

Understanding HIV Drug Resistance in the context of microbicides and pre-exposure prophylaxis (PrEP)

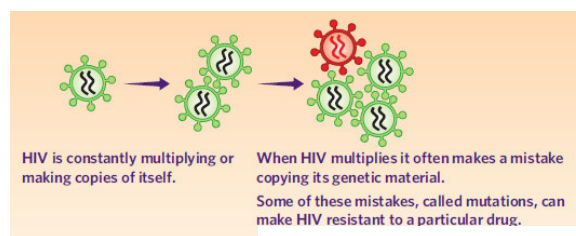
Antiretroviral drugs (ARVs) are used to treat individuals living with HIV/AIDS. They might also help prevent HIV infection if used as microbicides or oral pre-exposure prophylaxis (PrEP). ARVs have already been shown to prevent infection in some situations, such as when they are used to reduce the chance that a baby born to an HIV-positive woman will be infected at birth. Scientists hope that using ARVs as topical microbicides and as oral PrEP may help people reduce their risk of getting infected if exposed to HIV during sex.

One of the questions about using ARV-based microbicides is whether they may lead to HIV drug resistance. This fact sheet is designed to tell you about some of the basic concepts of HIV drug resistance and how it occurs.

How do ARVs work? ARVs work by preventing HIV from making copies of itself. People living with HIV take combinations of ARVs that work in different ways. The combination they take depends on what their doctors think will help them the most, given their current condition. But all ARVs interfere with key steps in the viral life cycle and stop the virus from reproducing. If HIV cannot reproduce, the amount of HIV in the body goes down.

What is “drug resistance”? Most people with HIV are infected with the type of virus that occurs most commonly in nature, so-called “wild-type” HIV. ARVs can stop “wild-type” HIV from reproducing. Drug resistance occurs when the virus changes itself in a way that lets it reproduce in someone who is taking an ARV. The mutated virus is called “drug-resistant” HIV—it resists the ARV and continues to multiply and spread.

How does drug resistance occur? All living things—plants, animals, people, and even HIV—store information in the form of genetic material. What an animal or a person looks like depends on the information stored in this material. You can think of the bits of genetic material as coloured beads that can be strung together in many different patterns. It is the unique pattern of the coloured beads that determines what each living thing looks like. Copying genetic material is like making a new string of beads with the exact same colour pattern.

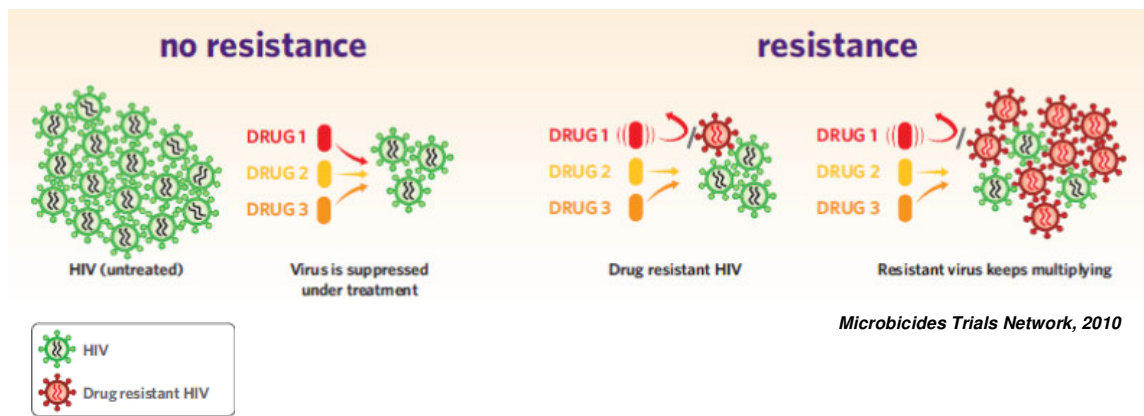


When HIV reproduces, it makes new copies of its genetic material. But HIV does not always make perfect copies of itself. Lots of small mistakes can be made – for example, a blue bead may be replaced by a red bead. These mistakes are called “mutations” and will create a “mutant strain.”

They occur naturally and make the new virus just a little bit different from the old virus. In a person

with HIV who is not taking ARVs, billions of copies of HIV are made every day. Mutations occur by chance. The more virus that is made, the more likely it is that a “mutant” strain will appear. Mutations can also occur while a person is taking ARVs—and specific mutations have been identified that can be associated with specific ARVs.

Mutations occur in all viruses, not just HIV. They are usually harmless to the host. In fact, most mutations are actually bad for HIV. Mutant strains of HIV are often weaker than the wild type. But once in a while a mutation can give HIV a new ability, such as the ability to resist certain drugs.



Will drug resistance occur with use of an ARV-based microbicide? If a woman remains HIV negative while using an ARV-based microbicide, drug resistance will not be a problem. There is no HIV making copies of itself in her body, so drug-resistant virus cannot emerge. But drug resistance may be an issue for women who:

- become infected while using an ARV-based microbicide, either because the microbicide did not work for her, because it was not used during every sexual act, or she became infected by another route of transmission;
- use an ARV-based microbicide when they are already HIV-positive. This could happen if a woman doesn't know that she is infected.

In either case, the woman has HIV, and the virus will be making copies of itself in her body. This may increase the chance that drug-resistant HIV might appear.

We do not yet know how much of the drug in an ARV-based microbicide will be absorbed by the body of a woman using it. Scientists are looking into this question. If very little of the ARV is absorbed, there may not be enough to allow for drug-resistant virus to be selected. If more is absorbed, however, the ARV may kill off the wild-type virus and allow any drug-resistant virus present to take over. If this happens—and it is not clear yet whether it would—this woman may have a resistance to that drug and no longer have the option of taking that particular ARV to treat her HIV. Drug resistance could disappear over the years between infection and the time she begins therapy.

Studies of ARV-based microbicides are designed to protect the safety of women enrolled. In most studies, these women will be tested for HIV every month. They will stop using the candidate microbicide if they become infected. Thus, HIV-positive women may be exposed to the ARV in the microbicide only for a short period of time. This should limit the chance that drug-resistant virus will emerge. Researchers also plan to closely follow study participants who become infected to see if a drug-resistant virus appears in their blood. If it does, advocates may urge that women receive ARVs that are effective against drug-resistant HIV.

We do not know if drug resistance will become a problem if an effective ARV-based microbicide is developed and widely used. Given regulatory restrictions for use of ARVs, it is likely that ARV-based microbicides will only be available by prescription to HIV-negative women who are regularly tested for HIV.

Important Points to Remember:

- Mutations are mistakes that occur when HIV copies itself.
- Some mutations allow HIV to reproduce even in the presence of ARV drugs.
- If a drug-resistant virus emerges, the drug in question may no longer work. It is possible that this may limit an individual's treatment options.
- Resistance is common in people being treated for HIV, but usually can be managed by changing drugs.
- We will not know whether ARV-based microbicides may select for drug-resistant virus until more research is done.
- 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.