New Science, New Hope: ARV-Based Microbicides

INTERNATIONAL PARTNERSHIP for 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 person placed on HIV treatment, two more become infected.[ii]

Women urgently need new prevention options like microbicides. Current prevention strategies are not enough to stop the spread 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 women who are at risk of violence. Vaginal microbicides are being developed to reduce the transmission of HIV to women during sex with an HIV-positive 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 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 successfully used to treat people living with HIV/AIDS and to prevent mother-to-child transmission. The success of two major studies in 2010 has provided proof-of-concept for ARV-based HIV prevention.

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

Findings announced in July 2010 from the CAPRISA 004 clinical trial offer a new case for optimism. Conducted among 889 South African women volunteers, this trial evaluated vaginal application of 1% tenofovir microbicide 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.

The December 2010 results from the iPrEx trial, a Phase III study testing pre-exposure prophylaxis, or PrEP, showed that the oral ARV medication Truvada® — an FDA-approved HIV treatment that contains both tenofovir disoproxil fumarate and emtricitabine — taken once a day in conjunction with comprehensive HIV prevention services led to a 44 percent reduced risk of becoming infected with HIV-1 in the clinical trial population.

In 2011, IPM will begin its Phase III program to test a long-acting vaginal ring containing the ARV-based drug dapivirine.

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 drug used in the CAPRISA 004 trial, works after HIV has entered the healthy cell and prevents the virus from beginning the process of replicating its genetic material.

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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 rings that would provide protection for a month or longer. ARV-based microbicides are being formulated to protect against HIV infection even during unanticipated sex by releasing the active ingredients gradually over time.

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 continues 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, "2010 Report on the Global AIDS Epidemic," November 2010