INTERNATIONAL PARTNERSHIP for MICROBICIDES

New Science, New Hope: ARV-Based Microbicides

Women continue to be disproportionately affected by the HIV epidemic in sub-Saharan Africa. Far too many women and girls are powerless against the threat of infection. HIV/AIDS is now the number one cause of death among women of reproductive age (15-44) in the world, particularly in sub-Saharan Africa.[i] The spread of HIV/AIDS continues to outpace the world's response to the epidemic. For every two people placed on treatment, five become newly infected.[ii]

Women urgently need new prevention options like microbicides. Current prevention strategies are not enough to stop the impact of HIV — particularly among women. Although methods such as condoms are very effective, they are not practical for women who cannot persuade their partners to use them, women who want to have children or those who are at risk for violence. Vaginal microbicides are being developed to reduce the transmission of HIV to women during sex with an infected male partner. Antiretroviral (ARV)-based microbicides are following the lead of other life-saving prevention methods that have been created by adapting successful treatments for diseases such as malaria, influenza and pneumonia.

ARV-based microbicides promise to give women a powerful new way to protect their own health and save millions of lives.

ARV-based microbicides have the potential to transform the global response to HIV infection. Multiple organizations have been working on developing microbicides that contain the same types of ARV drugs being used successfully to treat people living with HIV/AIDS and to prevent mother-to-child transmission. Findings announced in July 2010 from the CAPRISA 004 clinical trial offer a new case for optimism. Conducted with 889 South African women volunteers, this trial evaluated vaginal application of 1% tenofovir gel for prevention of male-to-female transmission of HIV. In an important milestone for HIV prevention, CAPRISA 004 found a 39 percent lower HIV infection rate in women using tenofovir compared to those women using placebo gel. Tenofovir gel also reduced transmission of herpes simplex virus type 2 (HSV-2), by 51 percent. HSV-2 is a lifelong and incurable infection that can increase risk of acquisition of HIV. The product demonstrated a good safety profile as tested. Additional confirmatory/complimentary trials are planned for 2011. Also in 2011, IPM will begin Phase III program to test another ARV-based microbicide, dapivirine, delivered in a long-acting, once-monthly vaginal ring.

ARV-based microbicides specifically target HIV. The drugs used in ARV-based microbicides are highly active and specifically target the HIV virus. These drugs block the ability of the virus to enter healthy cells or to reproduce once inside the cells. Tenofovir, the ARV used in CAPRISA 004, works after HIV has entered the cell and prevents HIV from starting the process of replicating its genetic material.

Microbicides would come in different forms to give women choice and convenience. Even the most safe and efficacious product won't work if women don't use it. Microbicides could take a variety of forms, such as gels used around the time of sex, once-daily gels, films and long-acting vaginal ring that would provide protection for up to a month at a time. ARV-based microbicides are being formulated to protect against HIV infection even during unanticipated sex by releasing the active ingredients gradually over time.

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ARVs act against HIV in a number of specific ways. Antiretroviral drugs act by interfering with one of the steps in the HIV life cycle. The first steps, where HIV attaches to and enters the human cell, can be blocked with compounds known as *entry* or *fusion* inhibitors. CCR5 and CXCR4 inhibitors, such as maraviroc, are examples of these drugs. Compounds such as gp41 inhibitors can also interfere with the first steps by blocking the ability of HIV to fuse with and become one with human immune cells. Once HIV has entered the cell, the virus begins the steps required to reproduce itself; these steps can be blocked by ARV drugs, such as tenofovir and dapivirine, which are known as *reverse transcriptase inhibitors*. Those compounds prevent the virus from initiating the process of replicating its genetic material. Similarly, *integrase inhibitors* prevent the virus from permanently inserting its genetic material into human chromosomes — another way to block viral reproduction. Beyond that, *protease inhibitors* can interfere with the final steps in the process by preventing HIV from constructing the protein components it needs to assemble new viruses.

Combination microbicides have potential to offer greater protection. Another advantage of ARV-based microbicides is the ability to combine multiple drugs into one product. Experts anticipate that microbicides based on a combination of ARVs that target HIV at different points in its lifecycle maximize their protective effect. In addition, products that combine an ARV with a contraceptive could provide prevention from HIV and birth control in a single formulation. Other products could combine an ARV to protect against HIV with additional active ingredients to prevent other sexually transmitted infections.

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[i] WHO, "Women and Health: Today's Evidence, Tomorrow's Agenda," November 2009
[ii] UNAIDS, "2008 Report on the Global AIDS Epidemic," December 2008