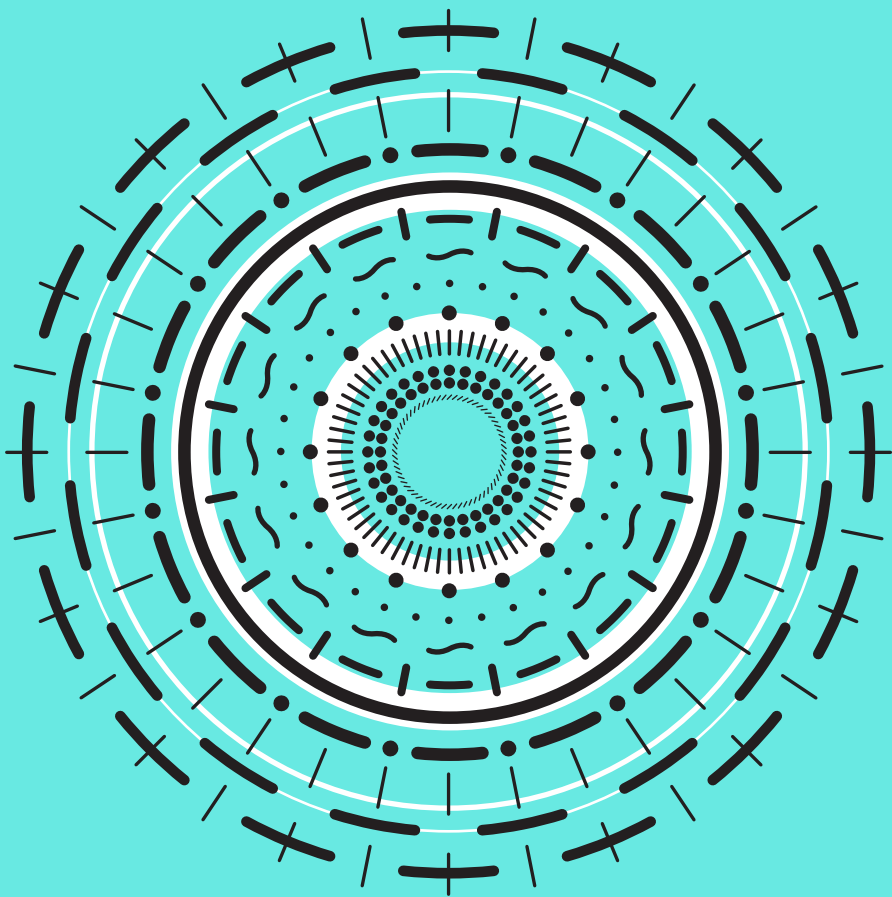
POTENTIAL PREVENTION TECHNOLOGIES

PREVIOUSLY INVESTIGATED TECHNOLOGIES

EXISTING PREVENTION TECHNOLOGIES



NEW PREVENTION TECHNOLOGIES

What are they and what is their relevance for people living with HIV?

BACKGROUND
NEW PREVENTION TECHNOLOGIES IN CONTEXT

To ensure a comprehensive approach to addressing HIV, 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 needs new prevention tools and technologies that will work with and complement existing prevention methods.

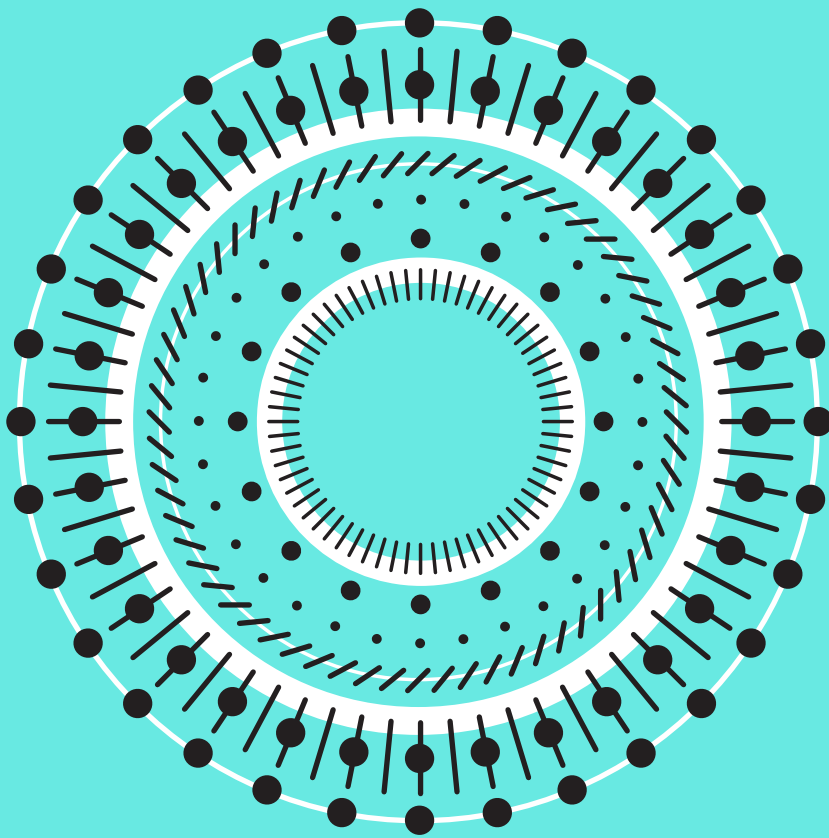
There are a number of global efforts underway to develop new technologies to prevent HIV. Currently, there is research being conducted on vaginal and rectal microbicides, vaccines, pre-exposure prophylaxis (PrEP) and the use of HIV treatment as prevention.

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

This toolkit provides a brief definition of each of the potential prevention tools being researched, gives an overview of the current state of research, and discusses their relevance for people living with HIV.[1]

It 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 toolkit provides an overview of the prevention technologies that we currently have at our disposal—female and male condoms, medical male circumcision, post-exposure prophylaxis and prevention of vertical transmission (sometimes called prevention of mother-to-child transmission or PMTCT)—and summarises recent findings about these technologies.

[1] Please consult the companion discussion paper: The Role of People Living with HIV in Biomedical Prevention Research and the Search for New Prevention Tools, Global Network of People Living with HIV (GNP+), 2010, www.gnpplus.net



POTENTIAL PREVENTION TECHNOLOGIES

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 were in the planning stages in early 2010.

Microbicides are not something just for HIV-negative people. A lot of HIV-positive people want them, too. A microbicide might reduce an HIV-positive person's risk of infection with other strains of HIV. Some products may also reduce the risk of getting other sexually transmitted infections or yeast infections (also called vaginal thrush). For people with compromised immune systems, this could be an important advantage. It is also possible that a microbicide that is not contraceptive could help an HIV-positive woman conceive a baby with little risk of endangering her HIV-negative partner.

ARV-based microbicides are likely to be more potent against HIV and may be longer-lasting than microbicides not based on ARVs. But they also might cause more side effects, including drug resistance, if they are accidentally used by someone who is HIV-positive already. For this reason, users will have to see a health care provider and get an HIV test before receiving these products. They will only be available by prescription. ARV-based microbicides will not be appropriate for use by someone who is HIV-positive. Therefore, non-ARV-based microbicides should be pursued to ensure a safe new prevention alternative for people living with HIV.

PRE-EXPOSURE PROPHYLAXIS

Pre-exposure Prophylaxis or "PrEP" refers to an experimental HIV prevention strategy that would use ARVs 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.

PrEP is not recommended for HIV prevention now because we do not know yet whether it will actually work to prevent HIV. Research is going on to see if it works or not.

Current PrEP trials are testing tenofovir (Viread) or Truvada (tenofovir with emitricitabine), two antiretroviral drugs currently used as treatment for HIV infection. Five large-scale 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.

People living with HIV are involved as participants in one large-scale PrEP efficacy trial. The Partners PrEP trial taking place in Uganda and Kenya is enrolling 3,900 heterosexual couples in serodiscordant relationships. The trial will test whether PrEP (either tenofovir or Truvada) prevents the HIV-negative partner from becoming infected. The couples that are recruited include an HIV-positive partner that does not yet qualify for treatment, although they do receive ongoing HIV care.

Serodiscordant couples are also involved in the small study looking into alternative PrEP dosing, mentioned above.

HIV testing will need to be a condition for access to PrEP because only people who know that they are HIV-negative can use PrEP safely. If you use it when you are already HIV-positive, you are very likely to develop drug-resistant virus, which you may then pass on to other people. Having drug-resistant virus may also make it harder to treat your HIV infection.

VACCINES

A vaccine is a substance that teaches the body to recognise 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.

While preventive vaccines are designed to be given to HIV-negative people, it is thought that they might have a therapeutic effect if that vaccinated person eventually becomes HIV-positive. Since vaccines would only reduce the risk of infection—not eliminate it—someone who has been vaccinated could still become HIV-positive. It is hoped that the vaccine they received while HIV-negative could help them once they become HIV-positive by maintaining a lower viral load and a better functioning immune system than if they had not been vaccinated. The preventive vaccine taken while they were HIV-negative could therefore have a therapeutic effect once they became HIV-positive.

Therapeutic vaccines are also being tested, and are designed to boost the body's immune response to HIV in order to better control the infection among people who are already HIV-positive.

Currently, there are no preventive or therapeutic vaccines that have been proven to work. In early 2010, there were close to 30 clinical trials of experimental preventive 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 gay men and other men who have sex with men (MSM) in the United States, Canada and the Netherlands. The other trial was among persons who inject drugs (IDUs) in Thailand.

In late 2007, vaccinations in two large-scale Phase IIB proof of efficacy trials were halted after a planned initial analysis showed lack of efficacy. The trials were being held in Australia, Canada, the Dominican Republic, Haiti, Peru, South Africa, and the US. 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 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.

Education programmes 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.

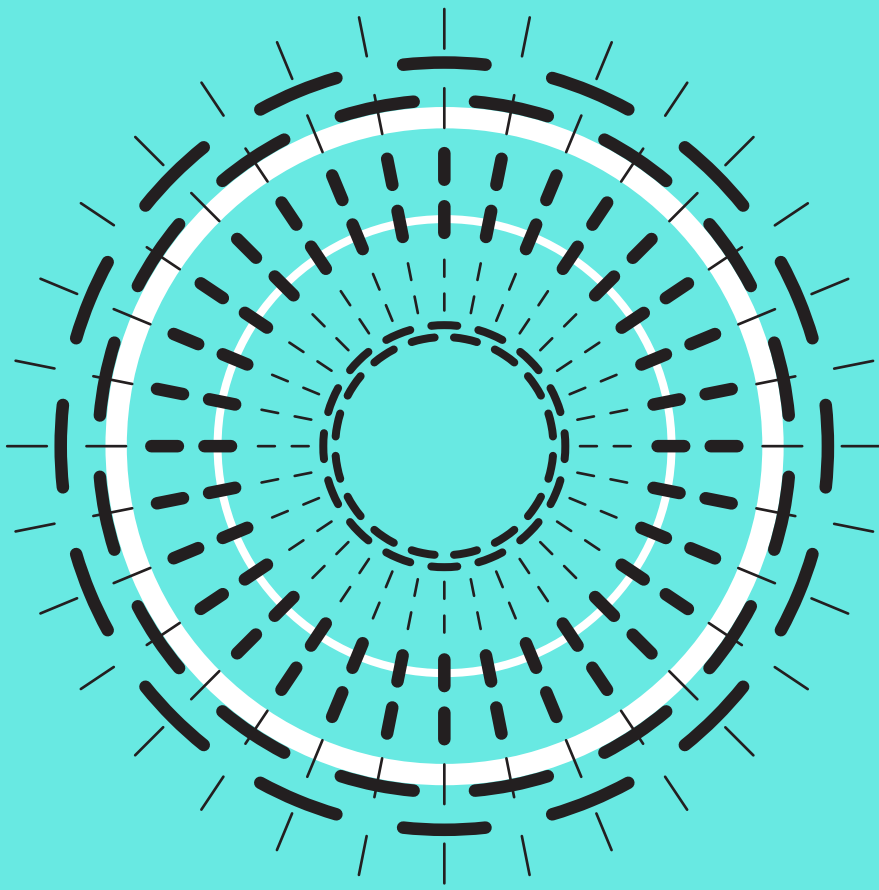
There is one ongoing efficacy trial, called HPTN 052, testing this approach. The trial aims to enroll 1,750 serodiscordant couples to look at whether HIV-positive participants who start ARVs upon enrollment, regardless of their CD4 cell count, are less likely to transmit to their HIV-negative partners, compared to participants who delay ARV initiation until it is clinically indicated. All participants in the trial receive a basic prevention package including treatment for sexually transmitted infections, condoms, and risk reduction counseling. The trial sites are in Brazil, India, Malawi, Thailand, the United States, and Zimbabwe.

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.

Treatment activists and networks of people living with HIV have long advocated for universal access to voluntary counseling and testing (VCT), following by universal access to treatment to anyone who needs it. In some cases, the treatment as prevention approach proposes starting HIV-positive people on ARVs when they are diagnosed—which may or may not be when it is clinically indicated to do so. There have been ongoing discussions at

the local, country, regional and global levels about these various approaches. Treatment activists, prevention advocates and networks of people living with HIV have expressed support for increased access to testing and treatment to the extent that it remains rights-based and voluntary, that it links testing to treatment, care, support and prevention, that it addresses the numerous barriers to access that still exist, and that it recognises that individuals may still decide to delay treatment for clinical, economic, social or personal reasons.

There are ongoing discussions and planning for a study that would evaluate the feasibility of a community-focused enhanced HIV test-and-treat strategy in the United States.



PREVIOUSLY INVESTIGATED TECHNOLOGIES

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.

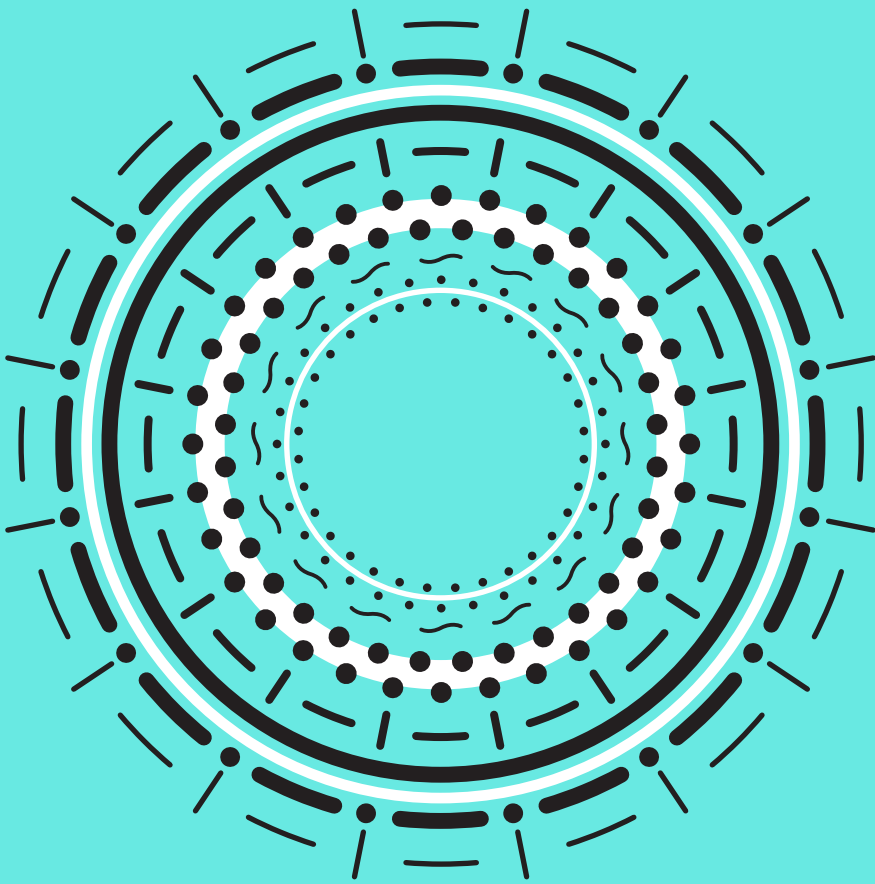
In July 2007, results were announced from the MIRA (Methods for Improving Reproductive Health in Africa) diaphragm study, which took place in South Africa and Zimbabwe. The trial found that there is no added benefit from the use of a diaphragm and lubricant in the context of a comprehensive HIV prevention 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 MSM.

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 treatment guidelines.



EXISTING PREVENTION TECHNOLOGIES

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 increase substantially 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, bias that service providers may have against new products, and lack of support for large-scale programmes. 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 organisation, 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 a microbicides and vaccines are 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 randomised 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, but this could be related to resuming sexual activity before complete wound healing, and more research is needed. There is no randomised clinical trial data on the impact of male circumcision on HIV transmission rates through anal intercourse.

Based on the data from the trials in HIV-negative men, there is a strong case for making medical 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.

POST-EXPOSURE PROPHYLAXIS

When someone takes ARVs for a full month right after an exposure to HIV—like a needle stick in a hospital—it is called post-exposure prophylaxis or "PEP". Most commonly, PEP is given to health care workers after occupational exposures to HIV. It may also be given in other situations of known exposure to HIV, such as unprotected sex and sharing needles with a partner known to be HIV-positive, especially if the situation was involuntary (such as after rape or when the condom breaks).

Access to PEP varies greatly. In most cases, it is very difficult to access after non-occupational exposure. Even after rape, women sometimes have difficulty getting access to PEP, even though the medication must be started soon after exposure in order to be effective.

PREVENTION OF VERTICAL TRANSMISSION

To prevent vertical transmission (transmitting HIV to the child of an HIV-positive mother) it is most important to provide ARVs to the mother during her pregnancy and labour, and to provide ARVs to the infant during the first few weeks after birth. When possible, delivery by Caesarian section and avoiding breastfeeding can also significantly reduce transmission risk. If avoiding breastfeeding is not possible, exclusively breastfeeding the baby is less risky than alternating between breastfeeding and using formula.

Ideally, we should scale up prevention programmes to ensure that fewer women become HIV-positive. If they are HIV-positive and it is clinically indicated, women should have ongoing access to treatment, not just during pregnancy and birth. By far, the greatest numbers of HIV-positive pregnant women live in sub-Saharan Africa. But in this region, less than half (45%) had access to ARVs for prevention of vertical transmission in 2008.[2]

[2] World Health Organization (WHO). Toward universal access: Scaling up priority HIV/AIDS interventions in the health sector. www.who.int/hiv/pub/2009progressreport/en/ Accessed October 26, 2009.

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 and promoting Positive Health, Dignity and Prevention,[3] as defined by people living with HIV.

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. People living with HIV 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 response to HIV. They can also work to ensure the inclusion of the voices of many stakeholders, particularly those communities most affected by HIV, in discussions around prevention research.

Please consult the list of resources and links below, where you can learn more about HIV prevention, NPTs and advocacy.

[3] GNP+, UNAIDS. 2009. Positive Health, Dignity and Prevention Technical Consultation Report. Amsterdam, GNP+. www.gnpplus.net Accessed April 20, 2010

REFERENCES

PREVENTION

Positive Health,
Dignity and Prevention
(GNP+ and UNAIDS)
www.gnpplus.net

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

Ethical and participatory
guidelines for biomedical
prevention trials (UNAIDS)
www.unaids.org

VAGINAL AND RECTAL MICROBICIDES

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

International Partnership
for Microbicides (IPM)
www.ipmglobal.org

Microbicide Trials
Network (MTN)
www.mtnstopshiv.org

International Rectal
Microbicide Advocates (IRMA)
www.rectalmicrobicides.org

PRE-EXPOSURE PROPHYLAXIS

PrEP Watch (by AVAC)
www.prepwatch.org

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

VACCINES

AIDS Vaccine Advocacy
Coalition (AVAC)
www.avac.org

AIDS Vaccine Clearinghouse
(by AVAC)
www.
aidsvaccineclearinghouse.org

International AIDS Vaccines
Initiative (IAVI)
www.iavi.org

Global HIV Vaccine
Enterprise
www.hivvaccineenterprise.org

HIV TREATMENT AS PREVENTION

AIDS Vaccine Advocacy
Coalition (AVAC)
www.avac.org/
ht/d/sp/i/421/pid/421

UNAIDS
www.unaids.org/
en/KnowledgeCentre/
Resources/FeatureStories/
archive/2009/
20091106_ART_for_HIVprev.
asp

Civil society statement on
treatment as prevention
www.icaso.org/
resources/2009/
ART_statementEN.pdf

DIAPHRAGMS AND CERVICAL BARRIERS

Women's Global Health
Initiative
wghi.org/research/
female_controlled_tools.htm

Cervical Barrier
Advancement Society
www.cervicalbarriers.org

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

HSV-2 TREATMENT

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

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

MALE AND FEMALE CONDOMS

Centre for Health and Gender Equity information on the female condom
www.preventionnow.net

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

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

PATH information on the female condom
www.path.org/projects/womans_condom.php

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

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

MEDICAL MALE CIRCUMCISION

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

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

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

POST-EXPOSURE PROPHYLAXIS

World Health Organization on PEP
www.who.int/hiv/topics/prophylaxis/en/

UNAIDS on PEP
www.unaids.org/en/PolicyAndPractice/Prevention/HIVPEP/default.asp

PREVENTION OF VERTICAL TRANSMISSION

World Health Organization
www.who.int/hiv/topics/mtct/en/index.html

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NEW
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TECHNOLOGIES