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FACT SHEET

HIV Drug Resistance and ARV-Based Prevention

The Basics of HIV 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 kill or weaken them. For HIV, drug resistance exists when the virus can multiply in the presence of one or more antiretroviral (ARV) drug.
- 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 HIV enzyme 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.
- 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.
- People being treated with ART can sometimes develop resistance to one or more ARV. 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.
- Mutations in HIV can cause resistance to one ARV drug or several ARV drugs, usually in the same class. 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.
- 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. 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. This is why tests to detect drug-resistant virus should be performed regularly when virus is detectable in the bloodstream of a person receiving ARV drugs so that appropriate changes in therapy can be made promptly. Depending on the type of resistance, however, treatment options may be limited.

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- An HIV-infected person who is doing well on ART, as evidenced by very low or undetectable virus in the bloodstream, has a smaller chance of infecting his or her sexual partner than does an HIV-infected person with detectable virus. Virus that is not adequately suppressed may include drug-resistant strains that may be transmitted to others.

The Unknowns about HIV Drug Resistance and ARV-based Prevention

- Oral pre-exposure prophylaxis, or PrEP, is an experimental HIV prevention approach that typically involves the daily use of ARVs by people who are HIV negative. Currently, only two ARVs are being evaluated as oral PrEP in clinical trials: tenofovir (Viread®) and Truvada®, which is a combination of tenofovir and emtricitabine. Both are ARVs routinely used as part of ART for treating HIV.
- 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 and, consequently, might not respond optimally to ART with that ARV or other ARVs in the same class. 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 from current trials and long-term studies, the potential risks are not known.
- In the meantime, researchers are cautiously optimistic about observations in primates that show the risk of resistance is low with oral PrEP. In addition, studies of women who have received the drug nevirapine to prevent mother-to-child transmission of HIV, also suggest that in most cases, if resistance does occur, it decreases with time such that response to ART when clinically indicated is not compromised. However, additional studies will be required before definitive conclusions can be drawn.

The VOICE Study

- In sub-Saharan Africa where VOICE is being conducted, a woman's risk for acquiring HIV through sexual intercourse is greater than in any other part of the world. To reduce the risk of HIV for women participating in its trials, MTN researchers provide trial participants free condoms, frequent HIV testing and HIV risk-reduction counseling, including on the use of condoms, and routine testing and treatment for STIs.
- Despite these intensive, ongoing efforts, a woman who participates in a trial like VOICE could acquire HIV if she has unprotected sex with a partner who is infected with the virus. VOICE has safeguards to minimize the potential for drug resistance if this should happen. 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.
- 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. As with all Microbicide Trials Network (MTN) trials, women who become infected will be counseled and referred by study staff to local facilities that provide medical care and treatment, including ART, and psychological and social support. Women will

also be invited to participate in MTN-015, a long-term observational study that aims to determine whether there are differences in HIV disease progression and response to ART that result from becoming HIV-infected while in an MTN trial of a microbicide or oral PrEP product. As part of MTN-015, additional tests for resistance will be performed that may suggest modifications to her treatment and help improve the level of her care.

- VOICE researchers don't know if or to what extent drug resistance might occur in women who become infected in the study. VOICE and similar studies will provide important information to help understand the potential for HIV drug resistance associated with ARV-based prevention.

MTN-009: The HIV Drug Resistance Study

- 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 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.

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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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