



Chuck Wira's lab has identified naturally occurring secretions of the female reproductive tract that inhibit HIV.

Tract record: Three decades of chasing HIV

"HIV is a sexually transmitted disease," DMS physiologist Charles Wira, Ph.D., often says at the beginning of his lectures. That may seem obvious, but, he adds, researchers tend to forget about the actual site of transmission of the disease from men to women: the female reproductive tract.

Tract: Wira was one of the first scientists to realize the important role that the tract's mucosal immune system plays in the male-to-female sexual transmission of pathogens like HIV. Now, he and collaborators have found that the reproductive tracts of healthy women with and without HIV contain naturally occurring microbicides capable of inhibiting HIV infection.

The study, published in the journal *PLoS ONE*, was based on secretions from 32 HIV-positive women not on antiretroviral therapy and 15 HIV-negative women. The samples were obtained by researchers at Brown University led by gynecologist Susan Cu-Uvin, M.D., a coauthor of the paper, and were analyzed in Wira's lab.

"One of the first observations . . . was quite a surprise," says research associate Mimi Ghosh, Ph.D. (among the innate anti-HIV microbicides measured in the study were two discovered by Ghosh—trappin-2/elafin and MIP3 α). The surprise was that while HIV was present in the secretions of most of the

HIV-positive women, the virus was not infectious. Only 3 of the 32 had an infectious form of it. The team also found that the cells lining the cervix and uterus, previously thought to be only a physical barrier against pathogens, secrete anti-HIV microbicides and produce chemokines, molecules that recruit other immune cells to fend off viruses.

The effectiveness of the microbicides varied widely. In some samples they completely blocked HIV activity; in others they didn't block it at all. The effectiveness didn't depend on whether the individual was HIV-positive or not. One possible explanation for this range in effectiveness is the profound influence that hormones exert on the immune system in the cervix and vagina, a topic Wira's lab has studied extensively. They've found that there is a window of susceptibility to HIV during the menstrual cycle, occurring around mid-cycle—a time when many aspects of the immune system are turned down in order to optimize conditions for successful fertilization.

Mode: Another new finding is that the mode of immune protection differs in women with and without HIV. Secretions from both groups displayed anti-HIV activity, with no difference in magnitude. But in the HIV-positive women, protection was taken over by antibodies at the expense of the innate im-

For a **WEB EXTRA** with video coverage of several talks during the AIDS conference that Wira organized in July 2010, see dartmed.dartmouth.edu/w10/we04.

une system, which includes natural protective substances that kill bacteria, fungi, and viruses. The innate immune system, which many believe to be unchanging, in fact is disabled in these individuals. This is of interest because "there is relatively little knowledge of the aspects of the innate immune system" that fight infection, explains John Fahey, Ph.D., a research assistant professor.

Wira and his colleagues are currently developing vaginal rings containing substances that turn on the innate immune system and sustain it, even during its mid-cycle decline. They are also engineering lactobacilli, bacteria that occur naturally in the vagina and inhibit pathogens, to boost anti-HIV substances in the genital tract. Wira sees potential for both interventions because of their affordability and ease of administration.

HIV/AIDS is usually seen as a problem in third-world countries, but it has also "reached epidemic proportions within [American] inner cities," says Wira. Antiretroviral therapy has been a tremendous success, but not everyone can afford the costly medications.

"Depending on where you are, in some locations, 70% to 80% of new cases are women," says Wira. "This is the disease of women worldwide." But it's "a forgotten epidemic" in the U.S., he says.

Theme: In fact, that was the theme of a conference funded by the National Institutes of Health that he organized at DHMC this past July. It brought top scientists in the field from all over the world and drew attention to the failure of many HIV researchers to fully recognize the importance in HIV transmission of the complex mucosal immune system and the female reproductive tract.

It's been three decades since Wira began studying the physiology, immunology, and function of the female reproductive tract, and nearly three decades since the identification of the HIV epidemic. Shifting his own focus to HIV "was a natural transition," he says. Now he's hoping more HIV researchers will make the transition to studying the role of the female reproductive tract. KRUPA PATEL