By Stefan Constantinescu, Science Editor

How HIV Kills Through a Diarrhea

Salmonella and HIV

HIV does not kill by itself. It just leaves humans defenseless against other killers. About 50% of all HIV-positive African adults die of Salmonella infection, a disease that otherwise is treated after a seven-day bout of diarrhea. A new research made at UC Davis School of Medicine and published in the "Nature Medicine" shows how salmonella becomes deadly in the case of AIDS patients. "We have found the defect in the immune response that allows Salmonella to cross the mucosal barrier of the gut, enter the bloodstream and infect other organs," said co-author Andreas Bäumler, a UC Davis professor of medical microbiology and immunology. The HIV infection of the intestine depletes of a type of white blood cell, called Th-17 (T helper lymphocyte), in the gut mucosa. These cells release a chemical messenger (cytokine) called IL-17, which signals the place of infection to the rest of the immune cells. "This kind of interruption in the gut's immune response could be allowing HIV to maintain reservoirs that evade drug treatments," said co-author Satya Dandekar, professor and chair of the department of medical microbiology and immunology. The non-typhoidal Salmonella serotype (NTS) is a bacterium commonly associated with food-borne infection worldwide, but usually, it is restricted to the gut, provoking gastroenteritis. This is not the case in AIDS patients, where the bacterium enters into the bloodstream, triggering NTS bacteremia. Dandekar had discovered in 2006 that HIV kept on multiplying in the gut mucosa, decreasing immune response in patients receiving antiretroviral therapy, even if T-cell numbers in blood samples showed that antiretrovirals had effect. "We think the real battle between an individual's immune system and HIV is happening in the gut mucosa where there is massive destruction of immune cells. Gut-associated lymphoid tissue accounts for 70 % of the body's immune system," said Dandekar.HIV-infected patients lose in time their T helper cells, which organize the immune attack on germs. "Unlike the steady decline of T cells in peripheral blood, there is a very rapid loss of T helper cells in the gut mucosa. We wanted to know whether the loss of the T helper cells in the gut contributed to the inactivation of the immune system one sees in HIV-infected patients," said Dandekar. The team imagined a technique that allowed the investigation of early intestinal responses to Salmonella infection in rhesus macaques with simian immunodeficiency virus (SIV), the monkey type of HIV. "We found that animals that had no SIV infection were able to generate immediate responses to bacterial exposure, producing Th17 cells in large amounts," said Dandekar said. But SIV-infected monkeys had weak or no release of cytokine. "This muted Th17 response led to dissemination of Salmonella from the gut to the peripheral blood," said Dandekar. Mice devoid of IL-17 receptor on their mucosa cells were vulnerable to Salmonella dissemination into their blood. "We believe IL-17 deficiency causes defects in the mucosal barrier of the gut," Dandekar said. Th17 seems to be a reliable biomarker for monitoring HIV infection and assessing the effect of vaccines and other therapies. "We are interested in looking at different molecules and compounds to see if we can boost mucosal immune defenses in the gut," said Dandekar. Th17 activity should also be monitored in long-term non-progressors, HIV positive persons that do not develop AIDS for years. The team could also detect how healthy gut cells get rid of Salmonella.