UT SOUTHWESTERN MEDICAL CENTER NEWS

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Existing antiretroviral drugs may thwart vaginal HIV transmission, UT Southwestern researchers report

DALLAS – Jan. 14, 2008 – Prescription drugs now used to treat human immunodeficiency virus infection in adults may prevent the vaginal transmission of HIV, researchers at UT Southwestern Medical Center have found.

Using a highly sophisticated human/mouse chimera or "humanized mouse" model, the UT Southwestern researchers discovered that anti-retroviral drugs given daily before and after exposure to HIV can prevent vaginal transmission of the virus that causes AIDS. Worldwide, the vast majority of newly acquired HIV infections occur through unprotected vaginal sex with an infected partner.

The study, appearing online today in *PLoS Medicine*, used human/mouse chimeras that have fully developed human immune systems and produce the infection-fighting cells that are specifically targeted by HIV in humans.

While almost 90 percent of the humanized mice inoculated vaginally with HIV became infected with the virus, none of the humanized mice given the anti-retroviral drugs emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) displayed any evidence of infection.

"Our motivation is to look for interventions that can be implemented rapidly and have the potential to make a big difference," said Dr. J. Victor Garcia-Martinez, professor of internal medicine at UT Southwestern and the study's senior author. "We don't want something in 10 years. We want female-controlled prevention measures now. Our observations support the potential for antiviral drugs to function as an effective pre-exposure prophylaxis against the further spread of AIDS."

HIV is predominantly transmitted by unprotected sexual contact with an infected partner. Women are more susceptible than men to HIV infection, and vaginal exposures result in a majority of the estimated 6,800 transmission events a day.

"There are 33 million people infected with HIV. This study is a highly significant breakthrough because it offers proof-of-principle that pre-exposure prophylaxis with currently available anti-retroviral

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drugs can potentially prevent vaginal HIV transmission, empowering women throughout the world to protect themselves from this deadly disease," Dr. Garcia said.

"More women are being infected by HIV now than at any other time during the history of the AIDS epidemic," Dr. Garcia said. "Over 15 million women worldwide are infected. Our findings should provide further impetus to continue clinical trials using oral anti-retroviral drugs as a preventive measure, particularly in areas with the highest rates of HIV infection."

Dr. Garcia said one potential caveat is that the experiments were conducted on humanized mice and not humans.

"This is a human/mouse chimeric model that clearly recapitulates very important aspects of humans, but at the end of the day, these are mice," he said. "It will take additional work to translate these observations to humans."

Investigators have long used mouse models to study human physiology and to test new drugs. But differences in mouse and human immune systems – and the fact that normal mice can't be infected with human-specific pathogens or produce human immune cells needed to fight them – have limited this type of research.

In 2006 Dr. Garcia, along with colleagues at UT Southwestern and researchers from the University of Minnesota, created humanized mice that developed fully functional human immune systems and infection-fighting cells, such as T cells, throughout their bodies. These humanized mice, known as Bone Marrow Liver Thymic mice (BLT mice), can develop T cells the same way as humans and can be infected vaginally with HIV.

In this latest study, the BLT mice were given the anti-retroviral drugs once a day for seven consecutive days starting 48 hours before being challenged intravaginally with HIV. None of the mice that had been given the anti-retroviral drugs contracted HIV; however, seven of the eight mice that didn't receive the anti-retroviral drugs tested positive for the infection as early as two weeks post-infection.

If this pattern proves to be true in subsequent trials, women someday might have to take one pill a day in order to potentially prevent vaginal transmission of HIV, Dr. Garcia said.

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"One important issue to keep in mind is that pre-exposure prophylaxis is not something that would be advantageous or cost-effective to use in areas where there's a very low incidence of HIV infection," he said. "If you take this pill on a regular basis, but you're not exposed to this virus, then the drugs are not doing any good and could potentially do harm. But, in parts of the world where the likelihood of exposure is significantly higher, the risk of contracting HIV may warrant taking these medications."

Dr. Garcia said it's possible that other more cost-effective drug combinations or concentrations could have the same effect. What this research does, he explained, is demonstrate that existing anti-retroviral drugs can help curtail the spread of the HIV/AIDS epidemic.

Other UT Southwestern researchers involved in the study were lead author and student research assistant Paul Denton; research assistants Daniel Powell and Florence Othieno; postdoctoral researchers Dr. Zhifeng Sun and Dr. Anja Wege; former postdoctoral researcher Dr. Bangdong Wei; and Dr. Deborah Payne, associate professor of pathology. Drs. Jacob Estes and Ashley Haase from the University of Minnesota also participated.

The National Institutes of Health supported the study.

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