



ANTICIPATING THE RESULTS OF THE PHASE III AIDS VACCINE TRIAL IN THAILAND

Preparing for results from the ALVAC-AIDSVAX Prime-Boost vaccine trial

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TABLE OF CONTENTS

Preparing for data: What will we know, and when? 1

What vaccine regimen did the Thai vaccine trial test? 2

Historical perspectives on the trial 2

HIV subtype and vaccine design 3

What was the trial design? 4

What kinds of results might come from the trial? 5

What happens if there is no effect? 5

What happens if there is a positive result? 6

Looking ahead 7

BOXES, FIGURES & TABLES:

Box: Advocates' Guide to Statistical Terms 3

Box: Why is the trial looking for vaccine impact on viral load? 5

Map: Thai Trial Locations 7

Table: Timeline of Results from AIDS Vaccine Efficacy Trials 8

PREPARING FOR DATA: WHAT WILL WE KNOW, AND WHEN?

In September 2009 results will be released from an AIDS vaccine phase III trial in Thailand. This test-of-concept trial is the largest AIDS vaccine trial ever conducted. The study, 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. The study was conducted by the Thai Ministry of Public Health (MOPH), sponsored by the US Army Surgeon General, and managed by the US Military HIV Research Program. The US National Institute of Allergy and Infectious Diseases (NIAID) and the US Army Medical Research and Materiel Command provided funding, with in-kind contributions from vaccine manufacturers Sanofi Pasteur and Global Solutions for Infectious Diseases (GSID). (GSID now holds the intellectual property rights to the AIDSVAX vaccine included in the trial which was originally manufactured by Genentech, and developed and previously owned by VaxGen.)

In late September, the first announcement of data will focus on the general findings: whether there was any evidence of vaccine impact on HIV infection and/or viral load. More detailed information on the findings will be released at the annual AIDS Vaccine Conference in Paris (October 19-22). Regardless of the content of these two announcements, in-depth analysis of the findings will continue well beyond October.

This document is designed to help advocates prepare for the initial announcement. AVAC will provide an updated and expanded version of this report after data are released.



WHAT VACCINE REGIMEN DID THE THAI VACCINE TRIAL TEST?

The vaccine regimen included two vaccine candidates: ALVAC-HIV (vCP1521) and AIDSVAX B/E. The strategy involved a total of six immunizations over six months: four immunizations (months 0,1,3,6) with ALVAC-HIV and two (months 3,6) with AIDSVAX B/E.

This combination of two different vaccines is called a *prime-boost* approach. In such an approach, two vaccines are given sequentially. The intent of this approach is to induce different types of immune responses and enhance the overall immune response compared to that seen if only one type of vaccine is given for all the doses.

The first vaccine used in the regimen, ALVAC-HIV, is a viral vector carrying synthetic versions of three HIV genes (*env*, *gag* and *pro*). A vector is a vaccine component that serves as a carrier. Vectors are selected for their ability to introduce the vaccine immunogen (in this case, the HIV genes designed to induce the HIV immune response) to the body. The ALVAC vector is a disabled form of a bird virus called canarypox, which has been altered so that it cannot make copies of itself or cause disease in humans.

Different AIDS vaccine candidates using the ALVAC vector were tested for safety in multiple smaller human trials in France, Thailand, Uganda and the US prior to the launch of the Thai Prime-Boost trial. All of these trials found the vaccine to be safe and well tolerated. The vaccine itself cannot cause HIV.

In these earlier studies, volunteers' blood samples were analyzed to learn about the immune responses caused by the vaccine. Scientists do not know exactly what kind of vaccine-induced immune responses, or immunogenicity data, will predict whether a vaccine will provide protection against HIV infection or disease. This is one reason why it is critical to test candidates in larger human efficacy trials.

Even though immunogenicity data cannot predict vaccine success, they contribute to decisions about which candidates are evaluated in efficacy trials. The trial partners' decision to move ahead with the efficacy trial in Thailand was informed by the immunogenicity data from these early studies of ALVAC candidates.

Some of these trials looked at strategies that combined ALVAC with vaccine candidates, like AIDSVAX, that are composed of a genetically engineered version of gp120, a protein on the surface of HIV.

Prior to its inclusion in the Thai Prime-Boost trial, AIDSVAX was evaluated on its own in two large efficacy trials—one trial tested the vaccine in Thai injection drug users (IDUs) and one largely in gay men and other men who have sex with men (MSM) in the US, Canada and Europe. Neither of these trials found any benefit. However, AIDSVAX was safe and well tolerated in both of these trials, and there was no evidence of vaccine-related harm. The data from the AIDSVAX trials were released in 2003.

HISTORICAL PERSPECTIVES ON THE TRIAL

The decision to move the ALVAC-AIDSVAX combination into an efficacy trial generated controversy. One reason for this was the previous history of the AIDSVAX candidate. During the planning for the Thai Prime-Boost trial, critics argued that AIDSVAX had not shown efficacy on its own and should therefore be abandoned. They also pointed out that if there were evidence of benefit from the planned trial, it would be impossible to know whether that benefit came from the vaccine combination or from the ALVAC-HIV component alone. Because of these and other factors, there has been scientific disagreement about whether this regimen was worth testing in a large, long efficacy trial. Few, if any, large-scale trials move forward with unanimous support. In this instance, investigators went through a series of reviews internationally that indicated the trial was well-designed and ethical, and they had the necessary funding and support, so the trial moved forward.

HIV SUBTYPE AND VACCINE DESIGN

Both of the vaccines tested in this regimen contain synthetic fragments of HIV that are based on HIV subtypes B and E. HIV has tremendous genetic variability. Different subtypes, or clades, of genetically related HIV viruses are found in different parts of the world. Subtype E is the most common subtype found in Thailand and Southeast Asia. Subtype B is common in the US and Europe.

A finding of benefit in this trial—should one be found—would apply to situations in which the vaccine matches one of the predominantly circulating subtypes. The Thai trial wouldn't provide information on whether this specific strategy would have benefit in areas where other subtypes were predominant. This is one of several reasons why additional research would be needed in the event of any positive finding.

ADVOCATES' GUIDE TO STATISTICAL TERMS

No study can produce a simple “yes” or “no” on whether a vaccine worked. To decipher the headlines and discussions regarding the data from this or any trial, it is useful to understand some statistical terms used to describe a trial result. For the Thai trial, the data analysis will include comparisons of rates of infections in vaccine and placebo recipients and the viral load levels in vaccine and placebo recipients who became HIV-infected during the trial.

One key term is **statistical significance**. If a result is described as statistically significant, it means that an observed difference (for example between rates of new infections in two arms of a vaccine trial) is very likely due to the vaccine and is not a coincidence. Significance is always given with a **confidence level**. A 95 percent confidence level, which is standard for many trials, means that there is at most a 5 percent likelihood of a statistically significant result having occurred solely by chance.

The trial team will also report on the **confidence intervals** associated with its findings. A confidence interval is a way of describing the reliability of the finding, which is given as a point estimate—such as a 50 percent reduction in risk of infection. The narrower the confidence interval around a point estimate, the more likely it is that the result is accurate and would be seen again if the trial was repeated.

This can be confusing because all these values are interrelated, but to fully understand the strength of a result, one must know (1) the point value; (2) whether the result is statistically significant; (3) the confidence level, which may be expressed as a percent (95 percent or more) or a p-value (.05 or less); and (4) the confidence interval.

Other terms that might be used in discussion of initial results are **per-protocol** (PP) and **intent-to-treat** (ITT) analyses of results. PP results only include infections that occurred in those participants who received the full course of vaccinations. ITT results count every infection after trial enrollment, regardless of whether a participant completed the full regimen. ITT is considered a gold standard because it considers every randomized participant. Both approaches provide important information. The safest route is to report both PP and ITT and to analyze any difference.

Advocates' take-home message: no matter what the headlines say, a single number is not the full result.

WHAT WAS THE TRIAL DESIGN?

The Thai Prime-Boost trial enrolled more than 16,000 HIV-negative men and women aged 18-30 from the Thai provinces of Rayong and Chon Buri. Several institutional review boards in Thailand and the US approved the trial design. This approval indicates that the review bodies found the trial design to be protective of the rights and welfare of the research participants. During discussions about whether the trial should go forward, the protocol was also considered and endorsed by the AIDS vaccine advisory committee of the US National Institute of Allergy and Infectious Diseases.

All participants in the trial received a standard prevention package, including treatment for sexually transmitted infections, condoms and behavior change counseling.

The trial was designed to evaluate whether

- 1) Participants who received the vaccine regimen plus the standard prevention package had lower risk of HIV infection than did those participants who received a placebo plus the standard prevention package;

and/or

- 2) Participants who received the vaccine regimen plus the standard prevention package and were subsequently infected with HIV had a lower viral load set point compared to individuals who received the placebo plus standard prevention package and became HIV infected.

The trial also evaluated safety of the vaccine regimen and gathered data on rates of reported risk behavior among trial participants over the course of the study. No safety concerns were identified by an international Data and Safety Monitoring Board, which met eight times over the course of the trial. It therefore seems unlikely that the final trial data will indicate vaccine-related harm, although this is always a possibility.

In the trial design, half of the participants were randomly assigned to receive the vaccine, with the other participants assigned to receive a placebo—a

harmless, inactive substance that looks like the vaccine but has no active ingredients and no effect on the body. The trial was double-blinded, meaning no participants, clinical staff or scientific investigators knew who received the experimental vaccine versus placebo. Each participant was counseled at every study visit that there was no evidence of the vaccine providing benefit; that they should assume that they had received the placebo; and that they should continue to use proven HIV prevention strategies to reduce their risk of contracting HIV.

Over the course of the trial, some participants became infected in spite of best efforts to reduce risk of HIV infection. This is consistent with what researchers and advocates know about the AIDS epidemic: even with information and services, people still acquire HIV.

The study's inclusion criteria were not aimed at recruiting members of specific high-risk groups, such as injection drug users. Trial participants were recruited from the general population. Overall, there was a relatively low rate of new infections (incidence rate) in this general population cohort. This low incidence rate informed the trial design and the number of volunteers enrolled in the study. Conclusions about whether a new HIV prevention strategy reduces risk of HIV are based on comparison of numbers of new infections in the intervention and placebo arms of the study. Trials are designed with the goal of being able to make statistically valid comparisons between these two arms. As the size of the Thai trial indicates, in settings where the HIV incidence rate is low, many participants must enroll to answer the study question.

All individuals who acquired HIV during the trial were counseled by the research team and referred to receive medical services from the Thai MOPH. Since 2000, Thailand has had a national treatment plan whereby the government provides antiretroviral therapy to those in need. All those who seroconverted in the vaccine trial were followed routinely and received antiretroviral treatment as per MOPH guidelines. If a participant became infected, whether in the vaccine or placebo arm, he or she was given the option of enrolling in a separate, longer-term study (RV 152), which included follow-up of HIV-infected participants.

At the end of the ALVAC-AIDSVAX trial, researchers will compare the rates of new infections in the participants who received the vaccine to those who received the placebo. They will also compare viral load measurements from individuals who became HIV-infected to determine whether there was any difference in viral load between participants who received the vaccine and went on to become HIV-infected and those who received the placebo and subsequently became infected.



WHY IS THE TRIAL LOOKING FOR VACCINE IMPACT ON VIRAL LOAD?

Observational data from other studies suggest that people with lower viral load set points have slower disease progression than do people with higher viral load set points. Set point is the level of viral load in the blood after the initial period of HIV infection. A vaccine that reduced viral load by a substantial amount could provide a clinical benefit for people who received the vaccine when they were HIV-negative and who later became HIV-infected. In theory, a vaccine strategy that reduced viral load could also help delay the time to initiation of antiretroviral therapy and perhaps reduce individuals' risk of transmitting HIV to their sexual partners.

A finding of a viral load impact from any AIDS vaccine trial would help advance AIDS-vaccine and medical science. It could also create confusion because many people's concept of a vaccine is an intervention that prevents symptomatic disease. Civil society groups in several countries are among partners considering the issues related to this terminology, the underlying concepts and how best to communicate this information more broadly.

WHAT KINDS OF RESULTS MIGHT COME FROM THE TRIAL?

Any clinical trial may show no effect, but if there is a positive result, it will be one or both of the following:

- The vaccine strategy reduces risk of HIV infection.
- The vaccine strategy reduces viral load in participants who receive the experimental vaccine regimen and go on to become infected.

Even a modest indication of either of these benefits will be exciting news for the field. It would be the first time that an AIDS vaccine shows an impact on either risk of infection or viral load.

WHAT HAPPENS IF THERE IS NO EFFECT?

There might be no evidence of benefit. If there were no detectable differences between those who received the vaccine and those who received the placebo (i.e., the rates of infection and viral load set point in infected participants are the same in both the vaccine and placebo groups), these vaccines would not be developed any further.

Nonetheless, researchers would still gather important information from this trial. They would be able to look at the infecting viruses and types of immune responses generated in participants to learn about what defenses do not provide protection.

Regardless of the outcome, there will be scientific lessons learned from the trial itself and important lessons from the experience of recruiting and retaining 16,000 participants in a community-based trial—the largest AIDS vaccine trial ever to take place. Getting a flat or negative answer is not the same as a failed trial. A trial is successful if it gives a clear result, even if that result is disappointing.

WHAT HAPPENS IF THERE IS A POSITIVE RESULT?

A positive finding would advance AIDS vaccine science. This trial was launched in 2003 in the midst of skepticism and is concluding when recent results from the Step and Phambili trials have triggered debates about the feasibility of developing AIDS vaccines aimed at T-cell responses. Like MRK-Ad5, the vaccine tested in Step and Phambili, the regimen evaluated in the Thai trial induces HIV-specific T-cells. A positive finding, no matter how small, would give scientists the chance to look more closely at what kinds of immune responses—including T-cells—might contribute to some form of protection. (By the same token, the debate about T-cell vaccines will not be settled even if there is no evidence of benefit from this trial.)

There would also be big questions about next steps. Some of the issues that might emerge are listed below. If there is any finding of benefit from the trial, these and other issues will be discussed in greater detail in an expanded version of this document. Please visit www.avac.org, or subscribe to AVAC's Advocates' Network (www.avac.org/advocatesnetwork_signup.htm) to ensure you have the most current version.

- **Mapping out the next steps for research:** What follow-up studies would be needed in Thailand, the surrounding countries and other parts of the world? The trial sponsors are working with the Global HIV Vaccine Enterprise and other partners to outline a process for developing a comprehensive research agenda should the trial results warrant it.

- **Regulatory decision-making:** Trial sponsors and the Thai MOPH have discussed scenarios in which the data from the Thai Prime-Boost trial might be used to seek licensure for the vaccine in Thailand. But this decision would only be made after close consideration of the data. These trial data would not be used to seek licensure in the US. Discussions with the US Food and Drug Administration before the trial started indicated that additional studies would be required before licensure in the US.
- **Ensuring post-trial access to participants in the placebo arm:** Trial collaborators have stated that if the vaccine shows unequivocal clinical benefit—defined as reducing the risk of infection by at least 50 percent—placebo recipients would be offered vaccination. The timing for delivering vaccine to participants who received placebo would depend on several factors, particularly the speed with which the vaccines can be manufactured, tested for safety and quality, and ultimately approved by regulatory authorities for use in humans. The two manufacturers involved in the study have estimated that it could take up to 2-3 years to supply vaccine to all placebo recipients should the results show a clear benefit, as defined by the Thai and international collaborators. The trial team has emphasized that these plans were developed and agreed upon through extensive consultation among the trial sponsors, manufacturers and the Thai MOPH.

LOOKING AHEAD

No matter what the results show, the field needs to:

- **Continue the drive for comprehensive prevention.**

A vaccine would not be a replacement for other methods of prevention, including male and female condoms, behavior change counseling, male circumcision, clean needles and harm reduction. Such a vaccine (or any new intervention) would likely not be 100-percent protective. Any partially effective strategy will need to be delivered and used as part of a combination approach. Given that many people equate a vaccine with complete protection from a disease, it may be quite difficult to convey what a partially effective vaccine would and would not do. This is particularly true for a vaccine—should one be discovered—that does not prevent infection but instead reduces viral load in people who receive it and later become infected.

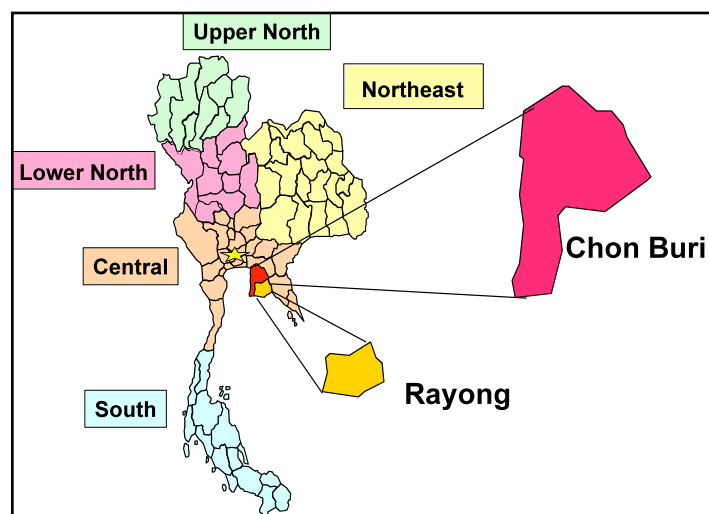
- **Stay the course—and keep a historical perspective.**

Many people in the vaccine research field will not be surprised if the ALVAC-AIDSVAX vaccine regimen proves to be ineffective. Recently, the disappointing results from the Step study of Merck's AIDS vaccine candidate, MRK-Ad5, have been cited as evidence of the tremendous difficulty, if not impossibility, of developing an effective AIDS vaccine. If the Thai trial also shows no efficacy, this may be taken as additional support for this argument. However, history tells us that the development of any vaccine involves decades of work and a range of disappointments before the first glimmer of success.

In the six years since the Thai Prime-Boost trial was launched, the field's understanding of the virus and its interaction with the human immune system has evolved. There will always be a need to test candidates based on the best available science—and to prepare for results that will be delivered after the science has moved ahead of it.

Whatever the outcome, a trial of this complexity and magnitude is a great accomplishment in the effort to stem the tide of the HIV pandemic. All persons involved, and especially the trial participants and study staff, deserve thanks and credit for their dedicated efforts and important contributions.

THAI TRIAL LOCATIONS



TIMELINE OF RESULTS FROM AIDS VACCINE EFFICACY TRIALS

YEAR COMPLETED	PRODUCT/CLADE/ TRIAL NAME	MANUFACTURER	FUNDER/SPONSOR/ TRIAL EXECUTOR	COUNTRIES	NUMBER OF PARTICIPANTS	RESULT
2003	AIDSVAX B/B/ VAX003	VaxGen	VaxGen	Canada, Netherlands, Puerto Rico, US	5,417	No effect
2003	AIDSVAX B/E/ VAX004	VaxGen	VaxGen/BMA	Thailand	2,546	No effect
2007	MRK-Ad5 B/ Step	Merck	Merck/DAIDS/ HVTN	Australia, Brazil, Canada, Dom. Rep., Haiti, Jamaica, Peru, Puerto Rico, US	3,000	Immunizations halted early for fertility; subsequent data analysis found potential for increased risk of HIV infection among Ad5- seropositive, uncircumcised men; follow-up continues
2007	MRK-Ad5 B/ Phambili	Merck	Merck/DAIDS/ SAAVI/HVTN	South Africa	801	Immunizations halted based on Step result; follow-up continues
2009	ALVAC-HIV (vCP1521) and AIDSVAX B/E Thai Prime- Boost/RV 144	Sanofi Pasteur and VaxGen (later Global Solutions for Infectious Diseases)	DAIDS/ US MHRP/ Thai MOPH	Thailand	16,402	To be announced in September

BMA: Bangkok Metropolitan Administration

DAIDS: US Division of AIDS

HVTN: HIV Vaccine Trials Network

MHRP: US Military HIV Research Program

MOPH: Ministry of Public Health

MRK: Merck

SAAVI: South African AIDS Vaccine Initiative

AVAC: GLOBAL ADVOCACY FOR HIV PREVENTION

Founded in 1995 as the AIDS Vaccine Advocacy Coalition, 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. More information is available at www.avac.org.