, national and/or local Ethical Review Boards (ERBs) and National

Research Process:
Vaginal Microbicides as an Example



Regulatory Authorities ensure that the only trials undertaken are those that are both scientifically valid and ethically conducted. A Data and Safety Monitoring Board (DSMB) oversees the trial to monitor results at regular intervals. The DSMB has the authority to stop a trial if:

1. The test product is definitely effective
2. The test product may be causing harm
3. The trial can no longer answer the original questions it was designed to answer

The ERBs also ensure that there is an appropriate informed consent process, including clear information about the trial in the language and format that is suitable to the local community where the trial will be conducted.

Advocates are working hard to ensure that participants who become infected with HIV during the course of any HIV prevention trial are assured access to HIV care and treatment, including antiretroviral drugs when needed. For example, the Global Campaign for Microbicides's *Consensus Statement on Standard of Care* has called on all trial sponsors to establish durable mechanisms, prior to the start of a trial, to ensure participants access to HIV care. Generally such care is arranged through partnership with local entities, or the creation of a reserve fund to pay for treatment. Many trials also try to facilitate access to care for women who test HIV positive at the time of screening, by providing tests and other assessments that can help them qualify for locally-available treatment programs.

Almost all HIV prevention research to date has been conducted by non-profit and academic institutions or small biotech companies. Studies are funded by charitable foundations and government grants. These public funds also support basic science, social and behavioural research, and clinical trial infrastructure that contribute HIV prevention research. Large pharmaceutical companies have not invested significantly in this field, primarily because most new prevention technologies are classic "public health goods" which would yield tremendous benefits to society but for which the profit incentive to private investment is low. One of the exceptions to this is HIV vaccines, which have seen some investment from large pharmaceutical companies already experienced in vaccine development. Still, most HIV vaccine research is conducted by non-profit and academic institutions and small biotech companies.

A WORD ABOUT PARTIAL EFFICACY

Products that have a less than 100% effectiveness can still have a significant impact on the HIV pandemic. In many cases, including with microbicides, vaccines, PrEP and cervical barriers, many researchers believe that only moderate efficacy rates will ever be achieved. However, statistical modeling of how HIV spreads suggests that a 60% effective microbicide could potentially prevent 2.5 million infections over 3 years. And a vaccine with even 30% efficacy could have benefit under certain circumstances.[iii]

UCLA researchers estimated in 2005 that the introduction of vaginal microbicides could substantially reduce HIV risk for female sex workers (FSWs). Even after accounting for condom migration, it was estimated that this population would see a reduction in risk of 17 to 28 percent depending on the efficacy of the microbicide and the level of condom use.[iv]

New prevention technologies with partial efficacy can still be of value in contexts where the use of prevention tools with higher rates of efficacy is widespread. However, education programs need to clearly explain the differences in efficacy rates of various prevention options. This is to avoid a situation where people switch from using a highly effective prevention tool to one with lower efficacy, which could result in an increase in HIV infections.

Canada and Research into the New Prevention Technologies (NPT)

Canada continues to play an important role in NPT research, particularly in the area of vaccines and microbicides.

Some HIV vaccine research has taken place in Canada, including part of the world's first phase III trial (AIDSVAX), and more recently, part of the STEP Trial (see vaccines section above). From 1999-2007, Canada had an active vaccines network (CANVAC), through which basic, clinical and social scientists working on HIV vaccines collaborated. Canada is a major financial contributor to global HIV vaccine research efforts, through its support for the International AIDS Vaccine Initiative (IAVI) and the Global HIV Vaccine Enterprise. In February 2007, the Canadian HIV Vaccine initiative was announced as part of a partnership between the Canadian government and the Enterprise. This will significantly increase Canada's contribution to research.

While little microbicides research has occurred in Canada, two candidate microbicides were developed in Canada (cellolose sulphate and the Invisible Condom). Canada has also contributed funding to the International Partnership for Microbicides (IPM), a non-profit microbicide product development organization.

Canada has developed the world's first multi-sector plans addressing Canada's potential contributions in the areas of discovery, clinical trials and testing, manufacturing, delivery, access and community engagement: the Canadian HIV Vaccines Plan and the Canadian Microbicides Action Plan.

Conclusion

Effective HIV prevention requires complementary approaches:

- ensuring a significant increase in access and uptake of existing prevention tools
- developing new prevention tools

- addressing the socio-economic, political and cultural structures that increase vulnerability

If this is to happen, there needs to be political commitment and increased funding. Only then will the prevention tools that are urgently needed be developed and made available

For information on how to become involved in NPT advocacy, please consult the Canadian *Microbicides Community Mobilization Kit*, (http://www.cdnaids.ca/web/mailouts.nsf/cl/cas-mailout-0326), produced by the Microbicides Advocacy Group Network (MAG-Net), and the AIDS Vaccine Advocacy Coalition (AVAC) *Take Action!* web page: http://www.avac.org/action.htm. Below is a list of resources and links where you can learn more about HIV/AIDS prevention, NPTs and advocacy.

Until recently, there have been few advocacy organisations dedicated specifically to HIV prevention and new prevention technologies. In mid-2007, the AIDS Vaccine Advocacy Coalition (AVAC) received major funding from the Bill & Melinda Gates Foundation to create a new international HIV Prevention Research Advocacy Network. The Advocacy Network will work with civil society, policymakers, and research partners around the world to advance ethical research and development of new HIV prevention interventions, ensure that communities are informed about and involved in prevention research, and ensure that the benefits of research are shared globally. To learn more, see http://www.avac.org.

Resources

• PREVENTION

HIV Prevention Research: A Comprehensive Timeline (by AVAC)
http://www.avac.org/timeline-website/index.htm

UNAIDS (includes general information on prevention)
http://www.unaids.org

• DIAPHRAGMS AND CERVICAL BARRIERS

Women's Global Health Initative
http://wghi.org/research/female_controlled_tools.htm

Cervical Barrier Advancement Society
http://www.cervicalbarriers.org

Global Campaign for Microbicides information on cervical barriers
http://www.global-campaign.org/barriers.htm

• HSV-2 TREATMENT

HIV Prevention Trials Network (HPTN) Study
http://www.hptn.org/research_studies/hptn039.asp

University of Washington, Bill and Melinda Gates Foundation Study
http://www.clinicaltrials.gov/ct/show/NCT00197574

• MALE CIRCUMCISION

AIDS Vaccine Clearinghouse information on MC (by AVAC)
http://www.aidsvaccineclearinghouse.org/MC/index.html

UNAIDS information on MC
http://www.unaids.org/en/Issues/Prevention_treatment/MC.asp

Global Campaign for Microbicides information on MC
http://www.global-campaign.org/malecircumcision.htm

• VAGINAL AND RECTAL MICROBICIDES

Global Campaign for Microbicides (GCM)
http://www.global-campaign.org

International Partnership for Microbicides (IPM)
http://www.ipm-microbicides.org

Microbicide Trials Network (MTN)
http://www.mtnstopshiv.org

Alliance for Microbicide Developent (AMD)
http://www.microbicide.org

International Rectal Microbicides Advocates (IRMA)
http://www.rectalmicrobicides.org

• PRE-EXPOSURE PROPHYLAXIS

PrEP Watch (by AVAC)
http://www.prepwatch.org

• VACCINES

AIDS Vaccine Advocacy Coalition (AVAC)
http://www.avac.org

AIDS Vaccine Clearinghouse (by AVAC)
http://www.aidsvaccineclearinghouse.org

International AIDS Vaccines Initiative (IAVI)
http://www.iavi.org

Global HIV Vaccine Enterprise
http://www.hivvaccineenterprise.org

• MALE AND FEMALE CONDOMS

Global Campaign for Microbicides information on female condoms
http://www.global-campaign.org/female-condom.htm#[femalecondom]

Family Health International (FHI) information on the female condom
http://www.fhi.org/en/topics/femcondom.htm

Planned Parenthood information on the female condom
http://www.plannedparenthood.org/birth-control-pregnancy/birth-control/female-condom.htm

Planned Parenthood information on the male condom
http://www.plannedparenthood.org/birth-control-pregnancy/birth-control/condom.htm

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[i] Joint United Nations Programme on HIV/AIDS. *AIDS Epidemic Update*, December 2007.
[ii] http://www.unaids.org/en/Policies/HIV_Prevention/default.asp, accessed December 9, 2007.
[iii] Foss, A.; Vickerman, P.; Heise, L.*" Shifts in condom use following microbicide introduction: should we be concerned?"* AIDS 2003, 17:1227-1237
[iv] Smith RJ, Bodine EN, Wilson DP and Blower SM. *"Evaluating the potential impact of vaginal microbicides to reduce the risk of acquiring HIV in female sex workers."* AIDS 2005, 19:413–421

ICAD's mission is to lessen the spread and impact of HIV and AIDS in resource-poor communities and countries by providing leadership and actively contributing to the Canadian and international response. Funding for this publication was provided by the International Partnership for Microbicides (IPM). The opinions expressed in this publication are those of the authors/researchers and do not necessarily reflect the official views of the International Partnership for Microbicides (IPM).

Ce feuillet est également disponible en français.