HIV Hiding from Drugs in Gut, Preventing Immune Recovery

July 31 2006

UC Davis researchers have discovered that the human immunodeficiency virus, the virus that causes AIDS, is able to survive efforts to destroy it by hiding out in the mucosal tissues of the intestine. They also found that HIV continues to replicate in the gut mucosa, suppressing immune function in patients being treated with antiretroviral therapy—even when blood samples from the same individuals indicated the treatment was working. Results of the three-year study appear in the August issue of the *Journal of Virology*.

"This is the first longitudinal study to show that, while current HIV therapy is quite successful in reducing viral loads and increasing T-cells in peripheral blood, it is not so effective in gut mucosa," said Satya Dandekar, professor and chair of the Department of Medical Microbiology and Immunology at UC Davis Health System and senior author of the study.

"The real battle between the virus and exposed individuals is happening in the gut immediately after viral infection," she said. "We need to be focusing our efforts on improving treatment of gut mucosa, where massive destruction of immune cells is occurring. Gut-associated lymphoid tissue accounts for 70 percent of the body's immune system. Restoring its function is crucial to ridding the body of the virus."

Results of the study suggest that patients being treated with antiretroviral therapy should be monitored using gut biopsies and that the gut's immune function be restored through earlier antiretroviral treatment and

the use of anti-inflammatory medications.

“We found a substantial delay in the time that it takes to restore the gut mucosal immune system in those with chronic infections,” Dandekar said. “In these patients the gut is acting as a viral reservoir that keeps us from ridding patients of the virus.”

Physicians treating HIV-infected patients have long relied on blood measurements of viral load and T-cell counts when choosing a course of treatment. Viral load is the number of viral particles in a milliliter sample of blood. T-cell counts reflect the number of CD4+ T-cells in the sample. These cells, also called T-helper cells, organize the immune system’s attack on disease-causing invaders. They are, however, the targets of the virus and their numbers decrease as the amount of HIV increases, leaving the body vulnerable to a variety of infections.

Last year, Dandekar’s team published a study of HIV-infected patients who, despite the lack of treatment, had survived over 10 years with healthy levels of T-cells and suppressed viral loads.

“We looked at their gut lymphoid tissue and did not see loss of T-cells there. This correlated with better clinical outcomes,” Dandekar explained.

Those results prompted Dandekar and her team to undertake the current study in which they set out to evaluate the effect of highly active antiretroviral therapy, known as HAART, on viral suppression and immune restoration in gut-associated lymphoid tissue. They followed 10 patients being treated with HAART, taking blood and gut samples before and after three years of treatment. Three of the patients were treated during four to six weeks of first being infected with the virus. The other participants were known to be HIV positive for more than one year.

Hoping to figure out why HAART does not work as well in the gut, Dandekar and her colleagues further examined the post-treatment of gut-associated lymphoid tissue samples. They found evidence of inflammation, which disrupts tissue function, promotes cell death and upsets the normal balance of gut flora. They also found that the activity of genes that control and promote mucosal repair and regeneration were suppressed, while the genes responsible for the inflammatory response were more active than in normal tissue.

Dandekar said these results suggest anti-inflammatory drugs may improve antiretroviral treatment outcomes. She also pointed out that genes involved with the repair and regeneration of gut-associated lymphoid tissue would make excellent drug targets.

Researchers then compared HAART outcomes in those who chose to be treated within the weeks of exposure to those with chronic infection. They discovered that newly infected patients had fewer signs of inflammation at the beginning of the study and experienced greater recovery of the gut mucosal immune system function by the end of it.

Dandekar and her colleagues are currently following additional patients being treated with HAART. Unpublished data on these patients supports the current findings, said Thomas Prindiville, a gastroenterology professor at UC Davis and a co-author of the study.

“What we continue to see is that restoration of immune function is more likely when treatment is started early,” said Prindiville. “Starting HAART before T-cell counts fall below 350 cells per cubic milliliter, would preserve immune function and hasten its full recovery.”

The team of physicians and researchers plan to keep testing ways of improving the efficacy of antiretroviral therapy in gut-associated lymphoid tissue. These include treating gut inflammation, starting

treatment earlier and using gut biopsies to monitor treatment success.

“If we are able to restore the gut’s immune response, the patient will be more likely to clear the virus,” Prindiville said. “You can’t treat any infectious disease without the help of the immune system.”

The research was supported with grants from the National Institutes of Health.

Source: University of California, Davis