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QUESTIONS AND ANSWERS

HIV Drug Resistance and ARV-Based Prevention

The Basics of Drug Resistance:

1. What is drug resistance?
Drug resistance refers to the ability of some microorganisms, including viruses such as HIV, to adapt so they can survive and multiply in the presence of drugs that would normally weaken or kill them. For HIV, drug resistance exists when the virus can multiply in the presence of one or more antiretroviral (ARV) drug. Because a combination of at least three ARVs is needed to keep HIV in check – an approach called antiretroviral therapy (ART) – any virus that becomes resistant to even one of these drugs can render treatment ineffective.

2. What causes drug resistance in HIV?
HIV is constantly multiplying, or making copies of itself. But when HIV multiplies, it often makes mistakes copying its genetic blueprint (RNA and DNA), errors which are caused by the HIVenzyme reverse transcriptase. Some of these mistakes, called mutations, can make HIV resistant to one or more ARV drug. HIV multiplies rapidly in the body, producing about 100 million virus particles daily – each with one or more mutation. As such, there are many drug-resistant viruses being produced on a daily basis in a person with HIV infection.

3. How can someone acquire or develop resistance?
The standard treatment for people with HIV infection is called antiretroviral therapy (ART), which consists of at least three ARV drugs from at least two different classes of drugs. For the most part, ART is safe and effective in suppressing the ability of HIV to multiply and in preventing AIDS or death from HIV infection. Under some circumstances, ART fails to suppress HIV replication. This could be due to suboptimal combinations of drugs, abnormal metabolism of the drug, or the person on ART not taking all the ARV drugs as directed. When HIV is not adequately suppressed, virus resistant to particular drug can emerge and keep multiplying to outnumber virus that is not resistant.

4. How common is drug resistance?
People being treated with ART can sometimes develop resistance to one or more ARV. If the drug is continued, the virus resistant to the ARV will keep multiplying. When detected, it can usually be managed by stopping the ineffective ARV drug and starting a new combination of drugs. Drug-resistant virus can also be transmitted to other people who are not on ART. In countries such as the United States, where ART is widely used, about 10 percent of new infections occur with drug-resistant HIV. In other regions of the world, such as Africa, where ART use is more limited, new infections are far less likely to be from drug-resistant HIV, but as therapy becomes more widely available, this situation could change.

5. Does having resistance to one drug mean no other options exist?
A mutation causing resistance to one ARV does not reduce the effectiveness of every drug in that class of drugs or of other types of drugs used to treat HIV infection. If detected early, most types of drug resistance can be readily managed by stopping the ineffective ARV drug and starting a new combination of drugs.

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Depending on the type of resistance, however, treatment options may be limited. In rare instances, virus may be resistant to every available drug. This would only happen after several courses of ART with many different drugs and regimens.

6. What happens if drug resistance is not detected and a person continues taking the ARV?
If the ineffective ARV is continued, resistant virus can keep multiplying and eventually outnumber other viruses that are sensitive to or can be weakened by the ARV. Once the ARV is stopped, however, the resistant virus no longer has the same competitive advantage and may decline with time.

7. Why is it important to test for resistance?
In recently infected or newly diagnosed people, resistance testing can help determine the best combination of ARVs to consider when treatment is later needed. However, because HIV, by its nature, is constantly mutating, the virus profile can easily change. Tests should be performed before beginning ART and regularly thereafter. This helps to identify the proper combination of drugs as well as gauge their effectiveness so that adjustments can be made promptly as needed.

8. How is it detected?
The most common type of resistance testing is genotypic resistance testing, which looks for the presence of specific mutations that are known to cause resistance to certain drugs. It is performed using a small sample of blood. More sensitive methods are also being developed and evaluated by researchers to detect drug-resistant variants that standard tests don't always identify.

9. Are these tests available in Africa?
Resistance testing requires specialized laboratories, equipment and trained staff. As such, in many parts of the developing world, including sub-Saharan Africa, the capacity to perform these tests largely does not exist at the present time. Even in places where there may be labs qualified to perform these tests, lack of infrastructure and/or high costs are likely to be limiting factors that prevent clinics from offering these tests to HIV-infected people being treated with ART. Different groups are working to address the current situation and improve access to much needed clinical laboratory and support services.

10. Can drug-resistant strains of HIV spread to other people?
A person whose HIV is well managed on ART, meaning the virus is suppressed to very low or undetectable levels, has a smaller chance of infecting his or her sexual partner than does an HIV-infected person with detectable virus. If virus is not adequately suppressed it could include drug-resistant strains, increasing the likelihood of infecting others with that drug-resistant virus.

Drug Resistance and HIV Prevention:

11. How are ARVs being used for prevention?
HIV prevention methods that use ARV drugs hold great promise for preventing HIV. ARVs have been used successfully for treatment by millions of HIV-infected people worldwide, and there is sound scientific reason to believe that some of these same drugs could be used for HIV prevention. At the present time, two ARV-based prevention approaches are being evaluated in clinical trials. One is called oral pre-exposure prophylaxis, or PrEP, which typically involves daily use of an ARV tablet by people who are HIV negative. Some oral PrEP trials are evaluating an ARV called tenofovir (Viread®), while others are evaluating an ARV called Truvada®, which contains both tenofovir and a second drug called emtricitabine in each tablet. A few trials, including the VOICE Study, are testing both tenofovir and Truvada. The second ARV prevention approach is a vaginal microbicide called tenofovir gel. In one trial, researchers are seeing if it can prevent HIV in women who use gel around the time of sex, while in VOICE, women use the gel daily. Tenofovir and Truvada are the only ARVs currently being evaluated for their effectiveness in HIV prevention trials. Other ARVs, such as UC-781, TMC-120 and MV-150, are being considered for possible testing in future trials. Others are still being studied in the laboratory or in animals.

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12. Can resistance happen in people who are taking ARVs for prevention?
Only a person infected with HIV can get drug resistance. But because both tenofovir and Truvada are drugs routinely used as part of combination therapy for treating HIV, there is concern that individuals who become infected while in an ARV-based prevention trial could acquire or develop virus that is resistant to the drug or drugs being studied. Trials of ARV-based prevention include several measures to prevent or reduce the risk of acquiring HIV, and by extension, the risk that resistance would occur in participants who, despite the study's efforts, become infected. Some experts believe HIV drug resistance in the context of prevention will be much less prevalent than it is in the treatment setting. But until more information is available, the potential risks are not known.

13. Has resistance been a problem in other prevention trials?
Very little is known about either the potential for or incidence of HIV drug resistance among those participating in trials of ARVs for prevention, either as oral PrEP or as a vaginal gel. Although at the present time no scientific or clinical information is available about the nature or incidence of resistance with these approaches, results of ongoing oral PrEP trials should shed more light on this issue.

14. How can you use ARVs for prevention if you don't know the risks?
HIV now affects more than 33 million people worldwide, more than two thirds of whom live in sub-Saharan Africa. Moreover, the proportion of women who are infected with HIV/AIDS is steadily growing. As a global crisis, HIV/AIDS shows few signs of slowing down. In fact, for every two people who are put on ART, there are five who are newly infected. ARV-based approaches to HIV prevention hold great promise for curbing the rate of HIV infection in at-risk populations. However, we cannot know the answers about either the potential risks or benefits of ARV-based prevention without conducting ethically designed clinical trials.

15. When will we have answers to questions about drug resistance and ARV-based prevention?
Extensive study is needed to better understand the potential for and control of drug resistance in HIV prevention trials of ARVs and ARV-based microbicides, which is a major focus of the VOICE Study and other prevention trials. But answers may be years to come. Researchers won't be able to gauge if and to what extent drug resistance is a problem until those participants who acquired HIV while in the trial begin ART. ART is not typically started until the medical condition warrants, which may be two or more years after testing positive for HIV. Even if current or future trials prove ARV-based strategies to be both safe and effective for preventing HIV, only by following trial participants for several years can researchers accurately assess long-term risks and benefits.

16. What is MTN's HIV Drug Resistance Study all about?
Nowhere in the world is HIV cutting a wider, more destructive swath than in sub-Saharan Africa, and women, who account for 60 percent of those getting infected, are bearing the brunt of the epidemic. The extent that these infections involve drug resistant virus is not known. MTN-009, also called the HIV Drug Resistance Study, aims to provide a reliable assessment of the prevalence of HIV drug resistance in a representative population of women from KwaZulu-Natal, South Africa, where a woman's HIV risk is among the highest. MTN-009 seeks also to understand if certain risk behaviors are associated with resistance. The study expects to enroll 350 newly diagnosed HIV-positive women and approximately 650 HIV-negative women, all between the ages of 18 and 40. Understanding the prevalence of HIV drug resistance will not only help inform public health decisions concerning the selection of ARVs that should or should not be used as part of ART, but will also help to guide HIV prevention efforts focused on testing different ARV-based approaches.

17. How can potential risks of drug resistance be minimized in trials such as VOICE?
The most effective way to prevent HIV drug resistance is to prevent infection in the first place. In sub-Saharan Africa, where the VOICE study is being conducted, a woman's risk of acquiring HIV through sex is greater than in any other part of the world. As such, researchers conducting trials like VOICE do everything possible to try to reduce HIV risk for all study participants. In VOICE, all study participants receive free condoms, monthly HIV testing and HIV risk-reduction counseling and routine testing and treatment for sexually transmitted infections (STIs). Despite these efforts, a participant may still become infected if she has

unprotected sex with a partner who has HIV. To minimize the potential for drug resistance in these women, additional safeguards are in place based on experience managing drug resistance in HIV-infected people on ART and information from preliminary studies involving ARVs for prevention. Because the chance that resistance might develop or worsen is likely higher if study products are continued, these safeguards aim to limit as much as possible the amount of time that someone who is infected is using study product.

18. What specific precautions or measures are being taken in the VOICE Study to prevent drug resistance?

Researchers screen all prospective participants for HIV infection to avoid enrolling anyone who is already HIV-infected, and women who are enrolled undergo monthly HIV testing so that investigators can quickly identify women who have acquired HIV and immediately stop their use of the study drug (tablet or gel). In addition, study products are dispensed monthly – and only after results of HIV testing are known to be negative – to prevent an infected participant from continuing to use the study product. This is especially important as neither the researchers nor the participants know if the study product they were randomly assigned to use contains an active drug or a placebo. Based on current understanding about viral resistance, VOICE researchers believe that these and other procedures will help minimize the potential that resistant virus will develop or persist in women who acquire HIV while in the study.

19. What happens if a participant acquires HIV during the study?

Any participant who tests positive for HIV will be immediately taken off the study product. Women who become infected will be counseled and referred by study staff to services at local facilities that provide medical care and treatment, including ART, and psychological and social support. When possible, participants who acquire HIV will be referred to other local research studies for HIV-infected women. In addition, study participants who acquire HIV will be invited to participate in another MTN study called MTN-015. MTN-015 is a long-term observational study of women who acquire HIV while participating in an MTN trial. Although MTN-015 does not provide HIV treatment, with a participant's permission, researchers can maintain close contact with her primary treatment provider and share results of laboratory tests that are performed as part of the study, which may suggest modifications to her treatment and help improve the level of care.

20. If a participant gets HIV, does this mean she will develop resistance?

At the current time researchers don't know if or how frequently resistance will occur in women who acquire HIV while using an ARV for prevention. Safeguards in VOICE aim to prevent or reduce the risk of resistance.

21. How will resistance be detected in VOICE?

Women who acquire HIV infection in VOICE will be tested at regular intervals, and more often if indicated, for the presence of HIV drug resistant virus. Small amounts of blood will be sent to the MTN virology laboratory at the University of Pittsburgh for both standard testing and more specialized analysis that can detect resistant virus that may comprise less than 1 to 2 percent of the viral population represented in a sample. Tests will also be conducted to help better understand how resistance developed and to which ARVs. Women who chose to participate in MTN-015 will have additional tests for resistance performed so that researchers can determine its prevalence and patterns over time.

22. How will resistance impact her treatment?

VOICE researchers do not know if resistance that is detected at the time of infection will impact the effectiveness of therapy later. However, it's important to understand that a mutation causing resistance to one ARV does not reduce the effectiveness of every drug in that class of drugs or of other types of drugs used to treat HIV infection. Most types of resistance can be managed by stopping or avoiding the ineffective ARV and using a different combination of drugs for ART.

23. What do we know about the success of treatment after developing drug resistance from trials to prevent mother-to-child transmission?

Between 15 and 40 percent of women who take a single dose of nevirapine to prevent mother-to-child transmission develop detectable resistance to nevirapine within a month of receiving the drug, according to published studies. More recently, the same researchers reported that most women who developed resistance

could be treated successfully with ART as long as therapy was initiated at least 6 months after nevirapine exposure. VOICE researchers are cautiously optimistic about these observations and related studies that suggest it may be possible to minimize the risks of resistance in people taking ARVs for prevention. But they also caution that additional studies are required before definitive conclusions can be drawn.

24. What if a participant becomes pregnant and HIV positive? What kind of care will she receive?
Participants who become both pregnant and HIV-infected will have expedited resistance testing performed that will help determine the best course of treatment to reduce mother-to-child HIV transmission and will also be referred to local providers for antenatal care, and prevention of mother-to-child transmission services. HIV testing for infants will be provided by the study if not otherwise accessible by the participant.

25. Is the risk of resistance the same for both the tablet and the vaginal gel?
At the present time there is no scientific evidence on which to base an answer to this question. VOICE and other MTN studies will provide important information.

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The VOICE Study is being conducted by a team of researchers working in the Microbicide Trials Network (MTN), an HIV/AIDS clinical trials network established and funded in 2006 by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the National Institute of Mental Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, all components of the U.S. National Institutes of Health (NIH).

Additional information about VOICE, other MTN studies and HIV drug resistance in ARV-based prevention is available at http://www.mtnstopshiv.org/news/studies/mtn003

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