



FAQs

Frequently asked questions regarding the RV144 Prime-Boost HIV Vaccine Trial

1. What is RV144?

The Prime-Boost HIV Vaccine Trial, also known as RV144, was the largest HIV vaccine study ever conducted in humans and involved more than 16,000 volunteers in Thailand. This was a community-based, randomized (vaccine: placebo +1:1), multicenter, double-blind, placebo-controlled efficacy trial. The trial tested a “prime-boost” combination of two vaccines: ALVAC[®] HIV vaccine (the prime), and AIDSVAX[®]B/E vaccine (the boost), designed to evaluate two co-primary endpoints, prevention of HIV-1 infection and impact of vaccination on viral load after infection. The vaccine combination was based on HIV strains that commonly circulate in Thailand and was conducted through the Thai Ministry of Public Health in the Rayong and Chon Buri provinces.

2. What was the trial period and who was enrolled?

The trial began screening in September 2003 and enrolled 16,402 volunteers through December 2005. HIV-uninfected Thai men and women between the ages of 18-30 years were recruited from the community without regard to HIV risk (community risk). Written informed consent was obtained, and volunteers were required to pass a written Test of Understanding. Women were counseled to practice effective contraception until three-months after the last vaccination; pregnant or breast feeding women were excluded from the trial.

3. What was the goal of the trial?

The trial was designed to test the vaccine regimen’s ability to prevent HIV infection, as well as its ability to reduce the amount of HIV in the blood of those who became infected after enrolling in the trial.

4. What were the results of the trial?

The results show that the prime-boost combination of ALVAC HIV and AIDSVAX B/E lowered the rate of HIV infection by 31.2 percent compared to placebo based on the modified intent-to-treat (mITT) population (n=51 vs. n=74, respectively; p=0.04). There was no effect on the amount of virus in the blood of the study volunteers who received either vaccine or placebo and subsequently became infected with HIV.

While this is a modest level of efficacy, it represents a major step forward for HIV vaccine research, providing the first evidence that development of a safe and effective preventive HIV vaccine is possible. Additional research is needed to better understand how the regimen reduced study volunteers’ risk of HIV infection.

5. Why were the top-line trial results announced on September 24, 2009 prior to the AIDS Vaccine 2009 Conference and publication of the full trial results in *The New England Journal of Medicine*?

The Thai Ministry of Public Health and other trial collaborators wished to inform the volunteers and Thai citizens of the results as soon as possible, instead of waiting for a scientific conference or publication. Therefore, on September 24, 2009 the top-line results were announced by the trial collaborators in Thailand followed by teleconferences to trial volunteers and staff in the two provinces. This was followed by an international teleconference from the U.S.

6. Why did the initial top-line results not include statistical analyses for intent-to-treat (ITT) and per protocol (PP) study populations?

The multiple statistical analyses are all consistent with the same conclusion: that the vaccine was modestly effective at preventing HIV. However, explaining the differences between them is complex and the researchers planned to present a detailed description of the variations between the statistical analyses at the AIDS Vaccine 2009 Conference in Paris on October 20, 2009 and in a scientific publication in *The New England Journal of Medicine*.

7. What is the mITT study population?

The mITT population included all randomized volunteers (that is, the ITT population), with the exception of the seven volunteers who were HIV-infected at baseline. The mITT analysis is the most clinically relevant analysis for this proof-of-concept study. The mITT analysis was the basis of the results of RV144 we announced at the end of September.

8. What is the difference between ITT and PP statistical analyses?

The ITT analysis includes everyone who entered the study and focused on the most clinically relevant population for this proof-of-concept study. PP analyses are critical for studies leading to U.S. product licensure. This study was not designed for this purpose.

The PP analysis excludes anyone who became HIV infected before all four vaccine visits and includes only those who completed all protocol vaccinations on time. That is very important since it would exclude those who were potentially protected after receiving just a part of the vaccine regimen of six shots. The PP analysis excluded one-fourth of the individuals and nearly one-third of the trial endpoints - only 86 of the 125 infected individuals in the study were included in the PP analysis - which substantially reduces the study power.

The result based on the PP population is consistent with the mITT analysis that was presented, even though the PP vaccine efficacy estimate was slightly lower (26.2 percent, n=36 for vaccine regimen vs. n= 50 for placebo; p=0.16), and did not reach statistical significance due to the large reduction in the number of volunteers and infections included in the PP analysis. In the ITT population, the vaccine regimen reduced infection rates by 26.4 percent compared to placebo (n=56 vs. n=76 respectively; p=0.08).

9. What are the study conclusions?

The ALVAC-HIV and AIDSVAX B/E prime-boost HIV vaccine regimen reduced the risk of HIV infection in a community-based population in Thailand with largely heterosexual risk factors without post-infection effect on viral load. The effect is modest and likely without immediate public health benefit but should offer important directions for future research.

10. What vaccines were used in this study?

The vaccine regimen included two vaccine candidates, ALVAC HIV (vCP1521) and AIDSVAX B/E (gp120), and involved a total of six immunizations over six-months: four immunizations with ALVAC-HIV and two with AIDSVAX B/E given at the same time as the last two ALVAC-HIV injections. This combination of two different vaccines is called a prime-boost approach. In this approach, two vaccines are given in sequence with the goal of inducing the strongest and most comprehensive immune response possible.

The first vaccine used in the strategy, ALVAC-HIV (vCP1521), consists of a viral vector and genetically engineered versions of three HIV genes (env, gag and pro). A vector is a weakened or disabled virus used to deliver vaccine contents to the immune system once they are injected into the body. The ALVAC vector is a disabled form of a bird virus called canarypox, which cannot grow or cause disease in humans. The second vaccine used in the strategy is called AIDSVAX B/E, which is composed of genetically engineered gp120, a protein on the surface of HIV.

11. Who manufactures the vaccines used in the study?

ALVAC-HIV, the prime vaccine, is manufactured by sanofi pasteur. AIDSVAX B/E, the booster vaccine, was manufactured by Genentech under a license and supply agreement with VaxGen, one of the original manufacturing collaborators for the RV 144 trial. Global Solutions for Infectious Diseases (GSID), a not-for-profit organization co-founded by three former VaxGen executives who played a prominent role in the development and testing of the AIDSVAX B/E vaccines while at VaxGen, has assumed responsibility for the continued development and, if necessary, manufacturing of this product.

12. Was the vaccine regimen safe?

The two candidate vaccines were shown to be safe and well tolerated with the common adverse reactions typical of most vaccines. Local and systemic reactions to the vaccine were common but well tolerated and similar to previously published safety data for the vaccines. Most reactions were mild-to-moderate and resolved within three-days.

Before agreeing to participate, all volunteers were informed of and consented to the potential risks associated with receiving the experimental vaccine combination used in this study. Study volunteers also received counseling on how to prevent

becoming infected with HIV at the beginning of the study and every six-months for three-years. There was no evidence that participants increased their HIV risk behavior during the study. The two study vaccine candidates do not contain all of the components of HIV and cannot combine to form an infectious virus, so the vaccines cannot cause HIV infection.

13. Who conducted the trial?

This HIV Vaccine Trial was conducted by the Thai Ministry of Public Health, in collaboration with a team of leading Thai and U.S. researchers. The trial was coordinated by the U.S. Military HIV Research Program (MHRP), which is based at the Division of Retrovirology, Walter Reed Army Institute of Research (U.S.) and the Department of Retrovirology at the Armed Forces Research Institute of Medical Sciences (Thailand) with support from Mahidol University's Faculty of Tropical Medicine. The official sponsor of this trial was the U.S. Army Surgeon General via the U.S. Army Medical Materiel Development Activity.

14. Who funded the trial?

The U.S. Government, specifically the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) and the U.S. Army Medical Research and Materiel Command, Department of Defense funded this clinical trial. The Thai Ministry of Public Health, GSID and sanofi pasteur, as well as each of the collaborators, provided extensive in-kind support.

15. How did the study enroll more than 16,000 people?

This study was a tremendous operational success that recruited more than 60,000 interested participants, screened 26,675 people to see if they met the study's entry criteria and enrolled 16,402 qualified volunteers.

16. What happened to volunteers who became infected with HIV during the trial?

Volunteers who acquired HIV infection during the trial were given free access to HIV care and treatment, including highly active antiretroviral therapy (HAART), according to the guidelines of the Thai Ministry of Public Health. They were also offered extended follow-up in a separate study (RV152). The study vaccines did not cause HIV infection because they are not made from and do not contain the entire virus, either live or killed.

17. How many people were retained throughout the trial?

At 42 months, 14,672 (89.5 percent) of volunteers completed the trial and were HIV seronegative. There were 52,985 person years of follow-up (15 percent more than planned).

18. Why did the U.S. Army conduct this study?

Development of a safe, effective and accessible vaccine to prevent HIV infection is critical to successful global control of the epidemic. For more than a century, the military medical community has solved many significant international health problems, particularly in the area of tropical infectious diseases, which have consistently posed a major threat to U.S. forces. With an estimated 33.2 million infections worldwide, HIV continues to pose a significant and persistent threat in terms of readiness and force protection, and may affect the stability and security of many nation-states.

With the emergence of an explosive HIV epidemic in Thailand in the early 1990s, U.S. Army researchers helped to characterize the heterosexual epidemic, isolated Thai viruses, and provided these sequences to companies making HIV vaccines. U.S. and Royal Thai Army researchers, the Thai Ministry of Public Health and other Thai vaccine experts together developed a plan to test this candidate vaccine in Thailand.

19. Why was the study conducted in Thailand?

The Thai Ministry of Public Health has long been committed to preventing HIV through risk reduction and believes that an effective HIV vaccine is part of a comprehensive approach to HIV prevention. Thailand had a severe, generalized HIV epidemic, and was one of the first countries to have developed a National AIDS Plan and a National HIV Vaccine Development Plan. A major goal of the plan is "to promote and support national and international collaborative research that will lead to the development and evaluation of effective HIV/AIDS vaccines for potential use in Thailand." The Thai government has shown a remarkable and successful commitment to HIV prevention, and it has a longstanding commitment to the development of an HIV vaccine as an additional HIV control measure.

20. What impact will this study have on the HIV vaccine field and what happens next?

We now have evidence that a safe and effective HIV vaccine is possible, and the results should accelerate research efforts towards a more effective vaccine. Experts are interpreting the results and planning additional studies to maximize the knowledge gained from this study. In addition, we have already learned a great deal from this study, particularly in terms of conducting large-scale HIV prevention trials, and will continue to learn more as additional research is conducted.

For additional Information regarding the trial, visit: www.hivresearch.org

Trial Collaborators

U.S. Military HIV Research Program (MHRP)

Ministry of Public Health, Thailand (MOPH)

National Institutes of Allergy and Infectious Diseases (NIAID)

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www.hivresearch.org

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