

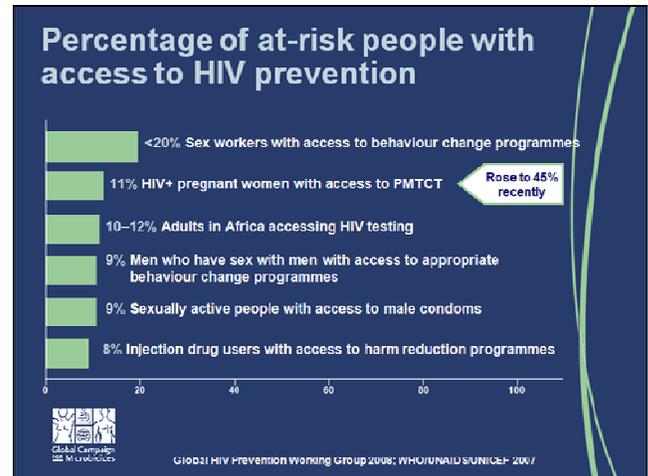
## TOOLS, TRENDS AND NEW TECHNOLOGIES IN HIV PREVENTION

### Introduction

In recent years, prevention has moved to the top of the global HIV and AIDS agenda. Michel Sidibé, Executive Director of UNAIDS, recently reiterated the need for sustained investment in prevention: *“We must not forget: for every two people who start antiretroviral treatment, five are newly infected with HIV. To break this vicious circle, there is only one solution—to stop new HIV infections. Prevention must become our watchword, the banner we raise in this critical stage of the response.”*

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



Global Campaign for Microbicides, 2009

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

Research into new prevention technologies (NPTs) is a lengthy process that takes 12 years or more to go through laboratory and animal testing, safety and efficacy studies, regulatory approval and post-marketing studies.

This fact sheet provides a brief definition of each of the potential prevention tools being researched, and gives an overview of the current state of research. The fact sheet then provides an overview of the prevention technologies that we currently have at our disposal—female and male condoms, and medical male circumcision—and summarizes recent findings about these technologies. The fact sheet then outlines research into prevention technologies that have had unsuccessful results—diaphragms and cervical barriers, and treatment for herpes simplex virus type 2 (HSV-2).

Finally, the fact sheet summarizes Canada's role in research of new HIV prevention technologies, and the role that advocates can play in this research.

### Potential Prevention Tools

*"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 than the search for an effective microbicide."*

– Graça Machel, Opening Address, Microbicides 2006, Cape Town, South Africa

### Microbicides

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

A number of vaginal microbicides have been tested in clinical trials. Six vaginal microbicide candidates—nonoxynol-9, Savvy, cellulose sulfate, Carraguard, BufferGel and PRO 2000—have been tested in late-stage trials and have been found to be ineffective for HIV prevention.

A number of next generation candidates, based on antiretroviral (ARV) drugs, are in earlier stages of clinical trials. The results of a Phase IIB tenofovir vaginal gel study are expected in 2010.

Research into rectal microbicides is several years behind vaginal microbicides. In mid-2008, the world's first rectal microbicide safety trial was completed. Another trial testing tenofovir began in late 2009, and up to two more rectal safety trials are in the planning stages.

### Pre-Exposure Prophylaxis

Pre-exposure Prophylaxis or "PrEP" refers to an experimental HIV prevention strategy that would use antiretrovirals to reduce the risk of HIV infection among HIV-negative people. In the strategies that are currently being tested, HIV-negative 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, PrEP could be taken once daily to prevent HIV infection in case of exposure.

Current PrEP trials are testing tenofovir (Viread) or Truvada™ (tenofovir with emtricitabine), two antiretroviral drugs currently used as treatment for HIV infection. Five studies underway are testing whether PrEP is effective. These studies involve from 1,200 to 5,000 individuals. Results from these trials will be available from 2010 to 2012. One study taking place is an expanded safety study involving 400 MSM. This study is investigating side effects, adherence, and the impact of PrEP on risk-taking behaviours. Another study being planned will involve 150 participants and will evaluate the feasibility of PrEP that is taken twice weekly and before sex, rather than daily. In addition to these planned and ongoing trials, there were trials stopped or cancelled for different reasons in Malawi, Nigeria, Cameroon and Cambodia<sup>i</sup>.

### 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 studies.

Two efficacy trials of a vaccine candidate called AIDSVAX ended in 2003. Both of these studies found that the candidate did not protect against infection. One of the trials was among MSM in the US, Canada and the Netherlands. The other trial was among IDUs in Thailand.

In late 2007, vaccinations in two large-scale Phase IIB proof of efficacy trials (the STEP study) were halted after a planned initial analysis showed lack of efficacy. One of the trials had sites in Canada. Participants were unblinded in both trials (meaning they were told whether they were given the placebo or experimental vaccine) 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 counseling was offered throughout the trial, and is continuing. Data analysis is ongoing, and results are being made public as they are announced.

In September 2009, results from a large-scale Phase III efficacy trial in Thailand, RV144, were released. This prime-boost trial tested a combination of two vaccines called ALVAC and AIDSVAX, and found that the vaccine lowered the rate of HIV infection by 26.2 to 31.2 percent compared to the placebo. The trial results did not show evidence that the vaccine reduced the viral load of those who became infected. Some analyses indicate that the reduction in infections was statistically significant, meaning that the possibility of the result being due to chance is low. However, other analyses indicate that the results were not statistically significant. The results of the trial are undergoing continued analysis and will be important in guiding future vaccine research and provide important evidence that an effective HIV vaccine is possible.

Another recent and positive finding in the field of vaccine research was the discovery of two broadly neutralizing antibodies to HIV that reveal a previously

unknown site on the virus that could prove to be a good target for vaccine design.

### **A WORD ABOUT PARTIAL EFFICACY**

*Products that have less than 100% effectiveness can still have a significant impact on the HIV pandemic. In many cases, including with microbicides, vaccines and cervical barriers, many researchers believe that only moderate efficacy rates will ever be achieved. However, there is reason to believe that even a product with partial efficacy could have benefit under certain circumstances, particularly in cases where other more effective means of protection like condoms are not feasible or desirable.*

*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<sup>ii</sup>.*

*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.*

### **HIV Treatment as Prevention**

There are two ways in which treatment for the HIV-positive partner is thought to work as HIV prevention—at an individual level and at a population level.

At an individual level, trials are underway to find out whether the risk of transmission from an HIV-positive to an HIV-negative partner is reduced when the HIV-positive partner is on antiretrovirals (ARVs). ARVs

reduce the viral load—the amount of virus in the blood—of people who are HIV-positive. Reduced viral load is thought to decrease the chances of transmitting HIV. In 2008, the Swiss National AIDS Commission stated that HIV-positive individuals who are on treatment, have an undetectable viral load for at least six months and no other sexually transmitted infections (nor does their sexual partner), should not be considered at risk of transmitting HIV to others through vaginal intercourse. There has been significant debate about this statement, in part because viral load in blood may not always correlate with viral load in semen.

At a population level, some people argue that doing HIV testing on a massive scale and providing treatment to those who test HIV-positive could significantly reduce the number of new HIV infections. It is thought that in addition to lowering viral load by putting individuals on treatment, massive testing campaigns would lead to more people knowing their status and for those who test positive, decreasing their risk behaviour.

### Previously Investigated Tools

#### ***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, counseling, STI screening and treatment). The study authors concluded that a diaphragm should not be used or promoted as an effective means of HIV prevention at this time. 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 was anticipated to lower HIV risk—both the risk of acquiring HIV infection and the risk of transmitting it to others.

In 2007 the HPTN 039 study investigated whether acyclovir would prevent HIV acquisition among people who are HIV-negative and HSV-2-positive. The study concluded that there was no evidence that twice daily acyclovir prevents HIV-infection among HSV-2 infected women and men who have sex with men.

Furthermore, in May 2009, results were released from a *Partners in Prevention* trial that investigated whether acyclovir would prevent HIV-transmission from individuals who are both HIV-positive and HSV-2-positive. The trial, conducted at 14 sites in seven African countries, found that ongoing suppressive acyclovir therapy for HSV-2 in HIV-positive people did not reduce their risk of transmitting HIV to their HIV-negative partners. There was however evidence that acyclovir worked to reduce rates of genital ulcers and HIV viral load in people who are HIV-HSV-2 co-infected. This reduction in viral load was not enough to reduce transmission to HIV-negative partners; however, it did show evidence of slowing HIV disease progression among individuals with HIV and HSV-2 who also have

CD4 T-cell counts that are too high for HIV antiretroviral treatment under current US national guidelines.

### 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.

In March 2009, the Female Health Company (FHC) announced approval from the United States Food and Drug Administration (FDA) for the 2nd-generation female condom, known as the FC2. The FC2 has the same design, appearance and use as the FC1, but is made of a different material—a synthetic rubber called

nitrile. The FC2 is comparable in safety and effectiveness to the FC1 and will sell for about 30% less.

PATH (Partnership for Appropriate Technologies in Health), a non-profit health organization, is researching and developing a new female condom design. The Woman's Condom is ready for a combined Phase II/III clinical trial, the last step before FDA approval.

*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 as microbicides and vaccines are desperately needed.*

#### **Medical 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 at least 50%. There are 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 resuming sexual activity before complete 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.

### Canada and Research into New Prevention Technologies

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 vaccine 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 (CHVI) was announced as part of a partnership between

the Canadian government and the Enterprise. Through CHVI, Canada is increasing its contribution to vaccine research.

While little microbicides research has occurred in Canada, two candidate microbicides were developed in Canada (cellulose 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 of NPTs: 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 with proven efficacy
- 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.

Advocates have an important role to play in learning about and communicating advances in prevention research, and supporting research and development as a critical part of the HIV/AIDS response. Advocates can also work to ensure the inclusion of the voices of many stakeholders, particularly those communities most affected by HIV and AIDS, in discussions around prevention research.

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.

<sup>i</sup> For more information on Cameroon and Cambodia trial closures, see Research Rashomon: Lessons from the Cameroon Pre-exposure Prophylaxis Trial Site, Global Campaign for Microbicides, 2009 (<http://www.global-campaign.org/clientfiles/Cameroon.pdf>), and Preventing Prevention Trial Failures: A Case Study and Lessons Learned for Future Trials from the 2004 Tenofovir Trial in Cambodia, Global Campaign for Microbicides, 2009 (<http://www.global-campaign.org/clientfiles/Cambodia.pdf>).

<sup>ii</sup> 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.

### References and Sources of Additional Information

#### • 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>

Interagency Coalition on AIDS and Development: <http://icad-cisd.com/content/en/programming-areas/prevention/195>

#### • DIAPHRAGMS AND CERVICAL BARRIERS

Women’s Global Health Initiative: [http://wghi.org/research/female\\_controlled\\_tools.htm](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](http://www.hptn.org/research_studies/hptn039.asp)

University of Washington, Bill and Melinda Gates Foundation Study: <http://www.clinicaltrials.gov/ct/show/NCT00197574> ; <http://uwnews.org/article.asp?articleid=49611>

#### • MEDICAL 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](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.ipmglobal.org>

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

International Rectal Microbicide Advocates (IRMA): <http://www.rectalmicrobicides.org>

### • PRE-EXPOSURE PROPHYLAXIS

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

GCM's PrEP materials and links: <http://www.global-campaign.org/EngDownload.htm#prep>

### • 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

Centre for Health and Gender Equity information on the female condom: <http://www.preventionnow.net/>

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

PATH information on the female condom: [http://www.path.org/projects/womans\\_condom.php](http://www.path.org/projects/womans_condom.php)

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>