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HIV conquers immune system faster than previously realized

DURHAM, N.C. – New research into the earliest events occurring immediately upon infection with HIV-I shows that the virus deals a stunning blow to the immune system earlier than was previously understood. According to scientists at Duke University Medical Center, this suggests the window of opportunity for successful intervention may be only a matter of days – not weeks – after transmission, as researchers had previously believed.

Appearing in the August issue of the *Journal of Virology,* the finding may make the challenge of designing an effective HIV/AIDS vaccine appear daunting. But researchers say the study has also yielded a blueprint for what a successful vaccine should look like, and moreover, when such a vaccine would need to work.

Until now, scientists believed that the window of opportunity to intervene in the process of HIV-1 infection lay in the three to four weeks between transmission and the development of an established pool of infected CD4 T cells. HIV-1 cripples the immune system by invading and killing CD4 T cells, key infection-fighters in the body.

"But this new study shows that HIV-I does a lot of damage to the immune system very early in that time frame, and now we feel that the opportunity to intervene most effectively may range from about five to seven days after infection," said Barton Haynes, M.D., the senior author of the study and director of the Center for HIV/AIDS Vaccine Immunology (CHAVI) at Duke University Medical Center.

Haynes said the findings suggest that an optimal vaccine strategy would have to pack a double punch: First, establishing as much immunity as possible before infection, much as classic vaccines do, and then following a few days later with a mechanism to provoke a strong, secondary, broad-based antibody response. "Vaccine candidates to date have pretty much followed a single strategy. Now we know that we need to activate multiple arms of the immune system and we have a better idea of when to do it."

The conclusion comes from the study of 30 people who were newly-infected with HIV-1. Plasma from these individuals was sampled every three days for several months – before, during, and after the "ramp-up" phase of infection, when HIV-1 is multiplying rapidly and heading toward its peak viral load. In measuring the levels of four products of CD4 T cell death during this period in these samples, they were able to track and establish a timetable of the virus's destructive path.

The four byproducts of CD4 T cell death include TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), Fas ligand, TNF receptor type 2 and plasma microparticles, tiny bits of cell membrane that are broken up and left floating around in the plasma when the cell dies and breaks apart.

The researchers found that TRAIL levels increased significantly a full week (7.2. days) before peak viral load, which is approximately 17 days after HIV-1 transmission, suggesting that during the earliest period of infection, called the eclipse phase, TRAIL may actually initiate or hasten HIV-1's destruction of CD4 T cells. In contrast, they found that the levels of the other three cell death products were most significantly elevated during peak viral load.

"What this demonstrates is that significant T cell death is occurring much earlier during this period than we previously believed, and that TRAIL itself may be a co-conspirator in enhancing cell death," Haynes said. "This leads us to believe that the time frame for successful intervention has to move even close to the point of infection."

Researchers also examined the effects of cell death products upon B cells, another arm of the immune system responsible for the creation of antibodies. Previous studies have shown that the antibody response to HIV-1 is "too little, too late" – appearing after the virus has peaked and after the reservoir of infected T cells has already been established.

Through a series of in vitro laboratory experiments with peripheral blood cells, scientists found that microparticles suppressed levels of IgG and IgA, two classes of antibodies that normally would protect a person against infection. "This is important because many scientists believe that a fast-acting memory B cell response as well as a T cell response will be necessary to fight HIV-1" said Nancy Gasper-Smith, PhD, the lead author of the study.

Daniel Douek, M.D., PhD, chief of the Human Immunology Section of the National Institutes of Health, said the study sheds new light on key events in the earliest phase of infection. "The cohort is a gem. It is clear from the raised levels of TRAIL that the body senses the virus before plasma viral loads have peaked. This suggests that the virus begins to cause damage in ways

that may be unrelated to the well-described massive depletion of gut CD4 T cells that becomes apparent around peak viral load. For clinical practice, this means the window of opportunity in which antiviral therapies and vaccines must act is becoming ever narrower."

"These and other studies that recently revealed more about the singular nature of HIV-1 have given us valuable information that is helping us move closer to establishing a basic science foundation that can lead to novel technologies for vaccine design, Haynes said. Haynes. "It is becoming clearer why we have failed in our efforts to date, and what we need to confront to succeed in the future."

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Colleagues from Duke who contributed to the research include Deanna Crossman, John Whitesides, Nadia Mensali, Janet Ottinger, Steven Plonk, M. Anthony Moody, Guido Ferrari, Kent Weinhold, Sara Miller and Thomas Denny. Additional co-authors are David Pisetsky and Charles Reich, from the Durham Veterans Administration Hospital; Li Qin and Stephen Self, from Fred Hutchinson Cancer Research Center and the Statistical Center for HIV-AIDS Research and Prevention; George Shaw from the