Understanding the Thai Prime-Boost Vaccine Trial Results Update

October 2009

What was the Thai Prime-Boost trial?

The Thai prime-boost test-of-concept trial, also known as RV 144, began in 2003 and enrolled more than 16,000 HIV-negative Thai men and women between the ages of 18 and 30. It was conducted by the Thai Ministry of Public Health, sponsored by the US Army Surgeon General, managed by the US Military HIV Research Program and funded by the Division of AIDS of the National Institutes of Allergy and Infectious Diseases, NIH, and the US Army Medical Research and Materiel Command. The trial tested a combination of two vaccines: ALVAC HIV vaccine (the prime) and AIDSVAX B/E vaccine (the boost). The trial results were first released on September 24th stating that the prime-boost combination of ALVAC HIV and AIDSVAX B/E lowered the rate of HIV infection by 31.2% compared with placebo (*http://www.avac.org/ht/d/sp/i/3373/pid/3373*).

What additional data were presented at the AIDS Vaccine Conference?

On October 20, the Thai Prime-Boost trial team presented expanded analyses at the AIDS Vaccine 2009 Conference. These data were also published in the *New England Journal of Medicine;* the scientific article along with an accompanying editorial can be downloaded for free at the NEJM website: http://content.nejm.org/.

In the article and at the AIDS Vaccine Conference, the Thai trial team compared rates of infections in vaccine and placebo recipients using three different ways of analyzing the data: Intent to Treat (ITT), modified Intent to Treat (mITT) and Per Protocol (PP). Once a clinical trial is completed, it is standard to analyze data using several different statistical methods. This is to account for some of the complexities and realities experienced while conducting a trial. In each of the analyses different numbers of individuals were used:

- The Intent to Treat (ITT) analysis included all participants who were randomized and received any injections (the full course was six injections, but not all participants completed the full course).
- The modified Intent to Treat (mITT) included all participants who were randomized and received any injection (as with the ITT analysis) BUT excludes seven individuals who were originally believed to be HIV-negative at baseline, but were later determined to be HIV-positive at baseline. The mITT analysis is the analysis that was pre-specified in the trial's statistical analysis plan and used as the primary analysis for Data and Safety Monitoring Board reviews throughout the trial
- The Per Protocol (PP) analysis included all participants who were HIV-negative at baseline and who followed the protocol procedures exactly - including completing the full course of injections at the specified times defined in the protocol.

Since each of these analyses looked at a different numbers of individuals, each yielded slightly different results. However, all of the analyses followed the same trend of fewer infections in the vaccine recipients compared to the placebo recipients. The results from each type of analysis are described below:

Thai trial data	***Analysis***		
	ITT	***mITT***	***PP***
Participants	16,402	16,395	12,542
Infections in vaccine group	56	51	36
Infections in placebo group	76	74	50
Vaccine efficacy	26.4%	31.2%	26.2%
95% Confidence Interval	-4.0, 47.9	1.1, 51.2	-13.3, 51.9
P-value	0.08	0.04	0.16
Statistically significant?	No	Yes	No

So, did the vaccine have an impact on risk of HIV infection?
Yes—although a modest one that needs to be explored and better understood through additional data analyses. One of the most important facets of the Thai data is that all three analyses: ITT mITT, and PP show the same trend. In every case, there are fewer infections in the vaccine arm as compared to the placebo arm, indicating a reduction in risk of acquiring HIV between 26.2% and 31.2%. While only the mITT analysis was statistically significant (which means that the observed difference is very likely due to the effect of the vaccine) the fact that all the analyses trend in the same direction provides strong evidence that there was a modest vaccine effect.

What else do the data presented so far tell us?
As the trial collaborators presented at the conference, and as the published results indicate, there are no statistically significant conclusions that can be drawn about whether the vaccine worked better in high- versus low-risk individuals, men versus women or other demographic subgroups. There's also no clear answer about the respective contributions of each vaccine to the observed effect of the regimen. We don't know whether the protection was a result of ALVAC plus AIDSVAX or a single component on its own. Finally, there's no explanation yet for which types of immune responses were responsible for the observed protection.

What's the next step?
The next step for the Thai trial team, and the broader scientific community involved in AIDS vaccine research, is to look more closely at the data to understand as much as possible about the findings. The trial team has established a committee structure including a scientific steering committee with numerous advisory groups (humoral and innate immunity, cellular immunity, host genetics, animal models) and a product development advisory group that will provide independent expertise and advice on how best to proceed with additional analyses. In addition, they plan to establish an online submission process so other researchers can propose other studies that might be conducted with the samples collected from the trial. (This process is similar to the one established by the HIV Vaccine Trials Network for further analysis of the Step trial samples, which have generated important additional information.)

What's the bottom line for advocates?
The Thai Prime-Boost trial showed a modest reduction in risk of HIV infection in those participants who received the vaccine regimen (ALVAC plus AIDSVAX). The fact that the finding was statistically significant in one analysis and not in another doesn't mean that the finding itself is not real. The lack of statistical significance may be due to the very small number of infections and the modest vaccine effect.

There is still every reason to treat the results of the Thai trial as an important scientific breakthrough—in that they are the first evidence in humans that a vaccine can protect against HIV infection.

Moreover, the Thai prime-boost results are part of a larger AIDS vaccine discovery effort that is continuing on multiple fronts including basic science, clinical research, non-human primate research and many related disciplines. The AIDS Vaccine Conference at which the results were presented is a reminder of the scope and intensity of this effort—and of the urgent need to continue and build on the energy and excitement provided by the Thai result.

In the coming weeks, AVAC will issue an updated and expanded version of this *Understanding Results* document on the Thai trial and will also convene additional forums for advocates to discuss and learn about this finding and what it means for communities in Thailand and around the world. Additional background information is available at: *http://www.avac.org/ht/d/sp/i/3373/pid/3373.*

The latest issue of *Px Wire* with an initial summary of the Thai trial with key questions is available at: *http://www.avac.org/ht/a/GetDocumentAction/i/3432.*

AVAC's *Anticipating the Results of the Phase III AIDS Vaccine Trial in Thailand* was designed to help advocates prepare in advance for the initial announcement and provides basic background on the trial and is available in English: *http://www.avac.org/ht/a/GetDocumentAction/i/3377* and in Thai: *http://www.avac.org/ht/a/GetDocumentAction/i/3379.*

About AVAC: Founded in 1995, AVAC is an international, non-profit organization that uses education, policy analysis, advocacy and community mobilization to accelerate the ethical development and eventual global delivery of AIDS vaccines and other new HIV prevention options as part of a comprehensive response to the pandemic. For more information, visit www.avac.org.