

Study offers insights into failed HIV-1 vaccine trial

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Following the disbandment of the STEP trial to test the efficacy of the Merck HIV-1 vaccine candidate in 2007, the leading explanation for why the vaccine was ineffective - and may have even increased susceptibility to acquiring the virus - centered on the hypothesis that high levels of baseline Ad5-specific neutralizing antibodies may have increased HIV-1 acquisition among the study subjects who received the vaccine by increasing Ad5-specific CD4+ T-cells that were susceptible to HIV-1 infection.

Now, a study by Dan Barouch, MD, PhD, and a scientific team at Beth Israel Deaconess Medical Center (BIDMC), reported in the July 20 Advance Online issue of [Nature Medicine](#), shows this was likely not the case.

"Our findings demonstrate that there is no correlation between Ad5 [neutralizing antibodies](#) and T-cell immune responses," explains Barouch, who is Chief of the Division of Vaccine Research at BIDMC and Associate Professor of Medicine at Harvard Medical School. "Moreover, subjects with baseline Ad5-specific neutralizing antibodies did not develop higher levels of Ad5-specific T-cell responses as compared with subjects without baseline Ad5-specific neutralizing antibodies."

The Ad5 virus is a weakened form of adenovirus, which is responsible for the common cold and is extremely widespread in the general population. In the Merck [vaccine candidate](#), Ad5 was used as a vector to transport three HIV-1 genes, a strategy that helps to overcome

limitations posed by the HIV-1 virus.

"Because HIV-1 does not appear to respond to conventional vaccine strategies, which work by triggering the body's immune system to manufacture antibodies against an infectious organism, the STEP trial was testing a vaccine that would, instead, stimulate the immune system's killer T-cells to root out and disable the virus," explains Barouch. While this method does not eradicate HIV-1, the thinking is that it helps the immune system launch a more aggressive response in the event a person is exposed to HIV-1.

However, prior exposure to the Ad5 cold virus leaves a large number of individuals with baseline neutralizing antibodies against Ad5. "This raised the possibility that these antibodies were triggering production of Ad5-specific T-cells [CD4+] that were susceptible to HIV-1 infection, thereby leaving study subjects at greater risk of acquiring the virus itself," explains Barouch. "But our findings challenge this hypothesis. It does not appear that the potential enhancement of the HIV-1 infection in the STEP study was the result of these secondary, vector-specific CD4+ T-cell responses."

Going forward, Barouch suggests another alternative.

"Safety considerations, including the possibility that vector-specific cellular immunity may impact HIV-1 susceptibility, have become major concerns for the HIV-1 vaccine field," notes Barouch. "Our findings suggest a path forward for HIV-1 vaccine development by using rare serotype vectors [not typically found in the general population] that are not suppressed by high levels of baseline vector-specific neutralizing antibodies." Barouch and colleagues are currently conducting Phase 1 clinical trials to test two such novel HIV-1 vaccines.

Source: Beth Israel Deaconess Medical Center

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