Researchers achieve sustained viral remission in SIV infection

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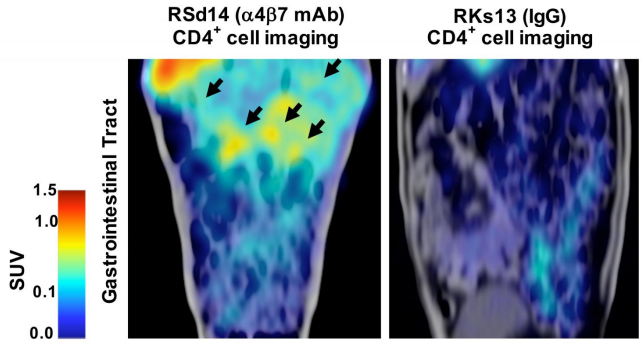

Immuno-PET/CT analysis confirms the preservation of CD4+ cells during a4b7 mAb treatment. Credit: Byrareddy et al., *Science* (2016)

Scientists have shown that they can achieve sustained control of infection by HIV's relative SIV (simian immunodeficiency virus) in rhesus macaques, by supplementing antiretroviral drugs with an antibody during and after drug treatment.

Sustained control means that when antiretroviral drugs were stopped, the virus did not re-emerge and cause disease. This was the first consistent demonstration of post-treatment immune control in monkeys infected with SIV, without previous vaccination. Post-treatment control of HIV has been reported in only a handful of people treated soon after infection.

Members of the research team at Department of Pathology, Emory University School of Medicine and the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, report that the virus is still present in the bodies of the antibody-treated monkeys. Yet it has stayed below the limit of detectability in their blood, lasting almost two years after withdrawal of antiretroviral drugs.

The results are scheduled for publication in *Science*.

The antibody the team used was designed to stop susceptible immune cells from entering intestinal tissues, a hot spot of damage during acute HIV and SIV infection. An analogous human antibody called vedolizumab was FDA-approved for the treatment of Crohn's disease and ulcerative colitis in 2014. Based on the current findings, a pilot clinical trial, testing the safety of vedolizumab and its effect on HIV in people infected with the virus, has begun at NIAID.

"This comes from an idea I had many years ago: stopping CD4+ T cells from circulating into the gut may protect them during acute infection," says senior author Aftab Ansari, PhD, professor of pathology and laboratory medicine at Emory University School of Medicine and Yerkes National Primate Research Center. "But how it precisely works in regulating viral replication is still far from clear. The antibody therapy appears to have helped reconstitute the entire immune system."

The co-first authors of the paper are Emory researcher Siddappa Byrareddy, PhD, now an associate professor at University of Nebraska Medical Center, and James Arthos, PhD, and Claudia Cicala, PhD both of the Laboratory of Immunoregulation. Arthos and Cicala worked under the overall direction of co-author Anthony Fauci, MD, director of NIAID. The study was conducted at Yerkes National Primate Research Center, Emory University. Collaborators at University of Maryland, University of Michigan and the German Primate Center contributed to the paper.

Several questions remain. How long can remission last? Which parts of the immune system are most important for viral control? And what differences between this experiment and HIV infection of humans might impede translation of this finding into the clinic?

More than a million people in the USA and more than 35 million worldwide are living with HIV, many of them for years. Although antiretroviral drugs can suppress viral replication, residual low-level infection and the drugs themselves can still negatively affect health. The virus integrates into the DNA of immune cells and is thought to lurk in hard-to-eradicate reservoirs.

In the *Science* paper, the antibody the team used is against alpha4-beta7 integrin, which helps T cells find their way to intestinal lymphoid tissues. In 2008, NIAID researchers identified alpha4-beta7 integrin as a cell surface molecule involved in the association of the virus envelope with CD4+ T cells, but the antibody does not appear to directly block viral entry. Previous research has shown that the administration of the same antibody can block SIV transmission in a significant number of rhesus macaques.

One possibly important difference between this experiment and HIV infection is that the macaques were infected for just five weeks, before beginning a three-month course of antiretroviral drugs. People usually don't discover they are HIV-positive so soon after infection.

At week 9, four weeks after starting on antiretroviral drugs, 18 monkeys began to receive infusions of the alpha4-beta7 antibody or control antibodies, every three weeks. Three developed antibodies against the alpha4-beta7 antibody and were excluded from further study. Drugs were withdrawn at week 18 and antibodies at week 32. When antiretroviral drugs were stopped, SIV came roaring back in the seven control animals. Six of eight alpha4-beta7 treated animals also showed some rebound of viral levels, but they controlled it within four weeks. The other two never even rebounded.

In the alpha4-beta7-treated monkeys, the researchers observed a gradual restoration of CD4+ T cells, the main target cells for the virus, and other immune cells. The team used a PET/CT imaging technique, developed by co-authors Philip Santangelo, PhD at Georgia Tech and Francois Villinger DVM, PhD at Yerkes, to visualize CD4+ T cells throughout the body.

Also, in the alpha4-beta7-treated monkeys, the team did not see neutralizing antibodies. HIV vaccine designers have made a goal of stimulating neutralizing antibodies, which may be able to prevent a nascent viral infection.

However, the researchers did see non-neutralizing antibodies against part of the envelope protein of SIV called the V2 loop. Antibodies against the V2 loop of HIV were beneficial in the RV144 study in Thailand, the only HIV vaccine study to demonstrate partial protection against infection.

"This finding could become a blueprint for an alternative therapy for HIV, which could make it so someone would not need to continuously take anti-retroviral drugs," Ansari says. "It could also help us craft more effective vaccines. We need to know more about how alpha4-beta7 antibody treatment exerts its effects."

Additional experiments are planned to determine which parts of the alpha4-beta7-treated macaques' immune systems are critical for maintaining control of SIV, he adds.

Before withdrawal of antiretroviral drugs, the alpha4-beta7-treated animals showed a restoration of the levels of retinoic acid, a derivative of vitamin A, and other immune regulators. Potentially, biomarkers like these could help predict whether someone's immune system is ready for stopping anti-retrovirals.

More information: "Sustained virologic control in SIV+ macaques after antiretroviral and ?4 ?7 antibody therapy," *Science*, science.sciencemag.org/cgi/doi … 1126/science.aag1276

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