

## Antiretroviral (ARV)-Based Microbicides:

### *The Promise and the Puzzle*

#### What are “ARV-based” microbicides?

Antiretroviral drugs (ARVs) are the main drugs used to treat people living with HIV/AIDS. Researchers are trying to find out if ARVs could be used to make microbicides to prevent HIV infection when used by people not infected with HIV. The products currently being developed and tested are called candidate ARV-based microbicides. The term “candidate” is used because we do not know yet if they will work.

#### How would an ARV-based microbicide work?

ARVs have been used successfully for years to treat HIV/AIDS. By blocking key steps of the HIV life cycle, ARVs stop the virus from reproducing. They do this by interfering with the proteins that the virus uses to enter or reproduce inside a target cell. Used in combination, ARVs can slow or stop viral reproduction. This reduces the amount of virus in the body of a person who has HIV and can help delay the onset of AIDS.

The idea of using ARVs to prevent HIV infection is not new. They are already being used to prevent babies from being infected during birth. Giving an ARV like nevirapine to an HIV-positive woman before she has her baby can reduce the baby’s chance of getting infected. ARVs are also given to health care workers exposed to HIV or women who are raped in the hope that these drugs will prevent them from becoming infected. After a person is exposed to HIV, it takes time (from several hours to a few days) before the virus spreads through the body. If the exposed person takes an ARV right away, the drug may stop HIV from taking hold in the body.

Scientists hope that microbicide candidates made with ARVs will prevent infection in an HIV-negative person who is exposed to HIV during sex. Because these drugs also remain active in the body for many hours, researchers also hope that some ARV-based microbicides can be used just once a day (or less). Ideally, people would have access to products used regularly and others that are used shortly before or immediately after sex.

#### What ARV-based candidate microbicides are being developed? Are they all alike?

One candidate ARV-based microbicide is a vaginal gel containing a drug called tenofovir. Tenofovir is an ARV that works by blocking a key viral protein called reverse transcriptase. HIV needs this protein to reproduce once it has entered a cell. Several studies of tenofovir gel have been done to make sure the gel is safe to use and that women will be willing to use it. Scientists at the CAPRISA research centre near Durban, South Africa conducted a study to see if tenofovir gel can protect women from HIV. The US-based Microbicide Trials Network (MTN) is conducting a study to see if tenofovir gel works, the results of which are expected in 2013.

Two other candidate ARV-based microbicides are being tested to see if they are safe and if women will be willing to use them. They are made with two other ARVs: dapivirine (also called TMC120) and UC-781. These two drugs also interfere with reverse transcriptase, but they do so in a way that is different than tenofovir. There are other candidate ARV-based microbicides being developed that work by stopping HIV from entering target cells in the first place. If the virus can’t get in, it can’t reproduce.

Not all of the candidate ARV-based microbicides are in the form of gels. Researchers are also putting ARVs like dapivirine into vaginal rings that look like the NuvaRing® birth control product. Vaginal rings are designed to release the product slowly over a long period of time. If an ARV can be put successfully into a vaginal ring, women could have a microbicide they could insert just once a month. If it works, such a microbicidal ring could give women long-term protection against HIV.



## How are ARV-based candidate microbicides different from the earlier candidate microbicides that were tested?

Most of the candidate microbicides in large scale effectiveness testing between 2002 and 2008 targeted a broad range of viral and bacterial pathogens (germs), not just HIV. Some were designed to boost the vagina's own natural defences. Others coated the vagina to create a physical barrier designed to prevent HIV from attaching to cells. Unfortunately, none of these candidates proved to be both safe and effective. The concept of a microbicide capable of preventing other sexually transmitted infections (STIs), not just HIV, remains important. Research to develop such options should continue.

**Do ARV-based microbicides present any special safety concerns?** Researchers look very carefully at all candidate microbicides to see if they are safe for use. Candidate ARV-based microbicides, however, may present potential safety concerns that other candidates did not.

ARVs have been used to treat people living with HIV/AIDS for more than ten years. Many people who take ARVs for treatment experience side effects, such as nausea, tiredness, and changes in body shape. But the amount of drug a person with HIV takes for treatment is much higher than the amount that would be used in an ARV-based microbicide. This could mean that an ARV-based microbicide might cause fewer side effects than the drugs for treatment. Scientists plan to watch clinical trial participants very closely to see whether any side effects occur.

Another potential concern is HIV drug resistance. Most ARVs work by blocking virus replication. That is, they prevent HIV from making copies of itself. Sometimes, however, the virus changes itself in a way that allows it to make copies of itself even in the body of someone who is taking an ARV. Since these changed viruses can resist the drug's effort to stop them from replicating, they are called "drug-resistant."

Drug resistance is not caused by the ARVs themselves. It is just something that occasionally happens in a small number of the viral copies made as HIV reproduces. Drug resistance can be a problem for people living with HIV/AIDS, but can be managed in most cases. When a person develops virus that is resistant to one ARV, the doctors prescribe a different ARV to see if it can stop the resistant virus. We do not know if drug resistance will be a problem for users of ARV-based microbicides. If an ARV-based microbicide user remains HIV negative, drug resistance will not be a problem. If you have no HIV in your body, no HIV copies are being made and so no drug-resistant virus can be created. Drug resistance may be an issue, however, for people living with HIV who use an ARV-based microbicide. To learn more about HIV drug resistance, see our fact sheet called "Understanding HIV Drug Resistance."

Scientists are still working to figure out whether toxic side effects and drug resistance will occur among people using ARV-based microbicides. They probably will not be able to answer these questions until clinical trials of candidate ARV-based microbicides advance. The researchers doing these trials have careful plans to protect the safety and well-being of the women enrolled. For example, only HIV-negative women will be enrolled in these trials. These women will stop using a candidate microbicide immediately if they experience severe side effects or if they become HIV-positive. Any women who become infected will be tested frequently to see if they develop drug-resistant virus, and arrangements will be made to ensure these women have access to effective drugs.

### Important Points to Remember:

1. Antiretroviral drugs (ARVs) have been used successfully for years to treat people living with HIV.
2. ARVs have also been used to prevent HIV infection, such as the use of these drugs to prevent mother-to-child transmission of HIV.
3. Scientists are developing ARV-based candidate microbicides that may reduce the likelihood of HIV transmission during sex.
4. Unlike the candidate microbicides BufferGel<sup>®</sup> and Pro 2000<sup>®</sup>, ARV-based microbicides are designed to protect only against HIV. ARV-based microbicides will not prevent infection with other STIs.
5. We will not know whether use of ARV-based microbicides will have toxic side effects or create drug-resistant HIV until more research is done.
6. Current trials of ARV-based microbicides are designed to protect the health and safety of participants by monitoring resistance and by arranging for women to have access to effective drugs.\*\*