

# Behind the Rising Doubts About Hailed AIDS Vaccine

By ALICE PARK Tuesday, Oct. 13, 2009

<http://www.time.com/time/health/article/0,8599,1929921,00.html>

It is an emotional cycle familiar to most AIDS-vaccine researchers: the high of finally making measurable headway against HIV, followed by the crushing low of discovering that the virus has once again found a way to elude them.

It happened again on Saturday when researchers learned that the first ever successful AIDS vaccine turned out not to be the triumph they had originally hoped. In September, scientists from the National Institutes of Health (NIH) and the U.S. Army announced the results of an AIDS-vaccine study in Thailand involving more than 16,000 volunteers. The data showed that the new vaccine had protected 31% of inoculated participants from becoming infected with HIV. But a closer look at a subset of the study's volunteers now reveals that the vaccine in fact protected only 26% of the people who received it. **(See pictures of Africa's AIDS crisis.)**

The difference is small but critical because the new success rate of 26% falls below the threshold for statistical significance. That means that the odds of being protected from infection by the AIDS vaccine may be no better than chance.

At issue is a matter of head count. If the entire group of volunteers who were enrolled in the study were included in the data, then the results would suggest a 31% effectiveness rate, with 51 in the vaccine arm and 74 in the control group becoming infected with HIV. These are the results that were announced in September. But because this particular vaccine comprised two older vaccines that were given in six doses over a six-month period — in what is referred to as a prime and boost regimen, in which the early shots prime the immune system to fend off HIV and the follow-up shots boost the body's immunity — some volunteers became infected with HIV before receiving all six shots, rendering them ineligible to complete the study. Had the study been designed to license the vaccine, researchers would be aiming to study how well the complete set of inoculations protects against infection, and would have focused primarily on the volunteers who became infected after receiving all six doses. **(Watch an audio slideshow about aging AIDS patients.)**

The resulting tally, then, would include a much smaller pool of participants, which automatically lessens the significance of whatever effect, if any, the vaccine appeared to have, says Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases. "When you lose statistical power, something that would have been significant in the [original, larger] population, could now fall below significance merely by the lower numbers. That's what happened with this trial," Fauci says.

According to Fauci, however, the trial was not designed to license the vaccine but to test whether the concept of using the two vaccines in sequence would work. In the latter condition, statisticians say scientists generally consider all data from the complete, original population, since these numbers more accurately reflect what might happen in the real world. In other words, it's a more rigorous analysis of how effective a vaccine might be in a population of people who, realistically, could be exposed to HIV before they finish the full six doses of the vaccine.

As for why investigators did not reveal both sets of data in their initial announcement, the Army researchers posted [this update](#) on the website of the U.S. Military HIV Research Program: "Explaining the differences between them is complex and the appropriate venue for this technical discussion of statistics is at an open scientific conference and in the scientific publication now under review at a major journal." **(See the most common hospital mishaps.)**

So does this mean the vaccine was not effective? That depends on whom you ask. Some experts argue that the vaccine's effect, if it exists, is so tiny that it's not worth pursuing in a significant way. They also question whether such a large trial can be considered as a proof of concept. "Doing a 16,000-person trial, it can't be a proof of concept at that point," says Dr. David Ho, director of the Aaron Diamond AIDS Research Center in New York City. "Would I invest in it? The answer is no. There are other things that are more likely to work, that are better, easier and more straightforward than this vaccine."

Fauci acknowledges that the vaccine's effect is small, but believes that it's an important first step toward understanding how the body fights off HIV. "It's barely significant, yes," he says. "But it's interesting in that it opens up a door for us to be able to pursue more research." Although the number of volunteers who were protected were few, they are still the first who may have been protected at all by an AIDS vaccine and are therefore considered a valuable starting point.

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Still, the manner in which the trial results were released raised suspicions among some in the AIDS-research community. Scientific results are generally vetted in a two-step process: first, they are published in a peer-reviewed journal, which means a panel of scientists has reviewed and evaluated the validity of the study's methods and the authors' conclusions before publication; once published, other research groups repeat or analyze the data in more depth to further ensure that they are legitimate. The results of the AIDS-vaccine trial did not benefit from either leg of this process. The investigators chose instead to announce the results in a press conference in Thailand, at the request of the Thai government, which wanted to inform its citizens of the positive findings as soon as possible. A U.S. press conference, including the U.S. Army researchers and Fauci, was

held several hours later, with a promise to follow up with more detailed data in a presentation at the annual AIDS Vaccine Conference in Paris on Oct. 20. **(See how to prevent illness at any age.)** To confound matters further, after the Thai press conference, a select number of scientists received confidential data on the study. After reviewing the numbers, some of them discussed their concerns over the discordant statistics with journalists at *Science* magazine's *Science Insider* blog and the *Wall Street Journal*.

From the outset, the vaccine strategy used in the NIH and U.S. Army study — giving two older vaccines in succession — has been controversial. In previous trials, each vaccine had failed to provide any protection against HIV, and in September 2004 a group of adamant scientists wrote a letter to *Science* arguing that the National Institute of Allergy and Infectious Diseases should not to continue with the trial. "We seriously question whether it is sensible now to conduct a ... trial that, in our opinion, is no more likely to generate a meaningful level of protection against infection or disease," they wrote.

The scientists' skepticism about the strategy seems to be at least partially justified. But even so, at least one of the 22 authors of that *Science* letter is waiting for the release of the full set of data before acknowledging complete vindication. "I think I will wait until after the Paris meeting next week to see more of the data before making any comments," wrote Dennis Burton, an immunologist at Scripps Research Institute, in an e-mail response to a request for his reaction.

While unfortunate, Fauci says the circumstances surrounding the release of the data should not detract from the potential benefit the results may yet extend to AIDS-vaccine research. The trial was never intended to serve as a demonstration of effectiveness to license a new vaccine, he says. As such, it was a proof-of-concept study that showed it is indeed possible to generate an immune response against HIV — even if only a small one.

**Correction:** *The original version of this article misstated that some AIDS researchers received confidential data prior to the Thai press conference in September; they received the data after. The article also misstated that these researchers published their concerns on the website of the journal Science; in fact they gave interviews to a Science reporter. Clarification:* *The original article did not elucidate the particular conditions under which researchers would analyze a smaller subset of clinical trial data, rather than the complete, original set; those details have been incorporated in the text.*

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