

# Treatment

## Understanding the results of RV144, the Thai prime-boost AIDS vaccine trial

By Deirdre Grant and Emily Bass

In September 2009 the world learned the initial results of RV144, known as the Thai prime-boost AIDS vaccine trial. This study was the largest AIDS vaccine trial to date, with over 16,000 participants. It evaluated the efficacy of a vaccine regimen consisting of two candidates, known as ALVAC HIV and AIDSVAX B/E. The trial data indicated that the vaccine regimen reduced HIV risk by approximately 30 percent. This is the first time a trial has found evidence that it is possible to reduce the risk of HIV infection with a vaccine. While this does not mean that an AIDS vaccine will be available in clinics anytime soon, the evidence that a vaccine can protect against infection is unprecedented. Scientists will spend the coming months reviewing the data, and testing blood samples from the trial to discover how the vaccine may have protected some trial participants. Researchers are already working hard to understand what these findings mean and to identify key next steps.

### What was the Thai prime-boost trial and how was it designed?

The Thai prime-boost test-of-concept trial began in 2003 and enrolled more than 16,000 HIV-negative Thai men and women between the ages of 18 and 30. A number of Thai and U.S. government collaborators worked on the trial. A combination of two vaccines was tested: ALVAC HIV vaccine (the prime) and AIDSVAX B/E vaccine (the boost). The trial was designed to evaluate whether this vaccine regimen reduced risk of HIV infection and/or whether participants who received the vaccine and later acquired HIV had lower viral loads than those who received the placebo and acquired HIV.

The trial was supported by the World Health Organization (WHO) and UNAIDS, whose HIV

Vaccine Advisory Committee (VAC) found that the trial was conducted to the highest scientific and ethical standards and with active community participation.<sup>1</sup>

### What data are available?

The initial data analysis was published in the *New England Journal of Medicine* in October 2009. The trial team used various statistical methods to compare rates of infections in vaccine and placebo recipients to determine whether the vaccine regimen had any effect on HIV acquisition or viral load in those who seroconverted. It is standard to use three different ways of analyzing the data: Intent to Treat (ITT), modified Intent to Treat (mITT) and Per Protocol (PP)<sup>2</sup>. The use of multiple statistical analyses helps scientists understand the data in greater detail in light of the complexities and realities of clinical trials.

Each of these three analyses looked at a different number of individuals and therefore yielded slightly different results. However, all of the analyses' findings followed the same trend of fewer infections in the vaccine recipients compared to the placebo recipients. One of the most important facets of the Thai data is that all three analyses show the same trend. In every case, there were fewer infections in the vaccine treatment group as compared to the placebo treatment group, indicating a reduction in risk of acquiring HIV between 26.2% and 31.2%. While only one of the three analyses was statistically significant (which means that the observed difference is very likely due to the effect of the vaccine, and not to chance), the fact that all analyses trend in the same direction provides strong evidence that the vaccine did reduce the risk of HIV infection in some volunteers.

The vaccine regimen had no effect on post-infection viral load levels among the recipients who became

infected. This vaccine was developed with the aim of preventing new infections and thus was only tested in HIV-negative individuals. There are trials of therapeutic vaccines that are being studied to determine their effectiveness at treating people currently living with HIV.

### Regional data limitations

The trial data are from a single trial in Thailand. The data from the trial do not provide information on whether this specific strategy would have a benefit in areas where other HIV virus subtypes predominate. The vaccine included synthetic fragments of genetic material from HIV subtypes B and what is often referred to as subtype E, but is more accurately classified as CRF01 AE. These are two of roughly nine circulating subtypes, or clades, of HIV worldwide. Subtype E is common in Thailand and Southeast Asia, while different subtypes predominate in other regions of the world. The trial data indicated the vaccine had a protective effect in an area with HIV subtype E, which is prevalent in Southeast Asia. There is not yet evidence that the vaccine would be effective in areas where other subtypes are prevalent.

### What happens next?

The RV144 trial steering committee has convened a scientific steering committee and a product development advisory group. Independent scientific advisory groups ensure that the expertise of the broader AIDS vaccine field is brought to bear on challenging, potentially field-altering results.

The scientific steering committee for the RV144 trial consists of four working groups, each including a range of scientists from outside the trial team. Those groups will explore the implications of the Thai trial data for the evaluation and design of other AIDS vaccine candidates and studies and make recommendations for the field. The trial steering committee plans to establish an online submission process for researchers to propose potential studies using lab samples collected from the trial. The product development working group is currently considering the options and implications for future clinical development of the ALVAC-AIDSVAX regimen.

### What are some of the challenges that lie ahead?

The Thai trial results are the beginning of an exciting chapter in AIDS vaccine research. There are unique challenges and opportunities that have already started to emerge. These include (but are not limited to):

**Limited numbers of samples:** Every trial collects specific quantities of blood (and sometimes other samples)

from its participants. At the end of the study, these samples can be used for a range of analyses to learn more about what happened. For the Thai prime-boost trial, the number of questions about the biological mechanisms underlying the observed effect far exceeds the number of samples available for further analysis. This means that there will be challenging choices about which analyses to conduct using the samples available. The steering committee and scientific advisory group described above will help make these difficult choices. It will also be critical for proposals submitted by outside researchers through the online process to be considered. These experiences with data analysis should be used to shape future trials' approaches to sample collection and data sharing.

**Striking the balance between seeking a correlate of protection and developing a product:** Right now the field is interested in finding out what types of immune responses were responsible for the apparent vaccine effect.

There is also interest in developing the regimen—either as is, or with modifications—as a product for

further study on its own. There are many licensed vaccines in use today that work in ways that are not understood. The Thai regimen could be studied in future trials without detailed knowledge of how exactly it provides protection. The challenge facing all of the stakeholders in the field is to map out a way forward that balances both agendas: to learn as much as possible about how the Thai vaccine regimen provided protection and to carefully consider whether the regimen should be studied in future trials.

### What now?

While the field is reinvigorated by the recent Thai prime-boost vaccine results, advocates continue to note the importance of comprehensive prevention. Even if the vaccine regimen had shown to be effective enough to warrant licensure in Thailand, it would not be a replacement for other methods of prevention, including male and female condoms, behavior change counseling, male circumcision, needle exchange and harm reduction. Any new strategy will need to be delivered and used as part of a multi-faceted approach.

The results of the Thai trial are a boon to AIDS vaccine research. While a highly effective licensed vaccine is still many years away, the evidence that one is possible is a new and exciting discovery for the field.

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