

Study defines effective microbicide design for HIV/AIDS prevention

Duke University biomedical engineers have developed a computer tool they say could lead to improvements in topical microbicides being developed for women to use to prevent infection by the virus that causes AIDS.

Providing women with improved microbicides is a pressing challenge because women now account for a growing number of new infections worldwide, the researchers said.

By applying fundamentals of physics and chemistry, the researchers developed a computer model that can predict the effectiveness of various microbicidal recipes in destroying human immunodeficiency virus (HIV) before it reaches vulnerable body tissues.

Using the tool, the researchers have determined that a thin, long-lasting coating of microbicide delivered to susceptible tissues in a woman's vagina can significantly reduce the spread of HIV.

The researchers reported their findings in the September 2006 *Biophysical Journal*.

The findings emphasize a critical role for the "delivery vehicle," the various polymer gels or creams that carry the active antimicrobial ingredients, in determining the success or failure of microbicides, according to the researchers. Yet, they add, most scientists have concentrated on improving the antimicrobial compounds themselves, rather than their delivery.

"There is a huge push to produce microbicides that would have any effectiveness at all in reducing the spread of HIV, particularly in places like Africa and Southeast Asia where the disease is rampant," said David Katz, a professor of biomedical engineering at Duke's Pratt School of Engineering and one of the computer tool's developers. "We are developing methodologies to make the next round of microbicides even better."

"Existing microbicides are excellent in terms of their ability to inactivate HIV," added Anthony Geonnotti, the study's lead investigator, who is a Ph.D. candidate in Katz's laboratory. "Improvements to future generations of microbicides will largely depend on the delivery system and applicators." However, he added, advances made through continued research on new and better drugs should not be discounted.

In addition to their role in drug delivery, microbicide formulations can act as physical barriers or filters to slow HIV's passage from semen into body tissues, Geonnotti explained. That slowing would give the HIV-neutralizing ingredient in the microbicide layer, as well as the body's natural defenses against HIV, more time to work. If left untreated, HIV attacks a person's immune system and can progress to AIDS, acquired immune deficiency syndrome.

The HIV pandemic continues to overwhelm current preventative measures as an estimated 12,000 people contract the infection each day, the researchers said. Increasingly, a disproportionate number of women are becoming infected. In several African countries, for example, HIV infection rates among young women between the ages of 15 and 24 are more than three times higher than among their male counterparts.

Women are about twice as likely as men to contract HIV during vaginal intercourse, according to the federal Centers for Disease Control and Prevention. In developing countries particularly, cultural and socioeconomic inequities between the sexes also can leave women more susceptible.

"In many cases, women lack control over their abilities to protect themselves against the virus," Katz said.

"Microbicide development is a response to the demonstrated need for new female-controlled methods for HIV prophylaxis."

In the current study, the researchers developed a mathematical model that simulates the biological interaction between HIV contained in semen and the protective coating that accumulates on the lining of a woman's vagina after she applies a topical microbicide. The model describes the diffusion of the virus and active ingredients into the tissues, as well as the chemical inactivation of virus by the microbicidal agent.

The model is easily adapted to studying different active ingredients and delivery vehicles simply by changing the data entered, the researchers said. For example, researchers might specify the thickness of the expected coating layer, the initial concentration of microbicide in that layer, and the microbicide's documented ability to bind to and disable the viral particles.

The researchers demonstrated their new tool by applying it to the promising microbicide Cyanovirin-N, a protein with anti-HIV activity that has been well documented by other scientists.

"Our results suggest HIV neutralization is achievable if coating thicknesses on the order of 100 microns remain in place after sex," Geonnotti said. One hundred microns is the approximate width of a human hair. "Increased microbicide concentration and potency hasten viral neutralization and diminish penetration of infectious virus through the coating layer, as do ingredients that restrict viral passage," he said.

"Our findings demonstrate the need to pair potent active ingredients with well-engineered delivery vehicles, and they highlight the importance of the dosage form -- especially its ability to restrict viral diffusion and remain in place -- in microbicide effectiveness," Katz added.

More than 20 microbicidal chemical compounds are now in development or testing and five of them have reached the final phase of clinical trials. The Duke group's new model provides a "rational guide" for design specifications that could further improve such microbicides' ability to cut the rate of HIV spread, the researchers said.

The researchers now are conducting studies to experimentally measure the diffusion of viral particles through various delivery vehicles. They also are collaborating with other researchers on developing high-performance polymer gels that might provide a more substantial physical barrier to HIV.

Source: Duke University

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