New HIV Prevention Technologies: What’s In It for Positive Women?

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Like their HIV negative sisters, HIV positive women need HIV prevention tools that are accessible, affordable, effective, and user-friendly. Although they are no longer concerned with remaining negative, most women with HIV still want to:

• have active, enjoyable sex lives without putting their partners at risk of HIV,

• enjoy healthy intimate relationships free of abuse and violence,

• protect their own health by avoiding infection with other strains of HIV and other STIs, and

• have a range of contraceptive options available to them, in addition to condoms. Access to non-hormonal options are particularly important for those concerned about possible interaction between hormonal contraception and anti-retroviral treatment (ART).

In addition to a pervasive lack of perceived risk or vulnerability, the Achilles heel of HIV prevention for women has always been the difficulty that millions of women experience with getting male partners to use condoms. This is no less true for
women living with HIV than it is for HIV-negative women. If anything, the issues this raises for a woman living with HIV can be even more complex. Studies show that HIV-positive women experience changes in feelings related to their own sexuality and desirability. In addition, because of gender and power dynamics within relationships, a woman may be unable to request condom use -- or even to disclose her own HIV status to her partner -- without fear of blame, stigmatization, abandonment, or even violence. Her dilemma in this situation is compounded by her ethical need to protect against passing HIV to her partner, together with her desire to protect her own health and her children (who could be orphaned if both parents contract HIV and care is not readily available). For women in this situation, the need for an alternative to male condoms is urgent.

Imagine the value in such situations of an effective microbicide that is bi-directional (that is, protects her partner from transmission as well as herself from reinfection). Imagine the value of access to pre-exposure prophylaxis (PrEP) to a woman whose partner is willing to take a pill to protect himself but does not, for whatever reason, use condoms consistently. Steady access to affordable female condoms may also be a major benefit, since international studies show that some men who object to male condoms do not perceive female condoms as interrupting pleasure. It remains to be determined whether this finding is applicable in a U.S. context.

Women living with HIV who choose to become pregnant also need acceptable options for conceiving safely and with minimal disruption to their relationships. Since condoms prevent pregnancy, the only available options at present are:
a) alternative insemination – or inserting semen in the vagina with a device such as a tube, like a turkey baster, or a diaphragm, rather than during intercourse (no risk of transmission),

b) using ARV treatment (Treatment as Prevention, see below) to lower a woman’s viral load to undetectable levels, thus reducing her partner’s risk of HIV exposure (risk reduction),

c) having unprotected sex only right after ovulation, when the chances of becoming pregnant are highest, thus reducing the number of times her partner is exposed (risk reduction).

Some of the New Prevention Technologies (NPT – such as microbicides, PrEP, vaccines, etc.) currently under development could expand this range of choices. A microbicide that is not contraceptive and is bi-directional (that is, protects the male partner from HIV in a positive woman’s vagina) could provide a couple trying to become pregnant with additional protection from HIV when they forego the condom. More data about the relative effectiveness of PrEP and its possible side effects might motivate an HIV negative man in a sero-different relationship to use PrEP for extra protection. It also may provide an HIV-positive woman with increased peace of mind and stabilize sero-different relationships.

Conversely, a bi-directional microbicide that is also contraceptive would give women who do not wish to become pregnant another way to protect themselves while also reducing their partners’ risk of HIV exposure. One study published
recently\(^1\) suggests the possibility that using some hormonal contraceptives (particularly Depo Provera, an injectable contraceptive) might increase a woman’s risk of transmitting HIV to her partner. These findings have not been confirmed and further research is needed. But contraceptive microbicides could offer a valuable option to women who prefer not to use hormonal birth control methods but who cannot consistently enforce male or female condom.

**What are these new prevention tools?**

The HIV prevention tools discussed in this paper are microbicides, PrEP, Treatment as Prevention (TasP), vaccines, and female condoms. People involved in research to develop new HIV prevention tools often refer to them as New Prevention Technologies (or NPTs). You can also think of the “T” in NPTs as tools. Some of them are high-tech (like vaccines) and some are not (like female condoms). But all of them are being developed for people to use in their everyday lives, like any other tool. In the following table, primary prevention is defined as an agent or strategy used by an HIV-negative partner to prevent HIV acquisition. Secondary prevention is defined as an agent or strategy used by an HIV-positive partner to prevent HIV transmission.

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When it comes to preventing infectious diseases like HIV, most people think first of “primary prevention”, which means helping people who do not have the disease to remain uninfected. But scientists also think of secondary prevention, which means helping people who have the disease to avoid transmitting it to someone else. Not all the the NPTs for HIV can be divided into one of those two categories. The following descriptions of each NPT show how some of them cross over and have the capacity to work for primary and secondary prevention.
Microbicides

A microbe is any living organism (such as a virus or bacteria) that can't be seen with the naked eye. Anything that kills or disables a microbe can be called a microbicide. In the world of HIV prevention, ‘microbicide’ refers to any product that is applied to the vagina or rectum to reduce the risk of HIV acquisition or transmission.

Microbicides work by killing or disabling HIV directly, or by blocking the virus from attaching itself to vaginal or rectal cells. They are currently being formulated and tested as gels, foaming tablets, films, rings, and in other forms. No microbicide is available yet on the market but dozens are in various stages of testing. A few are in advanced testing and could, if successful, reach the market in some parts of the world during this decade.

As discussed above, a microbicide could work for primary or secondary prevention. Most of the microbicides being developed now are ARV- based, meaning they contain anti-retroviral drugs. A vaginal gel containing tenofovir, for example, was shown to reduce the risk of acquiring HIV by 54% among the women when used for at least 80% of their acts of vaginal intercourse. The average level of protection provided to all the women in the trial was 39%. There was extreme variability in how the women participating in the trial used the product – some used the gel for most sexual acts and others did not. The lower overall result was an average of the amount of protection experienced by all the trial participants -- including those who

sometimes or frequently did not use the gel when they had sex, as well as those who used it regularly. All women in the trial were supplied with free condoms and advised not to trust the gel to protect them because it is still a test product.

ARV-based microbicide candidates are thought to have a better chance than non-ARV based candidates of being effective because they specifically target HIV. But because of the potential for drug interactions and for resistance, ARV-based microbicides may not be appropriate for use by women living with HIV. See Additional Information on Research to Develop Non-ARV-Based Microbicides below, if you would like to know more.

Pre-exposure Prophylaxis (PrEP)

PrEP is the term for taking a medicine while healthy to protect yourself getting a disease or condition. Some people call ARV-based microbicides ‘topical PrEP’ because they work this way, although they are applied topically (to a body surface like the vagina) rather than swallowed or injected.

Anti-malaria pills are a good example of PrEP. People start taking the pills before traveling to places where they could be bitten by mosquitoes carrying malaria. If they are bitten, the risk that they will get sick is lowered by the anti-malaria medicine already in their system. Hormonal contraceptives (birth control pills) can also be regarded as a form of PrEP. A woman using birth control pills, for example, is highly unlikely to become pregnant if exposed to sperm because the hormones...
the pill are designed to keep her egg from being released. If there is no egg to be fertilized, then no pregnancy can occur.

In the context of HIV, PrEP refers to the regular intake of an ARV orally by an HIV-negative person in an effort to stay negative. It is a method of primary prevention. When ARVs are used for secondary prevention, it is called Treatment as Prevention (or TasP, see next section).

If an HIV-negative person is exposed to HIV while taking PrEP, the drug may prevent the virus from multiplying rapidly and taking hold of the body. Using ARVs to prevent vertical (‘mother to child’) transmission is a familiar form of PrEP that has proven to be highly effective.

In 2011, the iPrEx study showed PrEP as providing up to 73% protection to men and transgender women who have sex with men, provided that they took the drug consistently (at least 90% of the time or more). It was less effective among those who did not take it every day. Another study, called Partners PrEP, showed it as being 62-73% effective when used by the HIV negative partners in heterosexual couples that were sero-different (that is, where one partner was living with HIV and the other was not).

But two studies done solely among women taking PrEP (FemPrEP and one arm of the VOICE study) did not show PrEP as being effective. TDF2 was an additional study of PrEP done by the Centers for Disease Control and Prevention (CDC) and
enrolling heterosexual couples. It showed PrEP effectiveness among participants overall but was not large enough to show conclusively whether the levels of protection the drug provided to women differed from the level of protection provided to men.

These conflicting data mean that we really don’t know yet how well PrEP will work when taken by women. Although the results were promising among women trial participants in the sero-different, heterosexual couple trials, this could be because of a different dynamic among the couple participants than a single women using PrEP is likely to experience. Couples in the trial were both aware of each other’s HIV status and this may have increased the commitment of the negative partner to taking PrEP regularly, without fail. So more research needs to be done before conclusions can be drawn about PrEP’s effectiveness for women in various circumstances.

Physicians in the U.S. are allowed to prescribe drugs “off label” (that is, for use in ways that the FDA has not officially approved) if they believe that doing so will help a patient. Although the CDC is now in the process of developing formal Public Health Service guidelines for prescribing PrEP, it is already available in the U.S. to people who can get a physician’s prescription for it and who can pay for PrEP or have insurance that will cover it. Using the iPrEx data, the CDC has already developed interim guidance for physicians who choose to prescribe PrEP to patients who are
men who have sex with men. It is now developing interim guidelines for physicians who want to prescribe PrEP to heterosexual patients.³

There are numerous questions that HIV negative people should consider before accepting a prescription for PrEP. Not only has its effectiveness in women not yet been fully established, but much remains to learned about its potential side effects, which generally appear to be mild but can be severe in some people.⁴ Someone who becomes HIV infected while taking PrEP (either because it didn’t work or because it was not taken consistently) also faces the risk of developing a strain of HIV that is resistant to the PrEP drug she or he has been taking. If this occurs, it limits the newly diagnosed person’s future options for HIV treatment. So, although PrEP is becoming available to those at high risk who have access to a physician willing to prescribe it, more research needs to be done to learn how best to incorporate it into everyday lives of HIV negative women and men who may have HIV positive partners

**Treatment as Prevention (TasP)**

Treatment as prevention (TasP) is a term used to talk about the fact that an HIV positive person who takes ARVs regularly and whose viral load is suppressed has a very low risk of transmitting HIV to another person. Research established in the 1990s that positive women who took ARVs during pregnancy and childbirth were

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much less likely to transmit HIV to their babies. In May 2011, data from a trial called HPTN 052 showed that people living with HIV had less than a 4% risk of transmitting HIV to their sexual partners if they took ARVs consistently, because the drugs lowered the amount of HIV in a person's body so dramatically.

This news was called a “game-changer” for HIV prevention and TasP, a secondary prevention strategy, is now a major topic in discussions about how HIV prevention should be funded. Some policy makers feel that we should be investing much more in getting people who test HIV positive onto ARV treatment right away to slow down transmission of the virus. They propose that routine HIV testing be combined with offering immediate, voluntary ARV treatment to anyone who tests HIV positive, regardless of her or his stage of HIV infection and medical need for treatment, in order to reduce and eventually almost eliminate new HIV infections.

But many serious concerns about this approach have been expressed, including:

1. It may be unethical since a doctor's first concern has to be the well-being of the patient. Once a person starts taking ARVs, he/she has to continue taking them consistently for life because stopping treatment may lead to the development of drug resistant virus. Some people aren't ready to commit to adhering to a daily ARV regimen. Others may have life circumstances may prevent them from taking daily ARVs, such as not having access to regular meals, for example, or having unmet needs for substance use services or housing. A physician may also feel that, given the possible side effects and the unknown impacts of long term
treatment, it may not ultimately benefit the patient’s own health outcomes and quality of life to start on ARVs right away.

2. Given that the U.S. government (and many other governments worldwide) are not yet successfully getting ARV treatment to all HIV-positive people who want and need it to preserve their health, it seems unrealistic to propose that it be provided to everyone who tests positive, whether they need it yet or not.

3. How can we be sure that people’s human rights will be protected? There may be a fine line between offering people the opportunity to start taking ARVs right away and requiring them to, whether they want to or not and whether their physician advises it or not.

4. People who are pushed into starting ARV treatment before they are ready are less likely to take their medication consistently. Whether it results from inconsistent use of ARVs or inconsistent access to them, lack of adherence to one’s ARVs schedule can trigger the development of HIV strains in one’s body that are drug resistant. Transmitting drug resistant HIV means giving another person a virus that is even harder to treat that non-resistant HIV. Approximately 15% of all new HIV infections in the U.S. already involve the transmission of drug-resistant HIV from one
person to another.\textsuperscript{5} Increasing this percentage is not in anyone’s best interests.

**Vaccines**

As with microbicides, no HIV vaccine yet exists but several candidate vaccines are in development. They are designed to train a person’s immune system to identify HIV and take steps to disable or suppress it. Work is underway to develop preventive vaccines (primary prevention), as well as therapeutic HIV vaccines (secondary prevention). People living with HIV would receive a therapeutic vaccine to help control their infection. A successful therapeutic vaccine could lower a person’s viral load by slowing down the process of HIV replicating in the body.

HIV vaccines are very difficult to develop because HIV mutates (changes) rapidly as it reproduces. A vaccine that recognizes one version of HIV is unlikely to recognize, and be effective against, other mutations of the virus. Additionally, despite intensive research, scientists still do not completely understand now much and what type of immune response is needed to defend against HIV attack.

Nevertheless, the first evidence of success in a vaccine trial came in 2009 from a large-scale vaccine trial called RV144 that enrolling 16,402 men and women in Thailand. It found that 30% fewer HIV infections occurred among participants who

got the vaccine injections than among those who did not. As always, all trial participants were provided with free condoms and encouraged to use them at each sex act. Although 30% was a very low level of protection, it constituted what is called “proof of concept”—that is, evidence that it is possible to make an effective vaccine. Proof of concept is important for any NPT because it assures researchers and funders that this line of research is worth pursuing.

Data collected in this study also helped researchers to identify some particular characteristics in the participants’ blood samples that may explain why the vaccine worked for some people and not for others. This enables them to reformulate the vaccine, in the hope of making it work for more people. New vaccine trials are currently being planned in Thailand and South Africa.

RV144 was a “prime-boost” trial; one in which participants received two different vaccines, one after the other. The first vaccine “primes” (or revs up) the immune system and the second is supposed to boost the body’s ability to deal with HIV if it enters the body. Another prime-boost trial called HVTN 505 is enrolling over 2,200 men and transgender women who have sex with men in twelve U.S. cities. With enrollment ongoing, it is not yet known when that study will be completed or if it will also show that the vaccine is effective.

Female Condoms
The first female condom (FC) was approved by the FDA and sold in the U.S. in 1993. So FCs are not exactly a new prevention technology. But they are the most under-utilized of all the HIV prevention tools currently available. Their failure to catch on in the U.S. is primarily due to two factors; their high price and a lack of awareness due to the failure of health care providers and HIV/AIDS service organizations to educate people about them and promote them. FCs are not mentioned at all, for example, in the National HIV/AIDS Strategy. This is remarkable given that they are as effective for preventing HIV transmission as male condoms, which are mentioned repeatedly.

Access to affordable FCs is vital for women living with HIV, as they are currently the only way, other than male condoms, for a woman to protect both herself and her partner from HIV, other STIs, and pregnancy. FC advocacy campaign in several large U.S. cities are currently working to raise awareness of FCs and bring the price of them down to make them more widely accessible. In New York City, for example, the health department provides access to free FCs at nearly 1000 venues in the five boroughs and has even created a smartphone application to enable people to find their nearest point of access quickly. All distributors in this program (including shops, hairdressers, non-profit organizations, etc.) are required to receive FC training so that they can explain how to use the product correctly.

Correct female condom use is not as immediately obvious as male condom use is. But research has shown that—when people learn more about FCs, practice using
them in a relaxed environment, and have affordable access to them—most women and men become comfortable with them. Some prefer them to using a male condom, especially men who sometimes experience erectile problems with male condoms. One California study conducted two types of interventions with study participants—one that focused on FC skills training and one that was a general women's health training of the same length. Six months after the study intervention, the researchers found that women in the group that had received female condom skills training were not only using FCs more frequently than those who received a general training, but also reported a significantly higher percentage of protected sex acts (using either male or female condoms) than the group who did not receive a specific training on female condom use.\(^6\)

**Additional Information on Research to Develop Non-ARV-Based Microbicides**

This section offers more information on non-ARV-based microbicides. ARV-based microbicides contain small amounts of the same anti-retroviral drugs used to treat people living with HIV. Non-ARV-based microbicides contain other types of compounds that have various mechanisms for stopping HIV infection. These complex compounds are derived from proteins, peptides (small parts of proteins), or other molecules such as segments of genetic material (DNA or RNA). It is possible that non-ARV-based microbicides could play a very important role in the lives of women living with HIV. ARV-based microbicides will probably not be recommended to HIV positive women for two reasons:

1. If the woman is taking ARVs for treatment, the presence of a different ARV in her bloodstream (even in small amounts) could possibly interfere with the effectiveness of her treatment combination.

2. If the woman is positive but is not taking ARVs for treatment, the presence of a single ARV (as would likely be in a microbicide) in her blood might cause her to develop drug resistant virus. If this happens, it would limit her future treatment options and she might not be able to benefit from the drug in the future if she wants to take it as part of her treatment combination.

Microbicide research started in the last 1980s, long before ARVs were developed. So the first candidate microbicides were based on other approaches to HIV prevention—such as creating products that might physically prevent HIV from attaching to cell walls or keep the vaginal pH so low that HIV could not survive in it long enough to infect. Unfortunately, these approaches were unsuccessful and once ARVs became available, researchers switched their focus to creating ARV-based microbicides.

There is currently one non-ARV-based microbicide candidate in clinical (human) trials. Others are being tested in laboratories but are not yet ready for human testing. Vivagel is non-ARV-based candidate microbicide that has been tested by small numbers of women who found it to be non-irritating and acceptable. The Australian company producing VivaGel is now planning a large-scale trial to test its effectiveness against both HIV and Herpes Simplex Virus (HSV).
VivaGel’s active ingredient belongs to a class of compounds called dendrimers - a type of well-defined, branched nanoparticles that are used in medical, chemical, and other industries. Nanoparticles are made using nanotechnology. Sometimes called molecular manufacturing, nanotechnology is a field that makes very precisely designed devices that are as small as molecules.

The dendrimers in VivaGel appear to have the ability to keep HIV from attaching to healthy cells. This product is the first of this new generation of non-ARV-based microbicide candidates to enter clinical trials. This generation is more scientifically sophisticated than the first generation of non-ARV-based candidates.

Use of probiotics is another approach that is still in pre-clinical (laboratory) testing. You hear the word “probiotics” in television advertisements for yogurt and other products that are eaten to maintain a healthy digestive system. In the context of vaginal microbicides, “probiotics” means an agent that works with the bacteria that naturally occur in the vagina.

Researchers at a California-based company are now exploring the possibility that lactobacilli (a “friendly” bacteria in the vagina which prevents yeast infections) might be genetically engineered to secrete a compound called Cyanovirin-N (CV-N), a small protein derived from algae that can block transmission of HIV. Animal data on this candidate are promising but, of course, we will only be able to determine its effectiveness against HIV once it is tested in humans. Currently, CV-N production...
expensive so researchers are also working to determine how CV-N can be produced in a practical, cost-effective way. The developers of this product hypothesize that, if effective, this approach could result in a product that is capable of colonizing the vagina with a “self-renewing bacteria continuously produc[ing] highly potent antiviral compounds”.

The probiotics advertised on TV are promoted as enhancers of digestions and intestinal health. They contain intestinal lactobacilli (which are different from vaginal lactobacilli). But intestinal lactobacilli can also be modified to produce CV-N. Studies in animals showed that CV-N could be detected in the feces of animals that were fed yogurt containing the modified bacteria. This suggests that it may be possible, eventually, to develop a non-ATV-based microbicide designed to offer protection against HIV during anal sex.

Some animal experiments have also shown that some microbicidal compounds, when applied in the rectum, are transported by the blood to the vagina and vice versa. This raised another very far future possibility -- that we might, someday, be able to get protection from HIV by eating a food designed to prevent HIV Infection. Research into these possibilities, however, still has a very long way to go before we will know which, if any, of them will actually work.

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A third non-ARV based approach is Griffithsin (GRFT). This molecule, capable of preventing HIV from entering the cell, is being studied by researchers at the University of Louisville in Kentucky (US) and colleagues at other institutions. It is in the same class of molecules as CV-N, but is more potent and has properties that suggest it might be safer to use than CV-N.

Using transgenic plant technology (a technology that transfers genetic material into plants), GRFT can be harvested from the tobacco plant (nicotiana benthamiana). This is done by tricking a virus that infects only tobacco plants (the Tobacco Mosaic virus) into carry the gene for GRFT into a young tobacco plant right after the seed sprouts. This gene forces the plant to make GRFT.

The plant-produced GRFT blocks both HIV and HSV transmission, and has been shown in laboratory testing to be non-irritating to animal and human vaginal cells. Developers of GRFT have calculated that an “environmentally controlled greenhouse producing 3,000 kg of leaf tissue per acre could yield ... over 2 million doses per year”.⁸

A fourth non-ARV-based approach is to use certain human antibodies that can prevent HIV from binding itself to its target cells. These particular antibodies are in a classification called neutralizing antibodies (Nab), meaning an antibody that protects the cell by inhibiting or neutralizing an invader’s effect on it. Some researchers have been suggesting for years that Nabs could be explored as a

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PWN, a project of WORLD
potential tool for preventing HIV Infection. Two obstacles have impeded progress on this research, however.

The first was that most of the antibodies we produce in response to HIV are not Nabs. They are binding antibodies – meaning that they just grab onto the invader and bind themselves to it. This binding signals a white blood cell that the invader has been detected and the white blood cell then destroys it. Even the antibodies that are Nabs generally only work against certain strains or types of HIV. Progress in overcoming the obstacle was made, however, when scientists at NIH discovered certain Nabs that are effective against more than 90% of HIV strains.

The second obstacle has been the ability to produce enough of these broadly effective Nabs to demonstrate that this approach would be safe and effective for use by women. Researchers at Boston Medical College and a company in California are now collaborating to produce the broadly effective Nabs in transgenic plants. They expect, within the next five years, to demonstrate that it is feasible to produce the amounts needed and deliver them in a convenient form as a candidate microbicide.

Unfortunately, none of these non-ARV-based candidates (even if successful) are likely to be available within this decade. They, and others that are not mentioned here, still face many hurdles before any of them become a microbicide that women can use to protect themselves. Progress is being made, however, and products are moving from the laboratory into clinical testing. The researchers working to develop non-ARV-based microbicides recognize an urgent need for these products.
but they also understand that this need must be balanced against the risk of rushing research and producing incomplete or misleading research findings.

It is critically important that HIV positive women, and all women and men, demand that this work to develop non-ARV-based microbicides continue. They are a much-needed option not only for women living with HIV but also for women who do not know their HIV status. If successful, non-ARV-based microbicides may be available without a prescription. ARV-based products, by contrast, are likely to be prescribed because of need for them to be used only by HIV negative people.

This means that a non-ARV-based, non-prescription microbicide may possibly be more accessible to people who have less access to health care and/or who have not been tested for HIV recently. Finally, some women may prefer not to use ARV-based microbicides because of possible side effects and/or because of concern about the possible effects on pregnancy or breastfeeding.

As noted above, ARV-based products are currently the primary focus of the microbicide field and far less attention and resources are being devoted to non-ARV-based microbicides. So positive women’s advocacy voices are urgently needed to keep this part of the field moving forward. This has to be part of the fight -- securing advancements in the technologies that women need to realize their full sexual and reproductive health and rights!