



Pre-Exposure Prophylaxis (PrEP)

An Introductory Factsheet

May 2020

This fact sheet provides basic information on PrEP, an HIV prevention strategy for HIV-negative individuals. For more basic fact sheets in this series on HIV prevention strategies visit www.avac.org/intro.

What is PrEP?

Pre-exposure prophylaxis, or PrEP, is another way to help HIV negative people protect themselves from getting HIV. PrEP uses antiretroviral medication (ARVs)—drugs created to treat people living with HIV—for HIV prevention. Two PrEP products, given as daily oral pills, are currently being marketed. Another ARV as PrEP, cabotegravir, was found to be safe and efficacious when administered via a long-acting injection. This finding came from a study, known as HPTN 083, cisgender men who have sex with men and transgender women. Another trial, HPTN 084, is a sister study looking at long-acting injectable cabotegravir among cisgender women. Results from 084 are expected in 2022. A vaginal ring is yet another option that may be available soon. The ring slowly releases an ARV called dapivirine. Each month, the ring would be replaced with a new one for another month of protection. The ring is under review by the European Medicines Agency (EMA).

Other PrEP strategies under development include a quick-dissolving vaginal film (containing ARVs) that can be inserted right before sex, and a long-acting implant that could offer protection for up to a year. This factsheet focuses on oral PrEP methods. For more on the other PrEP research underway, visit www.avac.org/infographic/arv-based-prevention-pipeline.

Among the two daily oral pills, the first to be approved, in 2012, uses a two-drug combination known as TDF/FTC, brand name Truvada. It is approved for all populations at risk of HIV. Another, brand name Descovy, was developed more recently. It relies on a drug combination known as TAF/FTC and its approval by the FDA excludes those at risk of HIV from receptive vaginal sex. A trial is being planned to gather the missing data needed to approve TAF/FTC in women. The Descovy trial design and the restricted approval by the FDA sparked criticism and discussion about planning for research that includes all populations that need HIV protection. For more information on this go to avac.org/ftaf and avac.org/podcast/f-taf-fuss.

Evidence shows both of these oral products can lower the chance of getting HIV by at least 90 percent.

National regulatory agencies in many countries have agreed that using oral PrEP is a good strategy for people at high risk of HIV to stay negative. In late 2015, the World Health Organization endorsed PrEP and now recommends it as another tool that HIV-negative people can use, along with voluntary medical male circumcision (VMMC) and male and female condoms, to protect themselves from HIV.

What's known about oral PrEP for cisgender men and transgender women?

In almost all of the PrEP studies conducted to date, the participants have been cisgender men and transgender women. These studies include clinical research trials, ongoing demonstration projects and data on the use of oral PrEP collected by national PrEP programs. Here's what we know from those studies. Caution: This information may or may not apply equally to cisgender women and transgender men:

- Daily oral PrEP is safe. No significant side effects have been observed in PrEP trials to date. Every medication, including aspirin, comes with some risk. But no major safety issues have been observed with the use of daily oral PrEP.

Resources

AVAC (www.avac.org)

PrEP Watch
(www.prepwatch.org)

Please PrEP Me (provider
directory)
(www.pleaseprepme.org)

- PrEP works if you take it on schedule. Adherence is essential. In every trial in which PrEP worked well, results showed that the people who took their PrEP pill on schedule had high levels of protection from HIV. Those who did not get little or no protection from PrEP.
- People with high rates of HIV risk behaviors can also adhere very well to PrEP. This is important because it shows “safer sex” does not just mean avoiding exposure to HIV. It can also mean choosing to take PrEP for protection if you do not always use condoms.
- TDF/FTC is highly protective in people of all genders when used correctly.
- If you take PrEP when you already have HIV — but don’t know it yet — you can develop resistance to the drugs in PrEP. Drug resistance is when a drug stops working in your body, and will no longer be effective treatment for HIV infection. You must get an HIV test before starting PrEP and every time you get a refill. The test makes sure you are still HIV-negative. For PrEP to work, you need to have a negative HIV test before you start, you need to take it as directed and get re-tested for HIV every time you get a refill. This way, there is very little risk of acquiring drug resistance.
- Research in gay men and other men who have sex with men showed that “event-driven” or “on-demand” dosing schedules can also be effective. The regimen tested taking two pills at least 2 hours before having sex and at least 2 more pills in the 24-48 hours after sex — instead of taking pills daily. When trial participants (gay men and a few transgender women) took 4-7 pills per week — regardless of whether they were in the “daily dosing” group or the “on demand” group, risk of HIV was greatly reduced.

What’s known about oral PrEP for cisgender women and transgender men?

- PrEP can protect the vagina from HIV as well as it protects the rectum — but it takes longer to build up protective levels of PrEP drugs in the vaginal (and it takes more regular dosing to maintain). The US Centers for Disease Control (CDC) recommends that people with vaginas take PrEP daily for 20 days *before* relying on it for protection from vaginal HIV exposure. After that, daily doses can maintain protection.
- Cisgender women and transgender men also need to be more careful about not missing PrEP doses. If you have a vagina and take fewer than 6-7 PrEP pills per week, your protection level will drop. That is why “event driven” or “on demand” PrEP use is not recommended for women and transgender men.

What is the status of oral PrEP today?

Access to oral PrEP is expanding. In 2015, WHO issued guidelines recommending, among other things, PrEP access for those at high risk of HIV. WHO’s recommendation motivated some countries to expand their PrEP program.

While some medium and low-income countries have expanded their PrEP programs, such as Kenya and South Africa, approximately 15 percent of the UNAIDS target of 3 million people have initiated. The US President’s Emergency Plan for AIDS Relief (PEPFAR) has recognized the benefits that PrEP could provide to pregnant women, men who have sex with men, high-risk heterosexuals, and other high-risk populations. They continue to support PrEP scale-up directly through country operating plans. With adequate resources and international commitment, PrEP can become a major tool for HIV prevention worldwide.

- For insights on the full scope of PrEP use around the world, [AVAC’s PrEP tracker](#) offers quarterly updates on programs delivering oral PrEP, planned, current and completed.

Status of PrEP research

- For a broad review of completed and ongoing PrEP trials, visit www.avac.org/pxrd.
- For an overview of the pipeline for next-generation PrEP, visit www.avac.org/infographic/future-arv-based-prevention.

About AVAC | AVAC is a non-profit organization that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of new HIV prevention options as part of a comprehensive response to the pandemic. This fact sheet is part of the Women’s HIV Prevention series, created to address HIV prevention strategies and the advocacy needed to bring them to reality.



HIV Vaccines

An Introductory Factsheet

April 2020

This factsheet provides basic information on preventive HIV vaccines. For more basic fact sheets in this series on emerging HIV prevention strategies visit www.avac.org/intro.

What is an HIV vaccine?

Researchers are working to come up with two kinds of vaccines against HIV. One kind, a **preventive vaccine**, would reduce HIV risk in people who are HIV negative. It would teach their immune systems to recognize the virus right away (for example, during sex), and block it from causing an infection. No preventive HIV vaccine exists yet.

A therapeutic HIV vaccine is also being pursued. People living with HIV would take a therapeutic vaccine to strengthen their immune systems for better control the virus. This kind of vaccine could, in theory, help people control the virus without anti-retroviral drugs (ART), or be used as a supplement to ART regimens. Research on therapeutic vaccines may also inform research on how to cure HIV. No therapeutic HIV vaccine has been proven to work yet.

This fact sheet is about research to find **preventive vaccines** for use by HIV-negative people.

What is happening in HIV vaccine research now?

Vaccine research starts in the lab. Next, the candidate vaccines are tested on animals. If it shows evidence of safety and potential efficacy in animals, it moves on to testing in humans. This starts in small trials and, if results show the vaccine is safe and causes beneficial immune responses, it moves on to larger trials. The last stages of the process involve efficacy trials, named Phase IIb or Phase III trials. Thousands of volunteers participate. Without them, it would be impossible to learn if the vaccine lowers people's risk of getting HIV. To learn more about how HIV prevention trials work, download AVAC's fact sheet, [HIV Prevention Trial Terms: An Advocate's Guide](#).

There are currently several large-scale efficacy trials testing various vaccine candidates against HIV. One is a Phase IIb/III trial called [HVTN 702 or Uhambo](#), that enrolled 5,407 South African men and women. At least 12 clades (different types) of HIV exist in the world. HVTN 702 was testing a vaccine candidate designed to prevent Clade C, the most common HIV clade in Southern Africa. Unfortunately, this vaccine was not found to reduce risk.

The second trial is called [HPX2008/HVTN 705 or Imbokodo](#), and is a Phase IIb trial that enrolled 2,600 women in five countries across sub-Saharan Africa. In this region, more women than men are becoming newly infected with HIV. The vaccine regimen being tested in the *Imbokodo* trial is known as a mosaic vaccine. It is designed to protect against multiple types of global HIV clades. The results of the study are expected in late 2022.

The third trial is called HVTN 706/HPX3002 or *Mosaico*, a Phase III trial enrolling 3800 men who have sex with men (MSM) and transgender people in Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain, and the United States. *Mosaico* is testing a mosaic vaccine regimen that is very similar to the regimen being studied in *Imbokodo* but differs slightly.

Mosaico includes an additional ingredient, a protein, aimed at Clade B. The hope is that this additional protein will help this vaccine work in other regions of the world such as North America and Europe where the Clade B strain of HIV is found. If the vaccine regimen used in *Mosaico* is successful in offering some protection against getting HIV, it will result in a safe and effective vaccine that will be suitable for global populations at risk of HIV acquisition. The study is expected to come to an end in late 2023.

Resources and links

AVAC (www.avac.org/vaccines)

Global HIV Vaccine Enterprise
(www.iasociety.org/Global-HIV-Vaccine-Enterprise)

HIV Vaccine Trials Network
(www.hvtn.org)

International AIDS Vaccine Initiative
(www.iavi.org)

US MHRP (www.hivresearch.org)

NIH-NIAID (www.niaid.nih.gov)

A fourth vaccine trial program, known as [PrEPVacc](#), has started to gather data on HIV risk and other demographic data, in preparation for a Phase III clinical trial. The clinical trial was expected to begin in early 2020. This date is now expected to be delayed to 2021 because of the COVID-19 pandemic. It will enroll 1,688 men and women from general and key population groups in four countries in East and Southern Africa. The trial will be testing a combination of experimental HIV vaccines and oral PrEP at the same time.

What are the discoveries in HIV vaccine research so far?

In 2009, a trial in Thailand called RV144 showed that volunteers who got the test vaccine were 31% less likely to get HIV during the trial than those who got the placebo. The RV144 results showed that the vaccine was protective against some exposures to HIV. Since that trial, researchers identified some of the immune responses that might have led to protection. They also came up with adjustments that they thought would improve it and adapted it for use in other parts of the world. The outcome was the *Uhambo* trial (HVTN 702) described above, which used further refined versions of the components found in the RV144 vaccine strategy.

On February 3, 2020, the HVTN 702 protocol leadership for *Uhambo* stopped vaccinations early because data showed the vaccine did not prevent HIV acquisition. It neither increased or decreased the risk of acquiring HIV. The vaccine was safe but not effective. Although vaccinations were stopped, participant follow-up continues and will continue for a year. Participants' safety will be closely monitored during the follow-up period, and researchers hope to learn and understand why the vaccines did not work to prevent HIV infection. Participants will also continue to receive HIV counseling and HIV testing during the follow-up period.

Stoppage of vaccinations in *Uhambo* was informed by the recommendations of an independent body known as the Data and Safety Monitoring Board (DSMB), which reviews all data regularly to ensure the safety of participants and determine if the study should continue.

How is antibody research helping us advance HIV vaccine research?

Antibodies play a big part in fighting off disease. Certain types of antibody, known as broadly neutralizing antibodies (bNAbs), might be very useful to HIV prevention (and treatment and cure, too). They are Y-shaped proteins made by B cells, which are part of the immune system. They can attach themselves to a certain part of HIV's surface and stop the virus from infecting healthy cells. "Broadly neutralizing" means that this type of antibody can recognize and attach to multiple HIV clades that exist around the world.

It often takes a long time after HIV infection for a person's body to produce bNAbs, and many people never produce them. Scientists sometimes say that, "today's antibodies can neutralize yesterday's virus." Antibodies against any pathogen go through a series of changes that make them better and better at finding and blocking a given invader. This "maturation process" can take many months or years. Scientists hope to develop a vaccine that could speed up this process so that these protective antibodies could work as soon as a person is exposed to HIV.

bNAbs are also being studied for "antibody-mediated prevention" using a method called "passive immunization". Traditional immunization involves a vaccine that teaches your body to make its own antibodies against a disease-causing agent. With passive immunization, bNAbs are brought into the body through an infusion, or "drip". Once there, these bNAbs might be able to fight off HIV for a period of time. Two large clinical trials testing this idea are ongoing in the Americas, Europe, and across sub-Saharan Africa. Called the Antibody Mediated Prevention (AMP) Studies, these trials are testing the safety and efficacy of using an antibody known as VRC01 for HIV prevention.

A growing number of antibodies are going through animal testing and smaller, early-phase clinical trials. In future trials, researchers hope to test those that are especially strong and long-lasting, as well as combinations of antibodies. They will also test other ways of introducing bNAbs to the body, such as with an injection. For an ongoing list of bNAbs as they are discovered, visit www.bnaber.org.

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Microbicides for HIV Prevention

An Introductory Factsheet

April 2020

This fact sheet provides basic information on microbicides, a category of products that could provide additional tools to reduce the risk of getting HIV. For more basic fact sheets in this series on emerging HIV prevention strategies visit www.avac.org/intro.

What is a microbicide?

Microbicides in HIV prevention are products designed to be applied in the vagina and/or rectum to reduce the risk of getting HIV during sex. Their name means they kill microbes — in this case, HIV.

No microbicides are on the market yet, but the first one may be available in some countries by the end of 2020. The European Medicines Agency is reviewing the dapivirine vaginal ring. It resembles the vaginal ring that some women use for birth control. The dapivirine ring is inserted into the vagina. A woman can insert and remove the ring herself. The dapivirine ring is designed to be changed monthly for continuous protection against HIV. In studies, most women who used the ring said it was very comfortable, and they report their partners rarely felt it during sex.

The dapivirine ring could be provided by community health workers, as well as in clinics. See more details on the dapivirine ring further down.

Microbicides are also being developed in other forms. A vaginal film that looks like a small piece of thin plastic, smaller than a stick of gum, could be inserted right before sex. The film dissolves in the vagina and could provide on-the-spot protection from HIV.

Other microbicides being tested known as multi-purpose technologies, or MPTs, would protect women from both pregnancy and HIV. Still others are designed to offer protection during rectal sex. These may look and feel like the douches and lubricants that many people already use before or during anal sex. The goal is to make products for safe sex that also protect against HIV and are comfortable. The vaginal ring may be ready to go on the market soon, but these other products, if effective, would not be available for many years.



Why do we need microbicides?

Some people prefer to have protection from HIV throughout their bodies all the time. This is called systemic protection because the drug spreads through your whole body. Oral PrEP is one kind of systemic protection. Vaccines (when we have one for HIV) would also be systemic. These whole body methods are also useful to people who use injected drugs because they can protect you no matter how HIV enters your body.

Other people may prefer to use topical methods that provide protection in just one part of the body. Microbicides are products made to stop HIV just in the vagina or just in the rectum. They provide protection

Resources and links

AVAC (www.avac.org)

CONRAD (www.conrad.org)

International Partnership for Microbicides
(www.IPMglobal.org)

International Rectal Microbicide Advocates
(www.rectalmicrobicides.org)

Microbicide Trials Network
(www.mtnstopshiv.org)

Population Council
(www.popcouncil.org)

during sex without affecting the rest of the body. Some people call them “user-controlled” or “user-initiated” methods because they do not have to be inserted or removed by a doctor or health care worker. They are made for people who want protection that they can apply themselves, just when they need it.

Lessons learned from family planning show the benefits of having a lot of choices to offer when people are looking for protection. For example, some women like long-acting birth control methods, such as IUDs (some call this the loop), injectable products (like Depo Provera or Net-EN), or implants. Other women prefer user-controlled methods like birth control pills or rings or a diaphragm. Some women may like one strategy for a time and then change their preferences when conditions in their life change. Research shows that when people can choose their birth control method, the rate of accidental pregnancies goes down. HIV prevention can work the same way. We need choices —like microbicides, PrEP and vaccines — so people can choose the HIV prevention method they prefer and that will meet their current needs.

What is the status of vaginal microbicide research?

Scientists have challenges to overcome in microbicide research: How can we use anti-HIV drugs and other products in the vagina or rectum safely to stop HIV without hurting any fragile tissues, and provide protection at the place where infection happens? How can we make products that stop HIV from infecting someone but do not disturb anything else during sex? And how do we make microbicides that people like to use?

In 2010, scientists showed that a vaginal gel containing 1% tenofovir (an anti-HIV drug) reduced women’s risk of HIV when they used it correctly. But too many women in the studies didn’t use the gel, for various reasons, so it was dropped as a potential microbicide.

In 2016, the dapivirine vaginal ring, created by the International Partnership for Microbicides (IPM) was shown to work. IPM and the Microbicide Trials Network (MTN) did two related studies. They were large studies, conducted over a four-year period to test how well the ring worked. Over 4,500 women in Malawi, South Africa, Uganda and Zimbabwe volunteered to use the ring. They also came in for regular check-ups and reported on how they felt about using it. The studies showed that using the ring as instructed lowered women’s HIV risk by more than half (56%). Women over 21 years old were more likely than the younger women to leave the ring in place as instructed. Women over 21 showed much better rates of protection against HIV than did younger women in the study.

Since 2016, social and behavioral research has been done to explore what younger women think about the ring and what could make it more attractive to them. IPM and MTN are also doing trials now to test if the ring can be changed less frequently, every three months instead of monthly. They’re also designing rings for women who are pregnant, breast-feeding or menopausal. These trials are ongoing.

The ring is not short-acting, which makes it different from other the microbicides being created. But it is user-controlled because a woman can remove the ring any time she wants. And its effect is limited to the vagina, so it does not affect the whole body.

IPM submitted its first regulatory application for the ring to the European Medicines Agency (EMA) through a process called Article 58, which allows the EMA to deliver a scientific opinion on a product’s use in low- and middle-income countries, in cooperation with the WHO. EMA began reviewing the application in July 2018.

IPM also has plans to apply to the South African Healthcare Products Regulatory Authority (SAHPRA) and the US Food and Drug Administration (FDA) for approval. If approved, the vaginal ring will be the first microbicide to become publicly available.

What is the status of rectal microbicide research?

In 2016, we also got the first results from a Phase 2 rectal microbicide study. Called MTN 017, it was an “open-label” trial (participants know exactly what product they are getting) comparing people’s responses to:

- (1) using a tenofovir gel inserted rectally with an applicator, on a daily basis
- (2) using the gel and applicator “on demand” (before and after sex only)
- (3) using oral PrEP pills only, with no gel

The 195 MSM and transgender women participants spent eight weeks in each of these three categories. All three approaches were found to be safe but participants clearly preferred #2 — using the gel when they needed it for sex but not every day.

The MTN 017 participants also told the researchers that they wanted simpler methods, products more like the lubes, douches and enemas they already know. This feedback came from both trial participants and community consultations.

As a result, researchers started MTN 026 (called the Adonis study) in 2017. It is a Phase 1 safety trial to test dapivirine (an anti-HIV drug) in lubricant form as a possible rectal microbicide. It will test the product's safety and also explore how participants feel about applying it like a lube (with fingers and/or penis), rather than with an applicator. The big challenge is to find a method that feels natural and gets enough drug in the right place to provide protection from HIV. Other early-stage studies are testing other anti-HIV gels and douches for rectal use.

What other candidate microbicides are under study?

Numerous candidates are in the early phases of development—see more at www.avac.org/trials/microbicides.

See also the fact sheet on Multipurpose Prevention Technologies (MPTs) for more information about development of additional, dual-purpose HIV prevention options (www.avac.org/MPT). For related ARV-based prevention research, see AVAC's resources on long-acting injectable ARVs and pre-exposure prophylaxis at www.avac.org/prep.

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Voluntary Medical Male Circumcision for HIV Prevention (VMMC)

An Introductory Factsheet

April 2020

This fact sheet provides basic information on VMMC, an HIV prevention strategy for HIV-negative men. For more basic fact sheets in this series on HIV prevention strategies visit www.avac.org/intro.

What is medical male circumcision?

Medical male circumcision is the removal of all or part of the foreskin of the penis (the fold of skin that covers the head of penis when it is not erect). Circumcision is usually done by a trained health professional and is a quick, simple surgery. It can also be done non-surgically by using a special plastic device (either PrePex or ShangRing) placed on the penis by a health care provider. The device is worn for seven days while the foreskin gradually disconnects itself from the penis. Then the provider removes the device and, with it, the foreskin. Both types of circumcision cause little to no pain. Local anesthetic is used for both.

Resources and links

AVAC (www.avac.org)

Clearinghouse on Male
Circumcision
(www.malecircumcision.org)

Why does male circumcision work as an HIV prevention method?

It is not yet known exactly how medical male circumcision reduces men's risk of getting HIV during vaginal sex, but there are a few possible explanations. The foreskin of the penis has many cells that are vulnerable to HIV. Removing the foreskin removes these “target cells” and makes the penile skin more durable, which may also reduce risk. Medical male circumcision also reduces rates of genital ulcer disease caused by sexual transmission, which can increase HIV risk.

Why is VMMC a key part of combination prevention?

VMMC lowers a man's risk of getting HIV from a female partner by 60 percent. When enough men have been circumcised, the women in their community are also less likely to get HIV. That's because there are fewer men living with HIV in the community. Once a man is circumcised, the procedure cannot be reversed. His partial protection from acquiring HIV continues throughout his life.

Models developed by epidemiologists (scientists who study how and why diseases spread) predict that scaling up VMMC can help lower new HIV infection rates significantly. A country has reached “high coverage” of VMMC when 80 percent of all men and boys are circumcised. By the end of 2017, over 18.6 million men and boys in 14 eastern and southern African countries have had VMMC. The World Health Organization (WHO) predicts that those procedures had already prevented an estimated 230,000 new HIV infections by 2017 and are projected to prevent more than 1 million HIV infections by 2030.

A study done in Rakai, Uganda showed that VMMC can reduce the transmission of other sexually transmitted infections (STIs), such as herpes simplex virus type 2 (HSV-2), and the human papillomavirus (HPV) among adolescents and adult males. VMMC can also reduce the transmission of syphilis amongst men and women.

A 2017 literature review by Grund JM, Bryant TS, Jackson I, et al. included evidence that suggested VMMC led to increased protection for women against cervical cancer, cervical dysplasia, HPV type 2, chlamydia and syphilis.

VMMC is a core element of HIV prevention, along with immediate access to antiretroviral treatment (ART) for people living with HIV. Other elements include HIV testing, access to PrEP for HIV-negative people, male and female condoms, microbicides and vaccines (when they become available) and harm reduction programs.

What has VMMC research proven and what research is still going on?

In the 2000s, data from three large trials in Kenya, South Africa and Uganda showed that VMMC provided by well-trained health professionals was both safe and effective in preventing HIV transmission. WHO and UNAIDS then issued recommendations to add VMMC to the HIV prevention toolbox in countries and regions where HIV is often transmitted heterosexually and where circumcision was not common. Data since 2010 show that as rates of HIV among men decline, the rate of new HIV infections among women also declines. Data also show that VMMC does not significantly change sexual practices, such as lower condom use, among men.

VMMC is a proven prevention strategy but ongoing research is exploring additional questions:

- How can countries achieve maximum impact with their VMMC program? Operational research is teaching us the best ways to make VMMC programs efficient, cost-effective, and well supported by the communities where they are most needed.
- How does the age at which VMMC is offered affect HIV rates in a country? Mathematical modeling shows that age and location affect the program's success. Models suggest the fastest way to use VMMC to reduce new HIV infections would be generated by circumcising males ages 20–34 in Malawi, South Africa, Tanzania, and Uganda and males ages 20–29 in Swaziland. But new mathematical modeling shows that starting it even earlier can reduce the number of HIV infections even more. According to these models, the greatest drops in HIV rates, over a 15-year period, could be achieved by increasing VMMC among “males ages 10–19 in Uganda, 15–24 in Malawi and South Africa, 10–24 in Tanzania, and 15–29 in Swaziland.” Introducing VMMC to younger boys appears to be a strong strategy for HIV reduction.

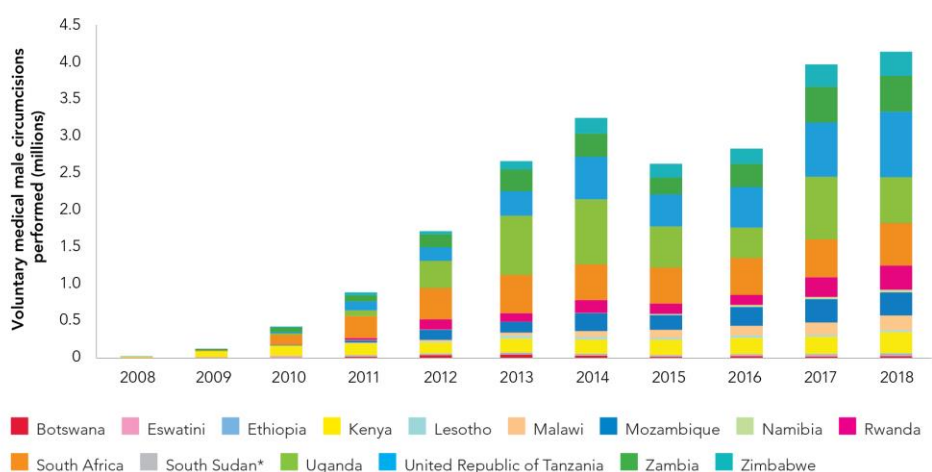
Engaging women and men who have sex with men

Women play important roles in campaigns to create demand, and scale up VMMC. They provide positive messages about the benefits of VMMC and influence decisions by their partners and sons. Women are well positioned to highlight VMMC as a way to reduce risk for their daughters as well because they are safer if their future partners undergo VMMC early in life. What we know about VMMC for gay men and other men who have sex with men (MSM) is less clear. Protection might depend on whether the individual is insertive or receptive during anal sex. Recent findings suggest circumcision might help reduce transmission in MSM who report that they are only the insertive partner during sex.

Annual totals: 2008-2018

Voluntary male medical circumcisions rising

Annual number of voluntary medical male circumcisions, 15 priority countries, 2008–2018



*South Sudan has only recently initiated a pilot voluntary medical male circumcision programme, and data were reported for the first time in 2018. This is the reason for low numbers.

Source: 2019 Global AIDS Monitoring.

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HIV Cure Research

An Introductory Factsheet

April 2020

This fact sheet provides basic information on HIV cure research. For more basic fact sheets visit www.avac.org/resources. Visit www.avac.org/cureiculum to access a suite of educational material on HIV cure topics.

What does the term “AIDS cure” mean?

The term “cure” refers to strategies that eliminate HIV from a person’s body, or permanently control the virus and render it unable to cause disease. A “sterilizing” cure would completely eliminate the virus from the body. This type of cure is impossible to measure with current technology. Remission, sometimes referred to as long-term viral suppression off ART (without drugs), or sustained viral remission, would suppress viral load, keeping it below the level of detection without the use of ART. The virus would be undetectable on the most sensitive tests currently available, but traces of the virus may remain in the body and could lead to reinfection. Just like cancer, a person in remission may be undetectable for many years and then rebound with a strain of virus dormant in their body.

Resources and links

AVAC (www.avac.org/cure)

International AIDS Society
(www.iassociety.org)

Michael Palm Basic HIV
Science, Vaccines and Cure
Project Blog
(tagbasicscienceproject.typepad.com)

Researchers are still debating and discovering what it means to be cured of HIV. Although some cases of remission have been reported, almost all have now rebounded. It takes time to be certain that HIV can no longer cause disease.

What types of cure strategies are being investigated today?

There are three broad strategies being explored. Each takes a different approach to the fundamental challenge of HIV infection—the ability of HIV to hide in cells that are inactive (also called resting cells) and not dividing. As long as the cells are not dividing, the virus isn’t copying itself and is considered “latent”. Cells that carry latent virus are, collectively, referred to as viral reservoirs. Most of the viral reservoir is in memory CD4+ T cells (latent immune cells), which are designed to live in the body a long time. A truly effective cure will either have to eliminate these viral reservoirs or ensure that an activated virus cannot reestablish infection in the body.

Shock and kill

This two-step strategy aims to flush (or shock) the virus out of resting cells with a latency reversing drug and then follow up with another intervention (likely something from the strategies below) to effectively kill infected cells. Many of the shock agents being considered are currently used as cancer treatments, although researchers are trying to discover new drugs as well. The kill component of this one-two punch could involve a therapeutic vaccine (which is different than a vaccine for prevention, see the vaccine fact sheet), if an effective one can be developed. The kill may also involve interventions to intensify or improve the immune response to HIV.

Gene therapy/manipulation

Some strategies to change the cells so that HIV can’t infect them involve editing genes to remove a protein receptor known as CCR5—the door HIV uses to enter CD4+ T Cells. Another approach modifies immune cells to better detect latent infected cells in the body. Another especially complex strategy would remove HIV from the DNA of infected cells. Researchers are working on developing a method to deliver gene editing technology directly into the body without removing cells. Currently, all gene modification involves extracting immune cells from HIV-positive individuals, modifying them and then reinfusing them back into the participant. The challenges are significant. It’s difficult to collect immune cells infected with HIV, and no one yet knows the quantity of modified genes needed to achieve results. The hope is modified genes would quickly spread through the whole body.

Immune modulation

Immune modulators refer to any type of drug or procedure that causes some type of sustained change in the immune system to better fight HIV. Successful immune modulation would both identify latent cells holding the virus BEFORE the cells reactivate, and intensify the capacity to kill HIV once cell division begins again.

Researchers are exploring natural killers and neutralizers of HIV and how to make them more potent through immune modulation. These include HIV-specific CD8+ T cells, NK cells and broadly neutralizing antibodies. Another immune modulation that could make a difference involves turning off immune cells' "exhaustion markers" that signal a cell to die.

What challenges face cure research?

Many issues make cure research difficult. First, there is no clear way to measure the HIV reservoir. The two most accessible approaches measure the number of HIV RNA copies in the blood, or the number of HIV DNA copies in cells. But HIV RNA in the blood does not detect viral copies already integrated into resting cells. Measuring DNA often doesn't provide an accurate picture either, since the cheapest and most available technologies cannot distinguish replication-competent virus from damaged, harmless virus. A more precise measure or assay, called the *quantitative viral outgrowth assay*, requires the use of large numbers of cells and cannot be done with a simple blood draw.

Unknown risks and benefits associated with all these current strategies represent a second major challenge to cure research. Trial participants must be able to understand these risks and potential benefits. In order to test for a cure, participants must stop treatment to enable researchers to look for a viral rebound of HIV. There are no standardized guidelines for how to time such "treatment interruptions" and minimize risks for trial participants and their partners. Finally, cure strategies may look different for men, women and children—biological differences between sexes and differences in adult versus pediatric immune systems mean that it is unlikely there will be a one-size-fits-all cure approach.

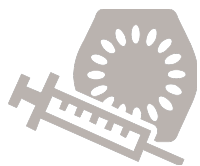
What happens next?

Cure research is expanding, with a range of trials planned or under way. See avac.org/pxrd for a list of these trials.

How can advocates get involved?

Many of the research strategies being developed require expensive equipment and specific training to administer. To show success or failure additional resources may be needed. These resources are not available in most global settings. Advocates can increase awareness around the need for these technologies in order to prepare for future cure trials in humans.

About AVAC | AVAC is a non-profit organization that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of new HIV prevention options as part of a comprehensive response to the pandemic.



Hormonal Contraceptives and HIV

An Introductory Factsheet

June 2019

Information is constantly evolving on hormonal contraceptive methods, their impact on HIV risk in HIV-negative women, and their use in women living with HIV. We encourage you to supplement this factsheet with a visit to www.avac.org/hc-hiv for the most recent information.

What are the available data about hormonal contraceptive use and risk of HIV infection?

The data are mixed. Some studies suggest that use of certain hormonal contraceptives—particularly injectable progestogen-only methods like Depo-Provera (DMPA)-IM and NET-EN—increase women’s risk of HIV infection. Other studies do not show an association between hormonal contraceptives, particularly DMPA-IM, and HIV risk. Far more information is available on DMPA-IM than on NET-EN at the moment, and that information primarily comes from observational data. This refers to data derived from trials or studies originally designed to answer other questions. Observational data is hard to analyze since there are many variables that could have influenced or biased the outcome.

The Evidence for Contraceptive Options and HIV Outcomes Study, or ECHO, is a randomized clinical trial designed to compare the risks of acquiring HIV among women who used copper intrauterine device (IUD), a levonorgestrel (LNG); Jadelle implant, and DMPA-IM. Results are expected by July 2019.

Resources and Links

AVAC

www.avac.org/hc-hiv

WHO

www.who.int/reproductivehealth/publications/family_planning/HC-and-HIV-2017/en

How are available data being used to guide contraceptive use and programs?

As of March 2017, the World Health Organization’s (WHO) Guidance Statement on “Hormonal contraceptive eligibility for women at high risk of HIV” states that there “continues to be evidence of a possible increased risk of acquiring HIV” among women using DMPA, NET-EN and other progestogen-only injectables. The guidance states that women should be counseled about this risk, and that no woman should be denied her method of choice, regardless of HIV risk. Even with this possibility, DMPA and other injectables remain important options, including for women living with HIV.

What exactly do available data say?

As of July 2016, a WHO-commissioned systematic review of available data found “increased concern” regarding the impact of DMPA-IM on HIV-negative women’s risk of HIV acquisition.

A “systematic review” involves gathering all available evidence on an issue, evaluating the quality of that evidence and summarizing it to provide a reliable overview of knowledge on a topic. Such reviews are often conducted by teams of independent researchers who agree on search terms and criteria for identifying quality evidence. This was the approach used in the WHO publication.

Two previous systematic reviews concluded that there was uncertainty about the relationship between DMPA-IM and HIV risk. This latest review indicates concern but does not draw a firm conclusion. The key findings from the 2016 review are summarized below:

- Data on the oral contraceptive pill and levonorgestrel implants do not suggest an association with HIV acquisition, though data on implants are limited. *Right now, there’s no suggestion that hormonal methods other than progestogen-only injectables might impact HIV risk. But the information available on some methods is limited.*

- The 2016 review noted that a previous systematic review had suggested a possible association between NET-EN and increased HIV risk, but the updated review did not show this association. *In March 2017, WHO gave NET-EN a “MEC 2” rating indicating that there is a possible increased HIV risk among users, but emphasized that while women should be informed about this possibility, they should not be restricted from choosing this or another contraceptive method.*
- Newer, higher-quality observational data on DMPA-IM, added to previous information, increase concerns about DMPA-IM use and HIV acquisition in women. *The cumulative data strengthen concerns that DMPA-IM might be increasing women’s HIV risk.*
- The study states that, “Recent analyses contradict the hypothesis that differential over-reporting of condom use by HC users explains observed associations between HC use and HIV infection in some studies.” *The argument that women who use DMPA-IM also use fewer condoms than women who choose other methods has been suggested to explain previous data. It’s important to note that this review directly addresses this argument and supports research suggesting that it is not valid.*

What’s the difference between hormonal contraceptive methods?

All hormonal contraceptive methods contain synthetic versions of the hormones that orchestrate women’s menstrual cycles. These synthetic hormones change the normal cycle in ways that prevent pregnancy. Hormonal contraceptives differ by type of synthetic hormone(s), level of dosage or frequency of dosage, and they include pills, injections and implants. Not all contraceptives use hormones. Non-hormonal methods include the copper intrauterine device (IUD), diaphragms, male and female condoms and others. Right now, concern around HIV risk is focused only on hormonal methods because they affect the lining of the genital tract as well as the immune environment. Non-hormonal methods like the copper IUD and male and female condoms do not have the same effects on the genital tract.

Do all hormonal contraceptives have the same effects on the genital tract?

No. Different contraceptive methods contain different synthetic hormones and/or different doses of the same synthetic hormones.

Is the current discussion on potential increased HIV risk about all hormonal contraceptives?

When it comes to concern about impact on HIV risk, the main focus is on DMPA-IM. Extensive data on the oral contraceptive pill offers no indication of increased HIV risk. Data are available on these two methods because the oral pill and DMPA-IM are among the most widely used contraceptive methods in sub-Saharan Africa.

This doesn’t mean that other hormonal methods do not affect HIV risk—there just isn’t as much information about rates of HIV in women who use them. NET-EN is also classified as having a possible association with HIV risk, however there are fewer data on this specific method than there are on DMPA-IM. Many other gaps in the data exist. For example, there are no data on a hormonal contraceptive called Sayana Press (also known as DMPA-SC), which is being rolled out globally and uses the same hormone found in DMPA-IM but at a lower dose.

What are the primary concerns for women living with HIV?

Drug interactions are an issue for women living with HIV. Do antiretroviral therapy (ART) regimens undermine contraceptive efficacy or vice-versa? There is some evidence that the hormones found in some contraceptive methods interact with some antiretrovirals (ARVs). For example, the efficacy of implants containing the synthetic hormone called etonogestrel can be adversely impacted by ARV treatments containing efavirenz. There may be more method failure—increased pregnancy rates—in women taking etonogestrel and efavirenz. There is evidence of interactions between ARVs and some other synthetic hormones as well. This is one of many reasons why DMPA-IM and a full range of contraceptive options need to be available for all women. At this time, no evidence suggests any contraceptive method increases women’s risk of transmitting HIV.

Who is most impacted by the concern about DMPA-IM, NET-EN and HIV risk?

Over the past several years, the question of what to do if DMPA-IM impacts women's risk of HIV has been widely debated, as has the question of where action, if any, should be taken. These debates reflect a painful reality: in East and Southern Africa, DMPA-IM is often the only discreet, long-acting method available to women, and HIV incidence is especially high among adolescent girls and young women. In an ideal world, all women, including those in East and Southern Africa, would have access to a full range of contraceptive methods, along with HIV prevention and treatment. Providers would have adequate time for counseling, and supplies would be on the shelves at all times. In such a context, a finding about DMPA-IM or any other method would be relatively simple to respond to: change the counseling messages, inform women, let them make the choice. However, in today's context of restricted options, human resource gaps and siloed programming, this isn't possible—yet.

A woman-centered approach that expands method mix, integrates HIV and family planning programs, and supports women, peers and providers in conversations based on informed choice is needed everywhere. Funders, governments and policy makers must act affirmatively to protect contraceptive access, including access to DMPA-IM, as an option for many women, including HIV-positive women.

Will there ever be a clear answer about how different contraceptives affect HIV risk?

The Evidence for Contraceptive Options and HIV Outcomes Study, known as ECHO, is designed to compare the risks of acquiring HIV among women who used the copper IUD, a levonorgestrel implant (Jadelle), and DMPA-IM. From 2015-2018, the trial recruited 7,830 women in eSwatini, Kenya, South Africa and Zambia who were sexually active, HIV-negative, ages 16-35, seeking highly effective contraception and willing to be randomly assigned to use one of three contraceptive methods. All of the women received counseling about the risks and benefits of the study method they were assigned to, HIV risk reduction and, where available, were offered oral PrEP either at a study site or through a referral. Daily oral PrEP—a single pill containing a tenofovir-based drug—taken correctly and consistently reduces risk of HIV acquisition in women and men.

The trial's primary question is: what are the relative rates of new cases of HIV among HIV-negative women randomly assigned to either DMPA-IM, the Jadelle implant or the copper IUD? The findings of the study may clarify if one (or more) of the evaluated methods increase women's risk of HIV compared to the other methods in the trial. It's also possible that the trial won't provide definitive answers. The data are now being analyzed and results are expected by July 2019.

For the latest on ECHO, visit www.avac.org/hc-hiv.

What's needed now?

The following actions are of paramount importance to ensure informed choice and should be ongoing. Many of these are recommended or suggested by the March 2017 WHO guidance on hormonal contraception and HIV.

- **Programs, policies and messages should reflect women's *right to know* all available information regarding the contraceptive method(s) they are being offered.** Women weigh risks and benefits all the time. If properly delivered, information about hormonal contraceptives and HIV risk should not cause women to abandon contraception or their method of choice.
- **Investment in programs should provide women with choices in contraception and HIV prevention.** In most of East and Southern Africa, DMPA-IM is the only invisible, long-acting method available for women. The way to learn about preference is to increase the number of options that women can choose from (improve method mix), train providers and engage with women as experts on their own lives.
- **Ongoing engagement with women affected by these issues is essential.** Their perspectives and experiences must guide policy, programs and messaging.

Do hormonal contraceptives protect against HIV infection?

No. Hormonal contraceptives do not protect against HIV or other STIs. Currently, there are no contraceptives, with the exception of condoms (male and female), that protect against HIV. Women using hormonal contraceptives must also use a condom or take other measures to protect themselves against HIV.

What is the history of World Health Organization guidance regarding hormonal contraceptive use and HIV risk?

Since 1991, there have been data suggesting a possible link between some hormonal contraceptives and HIV. The WHO has been tracking the issue for many years and has reflected its analysis in the grading system it uses to classify contraceptive methods. This grading system is known as the Medical Eligibility Criteria, or MEC. For a plain language explanation of the MEC see AVAC's fact sheet, "What is up with DMPA and 'grades' for family planning?" available at www.avac.org/dmpa-grades.

In early 2012, the World Health Organization issued a "technical statement" on hormonal contraceptives and HIV risk that stated: "The World Health Organization should continue to recommend that there are no restrictions (MEC Category 1) on the use of any hormonal contraceptive method for women living with HIV or at high risk of HIV." However, the statement recommended a clarification that changed the grade to a MEC 1*. The clarification stated that

[B]ecause of the inconclusive nature of the body of evidence on possible increased risk of HIV acquisition, women using progestogen-only injectable contraception should be strongly advised to also always use condoms, male or female, and other HIV preventive measures. Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential.

In 2014, WHO updated this technical statement. DMPA-IM and other similar methods remained a MEC 1* with the additional recommendation that women at risk of HIV selecting DMPA-IM be informed of the mixed data regarding that method's impact on risk of HIV acquisition. In March 2017, WHO updated guidance changes the MEC from a 1* to a 2.

WHO has said that immediately after ECHO results are released, it will release a statement to provide context for countries and other stakeholders on the next steps. After the statement, WHO will initiate its formal guideline review process to see how the ECHO trial impacts the current contraceptive guidance. This process can be lengthy; but WHO has committed to working on an accelerated timeline. African women impacted by the data must also be involved in this process.

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