MedicalXpress

Charting HIV's rapidly changing journey in the body

December 12 2008

HIV is so deadly largely because it evolves so rapidly. With a single virus as the origin of an infection, most patients will quickly come to harbor thousands of different versions of HIV, all a little bit different and all competing with one another to most efficiently infect that person's cells. Its rapid and unique evolution in every patient is what allows HIV to evade the body's defenses and gives the virus great skill at developing resistance to a pantheon of antiviral drugs.

"A huge amount of HIV diversity accumulates in the body of a patient with HIV, and it's a big reason why HIV is such a powerful virus," said Ha Youn Lee, Ph.D., assistant professor of Biostatistics and Computational Biology at the University of Rochester and corresponding author of the study.

Lee and colleagues have settled a longstanding question about just how HIV morphs in the body. In a paper published Dec. 12 in *PLoS Computational Biology*, scientists show that HIV evolution in the body does not occur at a constant rate. Rather, the virus's rate of change suddenly slows when the level of crucial immune cells known as CD4+ T-cells falls in a patient.

The team suggests several possible reasons for why HIV slows its evolution later in the disease process. One is that there are simply fewer immune cells left for the virus to infect. Another possibility is that since the immune system is no longer as effective targeting the virus, the virus no longer feels the "selective pressure" of the immune system, and the

virus slows its evolution in response.

Picture a criminal on the lam. When the police are out in force, the criminal must change his disguise more and more to survive, but when fewer police are present, the criminal can change his disguise less often. In the case of HIV, the virus actually eliminates the "police officers" – CD4+ T-cells patrolling the body. As time goes on and fewer immune cells are present to flag HIV, the virus no longer has the need to evolve as rapidly as it did when the cells were out in force.

"In a person with a strong immune system, the virus is constantly on the run – it has to change to survive," said co-author Thomas Leitner, Ph.D., of Los Alamos National Laboratory, who studies viral and bacterial evolution. "But even in a person who has lived with HIV for a decade or more, in most cases, at some point, the immune system weakens. The virus notices and evolves accordingly. It's a very dynamic process."

While the research shows that the virus is creating fewer new versions of itself late in the disease process, the researchers say the clinical implications of the research are unclear. Since the virus's ability to evolve is at the heart of the drug-resistance capability that makes HIV so deadly, the work could help scientists who are trying to figure out new ways to stop the virus.

"It's possible that this work would have some implications for our understanding of drug resistance late in the disease process," said Lisa Demeter, M.D., a University of Rochester virologist not involved in the study. "When HIV is evolving more slowly in a patient, that patient is less likely to develop resistance to treatment so quickly," said Demeter, an expert on how HIV develops resistance and professor of Medicine in the Infectious Diseases Division.

Scientists have debated the pace of change of HIV in the body. Some

studies have suggested that the virus evolves slowly in people who live many years with HIV before developing AIDS, while other studies showed that the virus evolves quickly in those patients.

To address the issue, the team developed a mathematical and computational model of how HIV evolves in the body. They tested the model by analyzing the blood from 15 HIV patients whose blood was sampled every few months for anywhere from three to 12 years. The data came from the HIV Sequence Database at Los Alamos National Laboratory, which holds more than 250,000 genetic sequences of HIV from patients around the globe.

The team found that the when the immune system is relatively healthy, the HIV virus evolves at a constant and rapid rate, but when a patient's CD4+ cells decrease, HIV's rate of evolution slows. The shift occurs long before a patient is considered to have AIDS, which is indicated when the CD4+ level drops to 200 cells per microliter of blood. The finding was true of 13 of 15 of the patients.

The team focused its attention on 600 nucleotides of the RNA that make up HIV's env gene, which codes for the protein's outer envelope that the virus uses to bind onto the cells of the host. In the team's study, on average, slightly less than one mutation per month occurred per patient in this swath of the HIV genome during the time when CD4+ levels were relatively high and the rate of change was constant.

That's a very rapid rate of change for one small portion of a virus, especially one so prolific: Every day, the HIV virus population in an infected person – up to 10 billion viral particles – copies itself and recreates 95 percent of its particles. With all that reproducing, and without a high regard for accuracy, one change leads to another, and the results are astounding: Most patients have literally many thousands of different types of HIV virus in their bodies.

"Every single person on Earth who is infected with HIV has his or her own unique HIV population," said Leitner.

As the virus mutates, giving birth to viral offspring called quasispecies, it presents an ever-changing face to the immune system, which is continually adapting itself to keep up with the onslaught. The immune system does a remarkable job fending off the assault, killing most of the viral particles every day. Even so, some of the virus is able to elude the body's defenses and ultimately devastates the immune system in most patients.

Source: University of Rochester