HIV vaccines should avoid viral target cells, primate model study suggests

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Vaccines designed to protect against HIV can backfire and lead to increased rates of infection. This unfortunate effect has been seen in more than one vaccine clinical trial.

Scientists at Yerkes National Primate Research Center, Emory University, have newly published results that support a straightforward explanation for the backfire effect: vaccination may increase the number of immune cells that serve as viral targets. In a nonhuman primate model of HIV transmission, higher levels of viral target cells in gateway mucosal tissues were associated with an increased risk of infection.

The findings, published in *Proceedings of the National Academy of Sciences*, suggest that vaccine researchers, when evaluating potential HIV/AIDS vaccines, may need to steer away from those that activate too many viral target cells in mucosal tissues.

"One of the reasons why it has been so difficult to make an AIDS vaccine is that the virus infects the very cells of the immune system that any vaccine is supposed to induce," says senior author Guido Silvestri, chief of microbiology and immunology at Yerkes National Primate Research Center.

Silvestri is also a professor of pathology and laboratory medicine at Emory University School of Medicine and a Georgia Research Alliance Eminent Scholar. The first author of the paper is senior research specialist Diane Carnathan, PhD, and colleagues from the Wistar

Institute, Inovio Pharmaceuticals and the University of Pennsylvania contributed to the study.

A large part of the HIV/AIDS vaccine effort has been focused on developing vaccines that stimulate antiviral T cells. T cells come in two main categories, defined by the molecules found on their surfaces. CD8 is a marker for "killer" cells, while CD4 is a marker for "helper" cells. CD4+ T cells are known to be primary targets for HIV and SIV (simian immunodeficiency virus) infection, while several studies have proposed that CD8+ T cells could be valuable in controlling infection.

In this study, researchers immunized rhesus macaques with five different combinations of vaccines encoding SIV proteins found on the inside of the virus only. This experimental strategy was designed to examine the effects of cell-mediated immunity, without stimulating the production of neutralizing antibodies, in what scientists refer to as a "reductionist approach".

The monkeys received an initial immunization followed by two booster shots after 16 and 32 weeks. The monkeys were then exposed to repeated low-dose intrarectal challenge with SIV, once per week, up to 15 times. In general, the immunization regimens did not prevent SIV infection. While all the immunized monkeys had detectable levels of circulating "killer" CD8+ T cells, there was no correlation between these cells and preventing infection.

The most important result, however, was that the monkeys that became infected had higher levels of activated CD4+T cells in rectal biopsies before challenge, Silvestri says.

"This study shows that if a vaccine induces high levels of activated CD4+ T cells in mucosal tissues, any potential protective effect of the vaccine may be hampered," he explains.

The study emphasizes the unique challenges that HIV poses in terms of vaccine development, and the importance of pursuing vaccine concepts and products that elicit strong antiviral immune responses without increasing the number of CD4+ T cells in the portals of entry for the virus.

More information: *Proceedings of the National Academy of Sciences*, www.pnas.org/content/early/201 … /1407466112.abstract

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