CONTACT: Lisa Rossi
+1- 412-641-8940
+1- 412- 916-3315 (mobile)
rossil@upmc.edu

QUESTIONS AND ANSWERS
MTN-009: The HIV Drug Resistance Study

1. What was the aim of MTN-009?

The global HIV epidemic continues to take its greatest toll on sub-Saharan Africa, a region that accounts for 71 percent of all people with HIV worldwide. While women represent more than half (52 percent) of all people living with HIV globally, nearly 60 percent of those living with HIV in sub-Saharan Africa are women, with young women up to five times more likely to become infected with HIV than young men. Few studies have assessed the extent that HIV infections in this region involve virus resistant to antiretroviral (ARV) drugs commonly used for treatment of HIV, some of which are also being evaluated as HIV prevention. MTN-009, also called the HIV Drug Resistance Study, aimed to assess the prevalence of HIV drug resistance among women in KwaZulu-Natal, South Africa, where a woman's HIV risk is among the highest in the world and where ARV-based prevention could feasibly be introduced alongside existing treatment programs offering ARV therapy (ART). The widespread use of ARVs brings with it concerns about drug resistance. If not recognized and properly managed, high rates of drug resistance could facilitate its spread and eventually compromise the effectiveness of mainstay drugs. As such, information on the prevalence of HIV resistance is critical to the success of both current and future treatment and prevention programs.

2. 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. This happens in HIV because the virus is prone to making mistakes when it multiplies. Some of these mistakes, called mutations, can make HIV resistant to one or more ARV drug.

3. How does someone with HIV develop resistance?

ART, the standard treatment for people with HIV infection, consists of at least three ARV drugs from at least two different classes of drugs that in combination are generally safe and effective in suppressing HIV's ability to multiply. However, people being treated with ART can sometimes develop resistance to one or more of the ARVs so that ART fails to suppress HIV replication, enabling virus that is drug-resistant to outnumber virus that is not resistant. Resistance may occur if the combination of drugs is not optimal, one of the drugs is not being metabolized properly or if not all the ARV drugs are being taken as directed. When detected, resistance can usually be managed by stopping the ineffective ARV and starting a new combination of drugs.

4. Can people get infected with HIV that is drug-resistant?

Yes. If an HIV-infected individual has developed resistance and continues to use the ineffective drug, drug resistant virus will keep multiplying unchecked and could feasibly be transmitted to others, such as through unprotected sex.

5. Is there a concern about resistance with ARV-based prevention?

While ARV-based prevention approaches hold promise, a concern is the emergence and potential spread of drug-resistant virus, especially from individuals who may not know they are infected and continue using the product. Products being developed for prevention typically involve just one ARV. While one ARV has the potential to protect against HIV in someone who is uninfected, one drug alone is not enough to suppress virus in someone who is infected. If a person who is infected continues taking a single drug, there is greater risk that virus would become resistant to that drug or drugs in the same class, thereby limiting treatment options in the future. Moreover, he or she could infect sexual partners with drug-resistant virus.

-more-

6. Who conducted and funded MTN-009 ?
MTN-009 was 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). The study was led by Urvi Parikh, Ph.D., of the University of Pittsburgh, and Photini Kiepiela, Ph.D., of the South African Medical Research Council (MRC) in Durban.

7. When and where did MTN-009 take place?
MTN-009 was conducted at seven sites affiliated with the MRC HIV Clinical Trials Unit in Durban and the surrounding KwaZulu-Natal region of South Africa. The study took place between September 2010 and March 2011, when these same sites were screening and enrolling participants into another MTN study, a large-scale HIV prevention trial called VOICE (Vaginal and Oral Interventions to Control the Epidemic.)

8. How was the study designed?
When women who came into an MRC site inquiring about taking part in VOICE, some were first offered enrollment in MTN-009. Those who voluntarily enrolled into MTN-009 were asked to complete a private, computer-assisted questionnaire about behaviors that could potentially increase the risk of drug resistance, such as prior use of ARVs by either the participant or her sexual partner. Participants were then tested for HIV infection, as part of the normal screening process for determining eligibility for VOICE. Women who tested negative continued screening for VOICE. Women who tested HIV positive had additional tests of blood to determine the presence of drug resistant virus. Such tests identify changes, or mutations, in the genetic makeup of HIV that are known to cause resistance to certain drugs. Additional tests of blood were done to see how advanced their HIV infection was. This was done by measuring the amount of virus in the blood (viral load) and estimating the number of healthy immune cells that remain uninfected (CD4+ T cell count). At subsequent study visits, participants were counseled on the results of these tests, told how the results may impact the effectiveness of certain types of ARV medications and referred to appropriate health care and counseling services for managing their HIV infection.

9. What were the results of MTN-009?
Of the 1,073women who came to the clinic to be screened for VOICE and who were subsequently enrolled into MTN-009, more than a third (400 of 1,073, or 37 percent) were confirmed to be HIV positive. Of the 400 women found to be infected, 156 women (39 percent) had CD4+T cell counts of less than 350, the threshold for initiating ART, and 50 women (13 percent) already met the criteria for AIDS, with CD4 counts below 200.

Drug resistance was detected in 26 of 352 women whose blood samples were analyzed – a prevalence of 7.4 percent. Most women (18 of 26, or 62 percent) had resistance to one class of ARVs, which is a class known as non-nucleoside reverse transcriptase inhibitors (NNRTIs). Five women (19 percent) had resistance to two classes – both NNRTIs and nucleoside reverse transcriptase inhibitors (NRTIs). The most commonly occurring mutation was the NNRTI mutation K103N, which was found in 19 of 26, or 73 percent, of samples.

Women were on average 25.6 years old. While all indicated having a primary sex partner, only 4 percent reported being married.

10. What does it mean to have NNRTI resistance – and the K103N mutation?
NNRTIs are a class of anti-HIV drugs that bind to and disable HIV's reverse transcriptase enzyme, a protein that HIV needs to make more copies of itself. Without functional reverse transcriptase, HIV replication is halted. NNRTI-resistant virus would render any or all NNRTIs ineffective. Instead of working to suppress virus from replicating, the use of NNRTIs by a person with this type of resistance would actually help the drug-resistant virus to keep growing and to eventually outnumber virus that is not resistant. There are nearly 20 mutations that make HIV resistant to one or more NNRTIs. The K103N mutation, however, makes the HIV resistant to most drugs in the NNRTI class. Nevirapine, for example, an NNRTI commonly used to prevent the transmission of HIV from mother to child, would not be effective in someone with the K103N mutation.

11. How did the women get infected with drug resistant virus?
MTN-009 was not designed to be able to pinpoint the source of NNRTI resistance. However, the research team surmises that women may have become infected with the HIV resistant virus by a partner receiving either the NNRTI nevirapine or efavirenz as part of ART, or women who were HIV infected while pregnant may have developed resistance if in the past they received nevirapine for prevention of mother to child transmission.

12. What are the implications of the study's results?
In countries such as the United States, where ART is widely used, between 7 and 19 percent of new infections occur with drug-resistant HIV. Where ART use is more limited, new infections are less likely to be from drug-resistant HIV. The Southern African Treatment and Resistance Network had last estimated that less than 5 percent of new infections in sub-Saharan Africa were of drug-resistant virus. The results of MTN-009, which found the prevalence of HIV drug resistance was 7.4 percent, suggest an escalating problem, with the majority of women with resistance having virus with the K103N mutation that confers resistance to NNRTIs. Of note, MTN-009 took place not long after South Africa's national treatment guidelines recommended tenofovir as first-line therapy. Although only 1 percent of the women in MTN-009 had tenofovir-resistant virus, the researchers believe this was likely because tenofovir had only begun to be used as treatment for HIV infected individuals and anticipate that the frequency of this type of resistance may increase over time.

Meanwhile, a Phase III trial called FACTS 001, which is being conducted in South Africa, is evaluating whether a vaginal gel containing tenofovir can prevent HIV in women. If FACTS 001 finds tenofovir gel to be effective, plans are in place to push for its approval and widespread use. MTN-009 calls attention to the potential challenges of implementing an ARV-based prevention product that overlaps with first-line therapy. Effective screening that includes HIV testing to prevent someone who may already be infected from starting ARV-based prevention will be critical to curb the potential spread of resistant virus.

13. Did women found to be HIV-positive in MTN-009 receive treatment for their HIV?
Although MTN-009 did not provide HIV treatment, women who tested positive for HIV received immediate counseling by study staff and were referred to available sources of medical care, counseling, and other services they may have needed.

14. Did women provide informed consent?
Yes. Women who volunteered to join the study were told about all the study procedures, any possible risks and benefits and the time requirements of the study. Study staff also explained that women didn't have to join and they could choose to leave the study at any time, without consequence. Information is provided in understandable terms and translated into local languages. Site community educators and Community Advisory Board (CAB) members also played important roles in helping prospective participants understand the purpose, potential benefits and risks of the study.

15. What kind of approvals were needed before this study could get underway?
MTN-009 underwent extensive and rigorous review by NIAID and the U.S. Food and Drug Administration. Moreover, the study was reviewed by an ethics committee for the MRC that must approve all clinical research being conducted at any MRC site.

# # #

More information about MTN-009 and other studies of the Microbicide Trials Network is available at http://www.mtnstopshiv.org/news

About the MTN

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners whose work is focused on the development and rigorous evaluation of promising microbicides – products applied inside the vagina or rectum that are intended to prevent the sexual transmission of HIV – from the earliest phases of clinical study to large-scale trials that support potential licensure of these products for widespread use. More information about the MTN is available at www.mtnstopshiv.org.

14-April-2014