Researcher tracks genetic journey of HIV from birth to death

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University of Florida scientists have discovered how HIV evolves over the course of a person's lifetime into a more deadly form that heralds the onset of full-blown AIDS. The findings could pave the way for new therapeutic agents that target the virus earlier in the disease process, before it takes a lethal turn, researchers say.

"We were very interested in understanding how the virus mutates from the beginning of the infection until the end," said Marco Salemi, an assistant professor of pathology, immunology and laboratory medicine in the UF College of Medicine and lead author on the study, which appeared in an online issue of the journal PLoS ONE in September. "Previously, the only thing known was that somehow the HIV population mutates. And as soon as that happens, patients start developing AIDS. But no one knew how and where the population evolved over time."

To find out, UF researchers began tracking four children born with HIV, studying blood samples taken at birth, throughout life and just after death, when tissues samples were also taken. Using a high-resolution computational technique, they monitored mutations in a protein that helps HIV attach to human cells and then categorized the virus into two groups, R5 and X4. The R5 population is usually present in high numbers during the early stages of infection. But the X4 population enters the scene later, just before HIV gives way to full-blown AIDS. The researchers tracked the viruses in each patient to find out when and where the telltale X4 population first appeared.

“The general dogma has always been that the X4 viruses are more pathogenic than the R5 viruses. And that really isn’t true. People die from the R5 viruses,” said Maureen Goodenow, senior author of the paper and the Stephany W. Holloway university chair for AIDS research in the UF College of Medicine. “But certainly evolution of these X4 viruses is not a good prognostic indicator. So if we could understand the selective pressures that push viruses to develop like that, and the steps involved in the conversion of viruses, then we might be able to set up new targets for drug development.”

Previous studies have relied on cell culture or animal models to follow the virus’ mutations over time. The UF researchers are among the first groups to study the progression of HIV in human patients.

As the study revealed new information about the evolution of HIV, UF scientists learned that most viral changes take place in the thymus, a small organ located behind the breastbone that is responsible for immune cell development.

“We found that the late-stage viruses, the X4 viruses, were localized predominantly in the thymus,” Goodenow said. “It says that the thymus is the place where these viruses develop, or at least where they’re localized and replicate.”

The origin of the X4 viruses has puzzled scientists for years. The UF research reveals that the X4 viruses are not present in the body all along, as some scientists had speculated, but rather, that they evolve directly from the R5 population just before the onset of AIDS. The researchers also found that HIV followed a similar path in each child, regardless of variations in the patients’ medical histories.

“We’re starting to see what looks like a program of virus development over time. And it doesn’t matter who the person is. And it doesn’t matter

what the time scale is," Goodenow said. "It's raising the possibility that, in fact, the evolutionary track of the virus is not totally random. There could be a real developmental program that the virus goes through."

Eight years ago, when the National Institutes of Health-funded study began, pregnant women infected with HIV had few therapeutic options. But recent advances in prenatal drug therapies have substantially decreased the rates of mother-to-child transmission. The Centers for Disease Control and Prevention estimates that less than 2 percent of American mothers currently infected with HIV/AIDS will transmit the viruses to their babies during birth. Without the drugs, about 40 percent of infected mothers would give birth to babies with HIV.

Those therapies may help future children, but they came too late for the subjects enrolled in the study. The children received minimal medication and all developed full-blown AIDS by their first birthdays.

"Their whole virus infection was what we call the natural history," Goodenow said. "This tells you what happens in the absence of combination antiretroviral therapy."

The next step, Goodenow said, will be to track the evolution of HIV in adults before and after treatment. The researchers hope their findings will pave the way for new drugs that interfere with the virus' ability to evolve in the thymus.

"This is an excellent study that reveals fine-scale patterns in the evolution and adaptation of HIV during infection," said Oliver Pybus, a research fellow in the department of zoology at Oxford University. Pybus was part of a team that, three years ago in Science, published descriptions of the high-resolution technique UF researchers used in their study. "For the first time, it shows how the movement of immune cells with the body is linked to the evolutionary behavior of the virus,

which in turn determines the clinical outcome of infection."

Source: University of Florida