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What Happens Next: Understanding the Results of HPTN 035 and MDP 301 and the Promise of ARVs for HIV Prevention

SUMMARY

- Both MDP 301 and HPTN 035 were well-designed and well-executed studies that answered the scientific questions they were designed to answer. HPTN 035 was an intermediate-sized study designed to determine the safety of PRO 2000 and BufferGel and establish whether either product showed sufficient promise for further testing in a Phase III trial or for licensure. It found that PRO 2000 was safe and reduced the risk of HIV by 30 percent, a finding that, although encouraging, was not statistically significant – the odds are one in 10 that the result was due to chance rather than to the product itself. As such, HPTN 035 indicated the need for more research. As a Phase III study involving nearly 9,400 women, MDP 301 was designed to give a more definitive answer about PRO 2000, which it did, finding PRO 2000 was safe but not protective against HIV. While these findings are a disappointment, it is important to understand that research is informed just as much from studies with disappointing outcomes as those considered breakthroughs.
- By no means do these studies represent the final act. Other promising approaches are being investigated, most notably, those involving antiretrovirals (ARVs). Because ARVs are effective for treatment of HIV there is good reason to think they can work to prevent HIV infection as well. Trials of ARV-based approaches are already underway. One ARV-based microbicide, tenofovir gel, is being evaluated in two clinical trials, including the VOICE Study – Vaginal and Oral Interventions to Control the Epidemic. VOICE is testing the daily use of tenofovir gel as well as daily use of an ARV tablet for preventing sexual transmission of HIV in women.

ABOUT THE STUDIES

HPTN 035

- HPTN 035 was a Phase IIb trial that evaluated the safety and effectiveness of the vaginal microbicides 0.5% PRO 2000 gel and BufferGel for preventing male-to-female sexual transmission of HIV. It was conducted between February 2005 and September 2008 among 3,099 sexually active HIV-negative women at seven clinical research sites in Malawi, South Africa, Zambia, Zimbabwe and the United States. Results were announced February 2009 at the Conference on Retroviruses and Opportunistic Infections (CROI) in Montreal. A manuscript detailing the major findings is currently under peer review at a major scientific journal.
- The study was not designed to compare the two gels, but rather to compare each against a placebo gel with no active ingredient, and with no gel at all. Women were randomized approximately in equal number to one of four study groups: BufferGel, PRO 2000 gel, placebo gel, or no gel. Participants assigned to the three gel groups were instructed to apply gel up to one hour before sexual intercourse using pre-filled applicators. All women received HIV risk-reduction counseling, free condoms, and testing and treatment of sexually transmitted infections throughout the study. Women took part in the study for 12 to 30 months (20 months on average).
- HPTN 035 found that 0.5% PRO 2000 gel reduced the risk of HIV by 30 percent compared to placebo gel, but this finding was not statistically significant. In other words, the odds are one in 10 that the finding was due to chance and that PRO 2000 gel offered no protective benefit. Although additional study was needed to provide more conclusive evidence about PRO 2000's effectiveness, the results nonetheless generated hope because they offered the first indication that a vaginal microbicide could potentially help prevent HIV.

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- In the final analysis, 194 women in HPTN 035 became infected with HIV. Of these infections, 36 occurred in the PRO 2000 group, 54 in the BufferGel group, 51 in the placebo gel group, and 53 among those in the no-gel group. Both gels were safe.
- HPTN 035 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 U.S. National Institute of Allergy and Infectious Diseases (NIAID) 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 (NIH). Prior to the establishment of the MTN, the study was led by the NIAID-funded HIV Prevention Trials Network (HPTN), from which it gets its name.

MDP 301

- MDP 301 involved 9,385 sexually active, HIV-negative women at six clinical research sites in South Africa, Tanzania, Uganda and Zambia and was conducted between October 2005 and August 2009. As a Phase III trial with three times as many participants, MDP 301 was expected to provide more conclusive evidence of whether and to what degree 0.5% PRO 2000 gel prevents HIV infection in women.
- Originally, women in the study were randomly assigned to use either 0.5% PRO 2000 gel, 2% PRO 2000 gel or a placebo gel (the same placebo gel used in HPTN 035). However, testing of the 2% strength gel was discontinued in February 2008 when the study's Independent Data Monitoring Committee concluded that it was not likely to show benefit in preventing HIV. Thereafter, women who enrolled were randomized to use either 0.5% PRO 2000 or placebo gel.
- As with HPTN 035, trial participants were instructed to apply a single dose of gel, using pre-filled applicators, up to one hour before every act of vaginal intercourse, and they were counseled on safe sex behavior and advised to use condoms, provided free of charge, every time they had sex. Most women took part in the study for one year. In Uganda, women were enrolled with their partners, many of whom were HIV-positive, and were in the study for up to two years.
- Researchers found 0.5% PRO 2000 gel was safe but no different than placebo gel for protecting against HIV, meaning PRO 2000 neither reduced nor increased the risk of HIV. The number of HIV infections that occurred in each group was about the same: 130 in the PRO 2000 gel group and 123 in the placebo group.
- The study also found that many of the women – and their partners – enjoyed using the gel, adding credence to the use of a female-controlled vaginal product for preventing HIV.
- MDP 301 was conducted by the Microbicides Development Programme (MDP), a not-for-profit partnership of African and European research institutions, and was funded by the U.K. Department for International Development (DFID) and the U.K. Medical Research Council (MRC). The researchers announced the study's primary results December 14 (2009) and plan to report additional findings at scientific meetings and in a peer-reviewed journal.

PRO 2000

- As an experimental microbicide, PRO 2000 was designed to reduce HIV's ability to infect healthy human cells by disrupting the initial process during which HIV attaches to and enters healthy cells. It had undergone extensive pre-clinical laboratory and animal research before clinical safety trials involving women and men from Africa, Europe, India and the United States concluded the gel was tolerated and sufficiently safe to be considered for further testing in larger trials such as HPTN 035 and MDP 301. Originally developed by a U.S. biotechnology company named Procept, Inc., PRO 2000 later was licensed to Indevus Pharmaceuticals, which was bought by Endo Pharmaceuticals, Inc., in March 2009. The two U.S.-based companies provided PRO 2000 free of charge for both studies.

UNDERSTANDING THE RESEARCH PROCESS

What's Involved

- The aim of HIV prevention research is to identify the most safe and effective approaches that can help the most people. Nine candidate microbicides are in various stages of clinical study and more than 50 are in preclinical development. But research, and drug development in particular, takes time. It begins with the screening of thousands of potential compounds, and only those showing the greatest promise are then subjected to rigorous laboratory and animal studies. Fewer still will make it into clinical studies in humans, first for safety, and then for effectiveness. The entire process can take more than 15 years before a single agent may or may not be approved for use.
- As with all science, clinical trials are designed to answer specific questions. Both MDP 301 and HPTN 035 were well-designed and well-executed studies that answered the scientific questions they were designed to answer. But it is important to understand that for every study that yields a promising scientific discovery, there are many more whose results may disappoint. There is as much to be learned from these studies as those considered breakthroughs. For instance, they help to inform the development of new hypotheses that can be tested and used to enhance understanding and further microbicide research and development.
- The success of any clinical trial depends on the volunteers who take part in the study. In the case of HPTN 035 and MDP 301, more than 12,500 women devoted their time and themselves toward making a difference in the fight against HIV. Neither study could have been completed without their dedication and commitment.

WHERE WE GO FROM HERE

Research Continues Because of the Need

- HIV prevention research is continuing in its search for safe and effective strategies to combat the epidemic. Many of these efforts are focused on women, who make up half of the 33 million people living with HIV/AIDS worldwide. In sub-Saharan Africa, women account for 60 percent of all infected adults. In several southern African countries, young women aged 15 to 24 are at least three times more likely than their male peers to be infected with HIV.
- Among women, heterosexual intercourse remains the primary risk factor for HIV infection, and in many parts of the world, heterosexual intercourse is the driving force of the epidemic. Women are twice as likely as their male partners to acquire HIV during sex, due in part to biological factors that make women more vulnerable. Although correct and consistent use of male condoms has been shown to prevent HIV infection, often women do not have a choice if they are used. Women need prevention tools that they can decide to use on their own.

The Promise of ARV-based Prevention

- ARV-based strategies incorporate some of the same ARV medicines used successfully for treatment of HIV and the hope is that they will also be safe and effective for HIV prevention. Many believe that ARV-based prevention strategies may be more effective than other methods tested so far because they have specificity against HIV.
- Trials of ARV-based approaches are already underway. One ARV-based microbicide, tenofovir gel, is being evaluated in two Phase IIb clinical trials. CAPRISA 004 is evaluating use before and after sexual intercourse, while VOICE is testing the daily use of tenofovir gel as well as daily use of an ARV tablet for preventing sexual transmission of HIV in women.
- The VOICE Study is a major NIH-funded HIV prevention trial being conducted by the MTN that seeks to determine the safety and effectiveness of the two approaches but also which approach women will prefer. The study will enroll approximately 5,000 HIV-negative women at sites in Uganda, South Africa, Zambia and Zimbabwe, and pending government approvals, in Malawi. It began in September 2009 and is expected to be completed in 2012.

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