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

Clare Collins
+1- 412-641-7299
+1- 412-770-8643 (mobile)
collcx@upmc.edu

QUESTIONS AND ANSWERS

MTN-015: An Observational Study of Women Who Acquired HIV While Participating in a Microbicide Trials Network Clinical Trial

1. What is the aim of MTN-015?
MTN-015 is a long-term, observational study being conducted by the Microbicide Trials Network (MTN) that aims to track the nature of HIV progression and treatment response among women who acquired HIV while taking part in an MTN "parent study" testing different products for the prevention of HIV. MTN-015 will help to understand what impact the use of these products, including antiretroviral(ARV)-based vaginal microbicides and ARV tablets, may have on the natural history and clinical course of HIV and on the prevalence and patterns of HIV drug resistance over time. The study also looks to describe how having an HIV diagnosis may affect women's sexual behaviors and partner status. MTN-015, which began in 2008, is expected to involve approximately 500 women who at the time they became infected were enrolled as a participant in one of MTN's large effectiveness studies HPTN 035, VOICE (MTN-003) and ASPIRE (MTN-020).

2. Why is this study important?
MTN-015 is the first study to monitor women who become infected incidental to their participation in an HIV prevention trial. It is uniquely poised for understanding whether the clinical course of HIV is made better or worse by the use of ARV-based products at the time of infection and whether there is any impact on the prevalence and/or patterns of HIV drug resistance. Information gained through MTN-015 will be critical for helping inform guidance on the use of products found to be effective so that their introduction at the community level is done in the safest manner possible.

3. Who is conducting MTN-015 and where?
MTN-015 is being conducted by a team of researchers who are part of the Microbicide Trials Network (MTN), a clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding by the National Institute of Mental Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, all of the U.S. National Institutes of Health (NIH). The protocol chair of MTN-015 is Sharon Riddler, M.D., M.P.H., of the University of Pittsburgh. MTN-015 has involved a total of 19 trial sites in Malawi, South Africa, Uganda, Zambia and Zimbabwe, where either HPTN 035, VOICE or ASPIRE was conducted. At the present time, 19 sites are participating.

4. What are the MTN parent studies from which MTN-015 draws its participants? What products were those studies designed to evaluate?
MTN-015 draws its participants from other MTN trials whose focus was or is the evaluation of different products for the prevention of HIV among women in Africa.

HPTN 035 was a Phase IIb trial that evaluated two different first-generation vaginal microbicide gels – PRO 2000 and BufferGel – among 3,100 women in Malawi, South Africa, Zambia, Zimbabwe and the United States between 2005 and 2008. As a vaginal defense enhancer, BufferGel was designed to boost the natural acidity of the vagina in the presence of semen, while PRO 2000 was an entry/fusion inhibitor designed to hamper HIV's ability to attach to and infect healthy cells. The results, reported in February 2009, found both products safe and PRO 2000 30 percent more effective than a placebo, although this was not statistically significant. BufferGel was found to have no protective effect. Of the 194 women in HPTN 035 who acquired HIV during the study, 100 subsequently enrolled into MTN-015 and were followed by researchers for approximately three and a half years.

-more-

VOICE – Vaginal and Oral Interventions to Control the Epidemic – tested whether ARV medicines commonly used to treat people with HIV are safe and effective in preventing sexual transmission of HIV in women. VOICE focused on two different ARV-based approaches: daily use of an ARV tablet – an approach called oral pre-exposure prophylaxis, or PrEP – and daily use of a vaginal microbicide containing an ARV in gel form. Specifically, VOICE evaluated the safety and effectiveness of three different products: an oral tablet containing tenofovir (known by the brand name Viread®); an oral tablet that contains both tenofovir and emtricitabine (known as Truvada®); and tenofovir gel, a vaginal microbicide formulation of tenofovir. VOICE was conducted between September 2009 and August 2012 and enrolled 5,029 women in Uganda, South Africa and Zimbabwe. The study's results, reported in March 2013, found none of the products effective; most participants did not use them daily as recommended. Of the 356 women who were diagnosed with HIV infection during VOICE participation, 255 were enrolled into MTN-015. All participants have been followed for at least 12 months, and most for more than two years.

ASPIRE – A Study to Prevent Infection with a Ring for Extended Use – was a Phase III study to determine whether a vaginal ring containing the ARV drug dapivirine is a safe and effective method for protecting against the sexual transmission of HIV when used by women for a month at a time. The study, which was launched in August 2012 and enrolled 2,629 women at sites in Malawi, Uganda, South Africa and Zimbabwe, found that the ring reduced the risk of HIV infection by 27 percent overall and by 56 percent in women older than 21. The dapivirine vaginal ring was developed by IPM, which conducted another Phase III trial, The Ring Study, in parallel with ASPIRE. As sister studies, ASPIRE and The Ring Study were designed to provide the strength of evidence for potential licensure of the dapivirine ring for HIV prevention. Of the 174 ASPIRE participants who acquired HIV infection, 123 have enrolled into MTN-015.

5. How is MTN-015 designed?

MTN-015 is an observational study in which researchers are following women for at least one year beginning as soon as possible after they tested positive for HIV in an MTN parent study. Women enrolled in MTN-015 make regular visits to the research site for physical exams and laboratory tests that help researchers assess how the disease is progressing and how women are responding to treatment. Tests include those measuring HIV in the blood (HIV viral load), the extent of damage to cells in the immune system (CD4+ T-cell count) and virologic response to therapy. At the end of the study, researchers will look to see whether there are differences in these measures between women who had been using an active product at the time of infection and women who had been assigned to use a placebo. Similarly, information about women's sexual behaviors and partner status collected through questionnaires administered at the beginning and end of participation will also be compared.

6. Do MTN-015 researchers know whether women were using active products or placebos when they acquired HIV?

Participants may be taking part in MTN-015 while the parent trial is ongoing. Therefore, study group information remains blinded to both the researchers and the participants until the parent trial is completed and its data been analyzed and verified. Only then will it be known whether an active product or a placebo had been used at the time of infection.

7. When will the study be completed and results known?

Although MTN-015 is ongoing, as each major parent study is completed, relevant data in MTN-015 are analyzed and reported. Data from HPTN 035 was presented at Microbicides 2010 and data from VOICE was presented at HIV Research for Prevention (R4P) in 2014. Data from ASPIRE will be available later in 2016.

8. What was learned from participants in MTN-015?

Several African countries are beginning to expand access to ARVs for treatment as well as for the prevention of mother to child transmission of HIV. In addition, the South African Medicines Control Council approved Truvada as PrEP in 2015, following the U.S. Food and Drug Administration's approval in 2012. The widespread use of ARVs brings with it questions about drug resistance. If not recognized and properly

managed, drug resistance could compromise the effectiveness of mainstay drugs. As such, what is learned in MTN-015 is especially important for successfully integrating treatment and prevention programs using the same or similar classes of ARVs.

9. How could a woman acquire HIV while taking part in an HIV prevention trial?

Learning about the safety and effectiveness of an approach requires the kind of trial in which participants are randomly assigned to different study groups, including groups that used a placebo, which has no active drug. Moreover, neither participants nor researchers know who is in which group during the trial. As such, participants in HIV prevention trials are reminded of the fact that the products being tested have not been proven effective and that not all women in the study may be using an active product. To reduce the risk of HIV infection in all participants, researchers provide free condoms, frequent HIV testing and HIV risk-reduction counseling, including on the correct and consistent use of condoms, and provide routine testing and treatment for STIs. A woman's risk for acquiring HIV is greater in sub-Saharan Africa than in any other part of the world, so despite a trial's intensive, ongoing efforts, a participant could acquire HIV if she has unprotected sex with a partner who is infected with the virus.

10. How do women learn that they have been infected with HIV? What happens to them?

Women in MTN clinical trials undergo frequent HIV testing throughout the course of the study. In ASPIRE, for example, this was done at each monthly visit. As such, some women may learn they acquired HIV during their participation in the study. Women in a trial who test positive for HIV are taken off study product immediately. Especially for a product containing an ARV, its continued use could increase the risk of the virus becoming resistant to that ARV and similar ARVs. Women are counseled and referred by study staff to local HIV care and support services. Although off study product, women are encouraged to remain in the parent study and continue with routine study visits. They are also invited to participate in MTN-015.

11. Does MTN-015 include HIV treatment, including ARVs?

MTN receives funding to conduct clinical trials only, and is not permitted to provide HIV treatment. However, all MTN trial sites are required to have agreements with local service providers so that if a study participant acquires HIV she can be referred to the appropriate services and care in her community. Although MTN-015 does not provide HIV treatment, it does provide frequent laboratory tests indicating how the disease is progressing and how women are responding to treatment, information that may help local service providers to better manage the care of these women.

12. What is resistance and is it a concern?

The standard treatment for people with HIV infection is called antiretroviral therapy, or ART. ART 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 improving the health of people with HIV. However, people being treated with ART can sometimes develop resistance to one or more of the ARVs. This happens if the virus adapts to the drug so that instead of being killed or weakened by the drug, it instead allows the virus to survive and multiply. When detected, resistance can usually be managed by stopping the ineffective ARV and starting a new combination of drugs. If the ineffective drug continues to be used, drug resistant virus will keep multiplying unchecked and could feasibly be transmitted to others, such as through unprotected sex.

Resistance could also happen if people who are unknowingly already infected use ARVs or an ARV-based product intended for HIV prevention. That's because these approaches involve a single ARV. While one ARV has the potential to prevent 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. In trials like ASPIRE, safeguards are in place to minimize the potential for drug resistance. For instance, women are tested for HIV at every monthly visit. If a test indicates that a woman has acquired HIV, staff will immediately stop her use of study product.

13. What is being done to ensure the safety of the participants in MTN-015?

MTN-015 is an observational study, and therefore it involves no investigational products or procedures that are

associated with significant risk to participants. While few safety concerns are expected as a result of study participation, site investigators closely monitor all study participants and report any unexpected concerns to the protocol team so they can be managed appropriately.

14. What are the medical benefits for women participating in the study?

Study participants receive free laboratory tests and physical exams, counseling on preventing secondary HIV infection and free condoms. STI risk reduction counseling, testing and treatment is provided at no charge to both women and their partners. In addition, with a participant's permission, MTN-015 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.

15. What approvals were required for MTN-015 to get underway?

MTN-015 underwent extensive and rigorous review by NIAID, as well as by an institutional review board (IRB) or ethics committee (EC) at each trial site. Local IRBs and ECs ensure that studies are scientifically valid and ethically conducted and they provide oversight throughout the duration of a study or trial. In addition, each trial site has a local community advisory board to provide input on and oversight of study activities.

16. Do women participating in the study provide informed consent?

Written informed consent is obtained from each study participant prior to screening and enrollment using forms translated into local languages. The process ensures that women understand the procedures, as well as possible risks and benefits of the study. Participants are under no obligation to participate and may leave the study, without consequence, at any time.

# # #

More information about MTN-015 and other MTN studies can be found at http://www.mtnstopshiv.org/news.

About the Microbicide Trials Network

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.

15-August-2016