Understanding HIV Drug Resistance

Fact Sheet

Antiretroviral drugs (ARVs) are used to treat individuals living with HIV/AIDS. They might also help prevent HIV infection if they are used to make microbicides. 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 putting an ARV into a microbicide may help people reduce their risk of getting infected if exposed to HIV during sex.

One of the many questions we have about ARV-based microbicides is whether they will lead to HIV drug resistance. HIV drug resistance is a complicated topic. 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 can't 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, the so-called "wild-type" strain of 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. These changed types of HIV are called "drug-resistant" strains – they resist the ARV and continue 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.

In HIV, the string of genetic material is made up of about 10,000 coloured beads. 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 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 wild type. But once in a while a mutation can give HIV a new ability, such as the ability to resist certain drugs.

Do antiretroviral drugs themselves cause drug resistance? Drug resistance mutations are not caused by the ARVs themselves. They occur naturally as HIV multiplies. When a mutation creates a drug-resistant strain of HIV, a person living with HIV has two types of virus in her body. One is wild-type virus that is stopped by a particular ARV. The other is the drug-resistant "mutant" virus that survives and reproduces even in the presence of medicine. If she stops taking that ARV, the drug resistant virus usually disappears. But if she does not stop taking it, the drug-resistant virus can become dominant. This means she will have more drug-resistant virus than wild-type virus in her body. Imagine, for example, an HIV-infected woman who is taking AZT. By chance, she develops a mutant strain of virus that is resistant to AZT. She doesn't know this and keeps taking her AZT. The medicine will kill the wild-type HIV in her body but not the mutant virus. The drug-

resistant HIV will keep making more and more copies of itself. Soon, most of the virus in her body will be drug-resistant. At that point she is said to have developed clinical resistance to AZT. The drug will no longer work and it will do her no good to keep taking it. The same thing happens with all other kinds of ARVs. This process by which drug-resistant strains of HIV take over is called "selection." The ARV itself does not cause drug-resistant strains of HIV to arise. Continuing to take the drug, however, creates the condition that allows the drug-resistant viruses to be "selected" – or outgrow their drug-sensitive cousins and take over.

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:

1. Become infected while using an ARV-based microbicide, either because the microbicide did not work, because it was not used during every sexual act, or she became infected by another route of transmission;
2. Use an ARV-based microbicide when they are already HIV-positive. This could happen if a woman doesn't know that she is infected. Or, a woman may know she has HIV but use an ARV-based microbicide to protect an HIV-negative partner from infection or to protect herself from re-infection.

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 (taken up) 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 in the woman's body to allow for drug-resistant virus to be selected. If more is absorbed, however, it 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 would no longer have the option of taking that particular ARV to treat her HIV. She would already have clinical resistance to that drug. Studies of ARV-based microbicides are designed to protect the safety of women enrolled. While in the study, these women will be tested for HIV every month. They will stop using the candidate microbicide if they become infected. Thus, HIV-positive women will 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 take over. Researchers also plan to follow study participants who become infected closely to see if drug-resistant virus appears in their blood. If it does, advocates believe that these women should receive second-line therapy – that is, ARVs that are effective against drug-resistant HIV. Researchers hope to offer or refer women with drug-resistant virus for second-line therapy but the details still need to be worked out.

We do not know if drug resistance will become a problem if an effective ARV-based microbicide is developed and widely used. Some people say that ARV-based microbicides should only be available by prescription to HIV-negative women. That is one option, but it would limit access to the microbicide. It would also be difficult and costly to put a plan like that into place.

Important Points to Remember:

1. Mutations are mistakes that occur when HIV copies itself.
2. Some mutations allow HIV to reproduce even in the presence of ARV drugs.
3. If a drug-resistant virus takes over in the body, the drug in question may no longer work. This may also limit an individual's treatment options.
4. Resistance is common in people being treated for HIV, but usually can be managed by changing drugs.
5. We will not know whether ARV-based microbicides will select for drug-resistant virus until more research is done.
6. 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.

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