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Phase III HIV vaccine trial in Thailand: a step toward a protective vaccine for HIV

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Abstract

The large human efficacy trial in Thailand, RV144, was concluded in the summer of 2009. This is the first Phase III trial to show limited, but significant, efficacy in preventing HIV acquisition. This trial represents the first sign that a preventive vaccine for HIV may be feasible. The vaccine regimen tested in Thailand consisted of priming with a Canarypox vector carrying three synthetic HIV genes. The priming was followed by booster inoculations with two recombinant envelope proteins from HIV, clade B and E. The need to understand the role in protection from HIV acquisition of the new responses, induced by this vaccine combination, has brought together many researchers with the common goal of improving the development of a safe and effective vaccine for HIV.

Keywords

gp120; HIV; neutralizing antibodies; Phase III; prime–boost; T-cell responses; vaccine trial

Overview of the RV144 trial

The Phase III HIV-1 vaccine trial, also known as RV144, began in Thailand in October 2003 and concluded in the summer of 2009; this test-of-concept trial is the largest HIV vaccine study ever conducted in humans, enrolling more than 16,000 Thai men and women from the general population. This study, conducted by the Thai Ministry of Public Health, was sponsored by the US Army Surgeon General, managed by the US Military HIV Research Program (MHRP) together with Thai scientists, and was supported by the Thai and US governments, private companies and nonprofit organizations. The vaccine used in the RV144 trial is a combination of two vaccines given in a ‘prime–boost’ strategy: ALVAC-HIV from Sanofi Pasteur (Swiftwater, PA, USA) and AIDSVAX from VaxGene (San Francisco, CA, USA). Both vaccines were based on HIV-1 B and E clades that commonly circulate in Thailand. RV144 was designed to test the ability of this vaccine combination to prevent HIV infection, as well as its ability to reduce the level of HIV RNA in the blood of the vaccinees that became infected.

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Despite skepticism and controversies about the ability of the combination of these vaccine modalities to induce sufficient immune responses, the vaccine regimen proved to be safe and demonstrated 31.2% efficacy in preventing HIV infection [1,2]. While the results of this trial may suggest for the first time the feasibility of a vaccine for HIV, the limited level of protection from viral infection implies that more work will be needed to generate a vaccine that protects the general population from HIV acquisition.

HIV-1 prevalence in Thailand & volunteer recruitment

Thailand is one of the first developing countries that were successful in reducing the HIV epidemic through a thorough government program. Furthermore, in Thailand, there are suitable infrastructures able to support the testing of AIDS vaccines. A major goal of the national strategy has been to promote and support national and international collaborative research leading to the development and evaluation of effective HIV/AIDS vaccines for this region [3].

Despite several efforts, AIDS is still one of the leading causes of death in Thailand. More than one in 100 adults in this country of 63 million people are infected with HIV (Box 1) [4]. Soon after the first case of AIDS was detected in 1984 [5], HIV rapidly spread in the region among men who have sex with men (MSM), sex workers, injecting drug users (IDUs) and tourists. In 1991, AIDS prevention and control became a national priority [6]. Initially, the efforts promoted by the Thai government to contain HIV were directed at high-risk groups. In spite of this campaign, the number of HIV infections rose again in 2000, due to both historical and economic reasons. During this time, HIV-1 prevalence also increased in young heterosexual individuals previously considered at low risk. Since the change in the government composition in 2006, Thailand has reinvigorated its HIV/AIDS prevention and control efforts by adopting a 3-year strategic plan that focuses on preventive efforts [7]. Recent studies on the prevalence of HIV infection in different groups have shown that HIV-1 transmission between spouses account for more than a half of new infections, suggesting that a vaccine designed for this region should target both high- and low-risk groups.

The Thai trial is the continuation of a 10-year effort to find an effective preventive measure to halt the HIV epidemic in the country [8,9]. This is the first trial designed to vaccinate a representative cross-section of the Thai population with regard to HIV risk. For this study, volunteers were recruited from Chon Buri and Rayong provinces in southeastern Thailand, chosen for their relatively high HIV incidence, good logistic and public health infrastructures, and other favorable characteristics [10,11]. A total of 26,676 volunteers were screened for eligibility to participate in the trial. The screening was carried out under a separate protocol entitled 'Screening and evaluation of potential volunteers for a trial in Thailand of a candidate preventive HIV vaccine' or RV148.

The statistical assumption of the study required 16,000 subjects. A total of 16,402 HIV-negative individuals were enrolled: males (61.4%) and females (38.6%) between the ages of 18 and 30 underwent randomization based on age, sex and different behavioral risks (intent-to-treat [ITT] group) [12]. A total of seven subjects were then excluded as they tested positive for HIV-1 at the time of the first vaccination. Of the remaining group, called the modified ITT (mITT) population, 8197 were vaccinated and 8198 received placebo

(vaccine:placebo ratio of 1:1), in a double-blind manner. The vaccines were administered through many community health centers and local outpatient facilities (community-based, multicenter). A total of 12,542 volunteers were found negative for HIV-1 for the duration of the vaccination period and completed all the visits.

Choice of HIV vaccine antigens

HIV-1 clades in Thailand

The HIV-1 infection is characterized by genetic diversity, wherein distinct viral subtypes are expanding in different geographical regions, thus rendering the development of a globally relevant HIV-1 vaccine difficult. The vaccines used in the RV144 trial were therefore developed to match with the HIV clades circulating in Thailand.

There are two clades of HIV-1 in the Thai region: the B and the recombinant E/A strains. Clade B is the predominant species in Europe and America. However, with increasing immigration and globalization, greater than 40% of new infections in Europe are presently non-B African and Asian variants. Historically, in Thailand, the HIV epidemic was initially dominated by HIV-1 subtype B among IDUs [13,14]. A larger epidemic of sexually transmitted HIV followed, where the recombinant form, CRF01-AE, became the dominant subtype (90% of the circulating HIV strains in the country).

In relation to the HIV-1 clades present in Thailand, data from antibody cross-reactivity studies have demonstrated that binding and neutralizing antibodies from subtype B- and E-infected subjects react with viruses from the same subtype [15]. It was therefore assumed that a vaccine for Thailand should be able to induce HIV-specific cytotoxic T-lymphocytes (CTLs) to the clades B and A/E, and specific antibodies, possibly neutralizing, to the same HIV-1 clades. This strategy was tested on 92 Thai volunteers in 1998, demonstrating that rgp120, from genetically distinct subtypes, could be combined into a bivalent vaccine to increase the breadth of antibody responses [16]. Thus, the combination of three vaccines were chosen for further evaluation in a Phase III trial in the region with the goal to induce T-cell responses and antibodies to clades B and E. ALVAC-HIV (virus recombinant Canarypox vCP1521), a T-cell vaccine able to induce cell-mediated immunity [17–19], and AIDSVAX B/E (glycoprotein [gp]120), a bivalent protein vaccine that elicits significant levels of neutralizing antibodies in Thai subjects [20], were given with a prime–boost approach [21]. The selection criteria for the dose of these vaccines were based on results on the vaccines' component reactogenicities, and manufacturing feasibility, observed in several Phase I/II trials with ALVAC-HIV [22–28] and Phase III VaxGen trial [20,29].

The prime: Canarypox as a vector for an HIV-vaccine

The Canarypox virus-based vector, ALVAC-HIV, was used for priming. ALVAC-HIV is an attenuated recombinant Canarypox vector vaccine and was developed by Virogenetics Corporation (NY, USA) and manufactured by Sanofi Pasteur. The Canarypox virus is an etiologic agent of disease in birds; it can infect human cells but it is not able to replicate in humans. Therefore, Canarypox vectors (CPVs) used for vaccines are host-range restricted and safe [30–33]. Despite its abortive infection in mammalian cells, CPV can express and

present foreign proteins [34], processed via the MHC class I and class II pathways, thus stimulating both CD8⁺ and CD4⁺ T lymphocytes [35,36]. Differently from vaccinia virus, or other poxvirus-based vaccines such as modified vaccinia ankara (MVA) and New York Vaccinia (NYVAC) vaccines, Canarypox virus is not inhibited by pre-existing immunity to vaccinia virus [22,23], which has been induced in the majority of adults born before 1977 by routine immunization. A full description of biological properties, engineering and a review on the use of Canarypox as a vector for Simian immunodeficiency virus (SIV) and HIV vaccines can be found elsewhere [37,38].

ALVAC-HIV is a recombinant Canarypox vector that was genetically engineered to express HIV-1 Gag and Protease from the first HIV isolated, LAI (IIIB/Bru) [39], and the HIV-1 gp120 protein from the clade E. The construct contains the HIV-1-*gag* gene of the subtype B only because the *gag* gene is more conserved than *env* genes among virus subtypes [40]. In this construct, the envelope gene was isolated from a virus strain, code-named 92TH023, found in a HIV-1-infected Thai individual in Bangkok, by the WHO Network for HIV Isolation and Characterization. This CCR5-tropic virus strain is a clade A and E virus recombination form. In the ALVAC vCP1521 construct, the clade E gp120 protein has been linked to the transmembrane (TM) portion of the gp41 protein from LAI, subtype B (gp120TM). The TM region was added to anchor the gp120 to the cell surface. The deletion of the immunodominant peptide AVERY within the gp41 amino acid sequence renders the vaccine-induced antibody distinguishable from the ones induced by virus infection. The co-expression of Gag, Env and protease results in the formation of virus-like particles that bud from the cell membrane [41]. The genes for the expression of Gag and Env were inserted into the Canarypox C6 locus under the control of vaccinia virus H6 and I3 promoters. ALVAC-HIV vCP1521 was propagated in a chicken embryo fibroblast and formulated at a dose of 106 50% tissue culture infectious dose (TCID₅₀); virus preparation was lyophilized and reconstituted using sterile 0.4% sodium chloride.

ALVAC-HIV has been extensively studied in macaques [34,37,42–48] and in a Phase I/II human trial in combination with gp120 or gp160 protein boosts (TABLES 1 & 2) [28,46,49–53]. These studies demonstrated that recombinant ALVAC constructs alone were safe and immunogenic, eliciting specific T-cell responses in 30–60% of volunteers, depending on the dose and HIV-inserts proliferative responses in more than half the vaccinees, and low levels of antibodies to HIV. The level of antibodies were boosted by administration of the soluble gp120 protein [21,54,55].

The vCP1521 vector containing gp160 MN has been studied in Phase I trials conducted in France and the US (ANRS VAC01 and AVEG012). Taken together, these studies have shown that while ALVAC-HIV induced CTL-responses in one out of three of vaccinees, ALVAC-HIV boosted with SF2 gp120 protein induced both CTL responses in approximately 40% and neutralizing antibodies to laboratory-adapted HIV-1 strains in all the vaccinees [22,55]. Also, ALVAC-gp160 boosted with rgp120 resulted in higher levels of HIV-1 lymphoproliferative responses to Env proteins, and increased antibody-dependent cellular cytotoxicity activity to MN and SF-2 HIV strains as compared with ALVAC-gp160 alone [22].

The boost: the gp120 envelope protein

The boosting in the Thai trial was done using the recombinant envelope glycoprotein gp120-subunit vaccine (AIDSVAX B/E). This vaccine was developed by Genentech, manufactured by VaxGene, which gave the rights to the AIDSVAX to the newly formed Global Solutions for Infectious Diseases, a not-for-profit organization. The protein is a mixture of two highly purified glycoproteins produced by recombinant DNA procedures in Chinese hamster ovary cells, the HIV-1 MN gp120 (subtype B) and the HIV-1 A244 gp120 (subtype E). The gp120 sequences were covalently bound to a 27-amino acid sequence found in the gD protein of the herpes simplex virus type 1, that was cleaved during the purification procedure.

A variety of HIV-1 envelope vaccine candidates have been tested in animal models and in low-to high-risk groups of humans and they were found to be safe, well tolerated and immunogenic [16,29,56–60]. Protection was achieved from intravenous and mucosal challenge with homologous and heterologous HIV-1 strains, in two chimpanzees vaccinated with AIDSVAX IIIB, and three out of three animals vaccinated with AIDSVAX MN (TABLE 1) [57,59,61]. Following these results, the two vaccines have been studied in many Phase I and II trials in the USA and Thailand. The results from these studies showed that the HIV-1 envelope-specific antibodies in humans were comparable to what was observed in chimpanzees [57,58,62]. Two Phase I/II trials using the AIDSVAX B/E vaccine have been completed in Thailand so far, showing that three administrations using 600 µg of the vaccine candidate were safe and immunogenic.

Both vaccine candidates advanced to Phase III in 1998–1999. AIDSVAX B/B was tested in North America and Europe among MSM [29,63], and AIDSVAX B/E was tested in Thailand among IDUs [61,62]. AIDSVAX was safe and well tolerated in both of these trials and there was no evidence of vaccine-related adverse effects. AIDVAX B/B gp120 vaccines trial was prematurely terminated because the vaccine was not effective in reducing HIV infection [64]. The AIDSVAX B/E trial in Thailand was completed showing that the vaccine did not prevent HIV-1 infection or delay HIV-1 disease progression [20].

The RV144 trial was proposed before the results from these efficacy trials were disclosed and published (2003). Nonetheless, in the trial proposal, the principal investigators had stated that a nonefficacy outcome from a single-arm strategy in a high-risk population should not stop the study of a combined vaccine strategy in a mainly low- and medium-risk group.

A total of six immunizations over 6 months were given: four immunizations with greater than 10^6 TCID₅₀ /11domse ALVAC-HIV were given intramuscularly in the left deltoid at weeks 0 (baseline) 4, 12 and 24. Two immunizations with 600 µg (300 µg each antigen) in 1 ml of AIDSVAX B/E were given intramuscularly in the right deltoid at the same time as the last two ALVAC-HIV injections (weeks 12 and 24). Volunteers that received the placebo were given a mixture of virus stabilizer and freeze-drying medium (ALVAC Placebo, Sanofi Pasteur) and 600 µg of alum adjuvant (AIDSVAX Placebo, VaxGen Inc.) at the same time with the same route. All the volunteers were followed up every 6 months for 3.5 years. Counseling for HIV prevention was provided at each visit.

Results from the trial

The primary RV144 end point was to determine whether immunizations with a prime–boost strategy using ALVAC-HIV vCP1521 boosted with AIDSVAX gp120 B/E could prevent HIV-1 infection. The rates of infections in vaccine and placebo recipients were compared using three different analyses that included different numbers of individuals: ITT, mITT, and per protocol (PP). Of the 16,402 subjects enrolled (ITT group), 56 out of 8200 vaccinated and 76 out of 8202 placebo recipients were found positive for HIV-RNA [12] and the difference between the groups was not significant ($p = 0.08$). The PP analysis, that included 12,542 participants who were HIV-negative at baseline and who received all the immunizations, resulted in a nonsignificant difference (36 vaccinees; 50 placebo; $p = 0.16$). In the mITT group, seven volunteers, five in the vaccinated and two in the placebo group, were found to be seropositive for HIV at the time of the first vaccine administration and were excluded from the evaluation of the vaccine efficacy. Thus, by the mITT, that left a total of 16,395 subjects, 74 out of 8198 placebo recipients became infected with HIV compared with 51 out of 8197 vaccinated participants. This resulted in a significant 31.2% vaccine efficacy ($p = 0.04$) with a 95% confidence level, a standard for many trials, that ranged from 1.1 to 52.1%. Despite the differences in the number of subjects considered in the three analyses, a trend of fewer infections in the vaccine recipients compared with the control was consistently observed in all three groups.

Subjects' risk of HIV infection in the community was assessed through a self-administered behavioral questionnaire distributed at baseline and every 6 months thereafter. In the mITT population, approximately 48 and 28% of the volunteers were considered as having low- and medium-risk behavior to contract the virus, respectively. Only 24% were IDUs or reported high-risk sexual activity. When the mITT population was sorted based on the level of risk to contract HIV-1, the vaccine was 40% effective in the lower-risk population (limited number of low-risk sex partners and no drug use) but appeared to offer only 3.7% protection in the high-risk population. However, the trial was not powered to inform on the efficacy according to the vaccinees' risk.

When the mITT group was sorted based on the time of acquisition of HIV infection, a more dramatic difference of 50–60% efficacy was found between the vaccine and placebo groups within the first year following the last immunization, suggesting a limited durability of the vaccines effect. Although these findings are suggestive – the study was not powered to assess vaccine durability.

The second objective of the trial was to analyze whether immunization with this vaccine regimen could result in a decreased virus level and better CD4⁺ T-cell count among vaccinees that acquired HIV. The same vaccine modality tested in macaques had shown decreased SIV levels upon exposures to high-dose virus and protection from disease [45,65]. Surprisingly, there was no effect on virus level or on the CD4⁺ T-cell count in the vaccinated volunteers that acquired HIV infection. However, it may not have been possible to observe a transient effect on virus level, as in macaque [45], because the volunteers were sampled at 6-month intervals.

The combination of the vaccines was safe, and only a mild and transitory reaction to the products was observed. Also, no change in the behavior that may increase the risk of HIV acquisition was observed in the trial participants.

The Thai trial was not originally designed with the intent to find correlates of protection; nonetheless, any information on protective immune response could help to design future vaccines. Samples collected during the study have been analyzed to measure vaccine-induced T-cell responses and specific humoral responses. Vaccination induced HIV-gag and HIV-env specific responses measured by IFN- γ ELISpot in approximately 20% of volunteers at 6 months after the last vaccination. These results were similar to what was observed in the Phase II trial (17%) [12]. The rate of positivity for CD4⁺ Env-specific intracellular cytokines was significantly higher in the vaccine than in the placebo group (34 vs 3.6%; $p < 0.001$). Lymphoproliferative responses to gp120 E (A244), gp120 B (MN) and p24 were measured at 2 weeks post vaccination and were significantly higher in the vaccinated group compared with placebo group [12]. A total of 2 weeks after the administration of the fourth dose of vaccine, 98.6% of vaccinated subjects were found to have measurable binding antibodies to gp120 MN and A244, similarly to what was observed in the Phase II trial, and 52% of vaccinees also had binding antibody to HIV p24 Gag [27].

Expert commentary & five-year view

The vaccine platform used in the RV144 trial has conferred limited, but nonetheless significant protection from HIV-1 acquisition. However, the degree of protection (31.2%) elicited by this vaccine regimen would not be deemed sufficient for licensure. Few people in the field were expecting a positive outcome from this trial; some critics suggested that the results of this trial might be due to chance alone because of the relatively small number of infected individuals in the placebo and vaccine groups. This reasonable criticism can only be addressed by performing additional human trials. In spite of skepticism, the result from the Thai trial has energized the HIV vaccine field and it represents an important milestone for the development of an effective vaccine for HIV.

As soon as the results of the Thai Trial were disclosed to the public, four scientific working groups were created by the MHRP, with the aim to understand the basis of the protection from HIV infection observed in RV144 [101]. Three working groups were asked to distribute the cryopreserved samples collected from the RV144 participants, to be intensely studied for host genetic, humoral, innate and adaptive responses to HIV. Should immune correlates for protection be uncovered by these studies, it would be a tremendous step forward.

The initial results from these studies have shown that the vaccinated individuals mounted low T-cell immune responses, as well as moderate antibody responses to the HIV-1 clades used to engineer the two components of the vaccine. The combination of humoral and cellular immune responses, even if each were at a low level, may have contributed to the protection against HIV. While the results of the trials have refocused attention on B-cell responses and non-neutralizing antibodies, it remains unknown whether both the vaccine components are required to achieve this level of protection from HIV acquisition. A previous

trial using AIDSVAX alone failed to confer protection from HIV acquisition, suggesting that the combination of the two arms may be important to induce an effective anti-HIV-1 response. A possible significant difference is that the AIDSVAX vaccine was tested alone in a population at higher risk of HIV acquisition, while in the Thai trial only 24% of the participants were at high risk for HIV acquisition. The RV144 trial was not powered to assess the vaccine effect on volunteers with various degrees of risk for HIV acquisition.

A fourth working group will consider the pros and cons of using the macaque model to address the correlates of protection elicited by the RV144 vaccine platform. Animal models have been previously used to test these vaccine candidates for HIV (TABLE 1) [33,35,42–45,47,48,65,66], but their relevance to humans remains uncertain. Following the publications of the Step and the Thai efficacy trials in the last 2 years, many have doubted the relevance of the nonhuman primate model to study relative efficacy of vaccine candidates for HIV [67]. Still, in a certain number of studies, the macaque model has predicted the results of human trials; gp120 alone, given to macaques, failed to protect from high level of challenge exposure as did the VaxGen trial in humans [45]; the adenovirus 5 (Ad-5)-based vector expressing gag but not envelope has conferred no protection in macaques, like the equivalent vaccine in the STEP trial [68,69]. In the case of the ALVAC–SIV/gp120 protein boost, this strategy has conferred protection from infection in ten of 16 neonates exposed to repeated low-dose challenge. However, no protection was observed in vaccinated adult macaques exposed to a single high dose of SIVmac251 [45,65]. Our group has recently compared a similar strategy to the ALVAC-based/gp120 vaccine in adult macaques and directly compared a single dose, versus repeated low-dose challenges of the same SIVmac251 stock. Our data suggests that repeated low-dose mucosal SIV challenge of macaques, with vaccines similar to those used in the RV144, results in some degree of protections from infection. However, no protection was found when we used a single high-dose exposure to the same virus.

The differences observed between the degrees of protection in macaques and in humans may depend on experimental choices while designing the study in macaques. Macaques' age, MHC class I, the viral challenge stock and the dose of virus used can influence the results. The outcome of the three Phase III trials in humans, the AIDSVAX [20,29], the STEP [69] and the RV144 trials [12], represent an opportunity to validate the macaque model in the years to come. Macaque studies will be instrumental in understanding the nature and the durability of vaccine-elicited host responses that can protect from virus acquisition. Possibly, these studies will inform on how to improve vaccine regimes for humans that can protect from exposure to different risk of HIV acquisition.

In the clinical arena, the investigators involved in the RV144 trials have recently proposed the following studies in humans:

- An extension of the current trial, where the volunteers enrolled in the RV144 will be reboosted with the same vaccine strategy and then followed overtime (RV305);

- The RV152 study, whereby the 51 individuals who became infected, despite vaccination, will be followed up at 6-month intervals to assess virus level and immune responses overtime;
- Phase IIB human trial in Asian heterosexual populations considered at very low risk of infection, with the aim to increase the number of protected subjects to determine the correlates of protection from acquisition.

The success of the RV144 trial, even if partial, has changed the paradigms in the field of HIV vaccine research and will impact how to conduct future trials. The Thai trial has been a tremendous collaborative effort between the US Government, the US Army, and the Government of Thailand private and public research sectors. Such an effort has made the recruitment and retention of more than 16,000 participants possible, and very importantly, has also allowed for the clinical and scientific training of local personnel. Scientifically, RV144 has been appropriately powered to address its primary end point: HIV acquisition.

Over the years, the decision to continue the RV144 Phase III efficacy trial has been challenged [1,2] because of the failure of the AIDSVAX candidate alone in previous efficacy trials and because of the perception that the ALVAC-HIV-based vaccine was not as 'immunogenic' as other vaccine candidates, such as Ad-5-based vaccines [1]. In 2007, a sobering lesson has come from the results from the STEP trial using the Ad-5 vaccine HIV vaccine candidate from Merck [69]. Despite the stronger and more long-lasting CTL-responses induced in humans by Ad-based HIV vaccines compared with the ALVAC-HIV vaccine, no protection from acquisition was evident. The STEP and RV144 trials were not tested in equivalent populations and several variables, including the lack of the envelope antigens in the former, may accounts for the different outcome. Nevertheless, at present, we have learned from these two trials that neither the knowledge on vaccine immunogenicity in humans, nor the relative efficacy of these vaccines in certain animal models [67], allows for an accurate prediction of vaccine efficacy in humans. Hopefully, a well-orchestrated use of animal models to understand the correlate of protection, will allow rapid progress in the development of HIV vaccines to be tested in humans.

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Financial & competing interests disclosure

The US Government holds patent rights on the vaccine used in the RV144 trial. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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- of interest
- of considerable interest

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Key issues

- The vaccine regimen tested in Thailand, in the RV144 trial, consisted of priming with a Canarypox vector carrying three synthetic HIV genes. The priming was followed by booster inoculations with two recombinant envelope proteins (glycoprotein [gp]120) from HIV. Both vaccines were based on HIV DNAs that represent the HIV strains B and E found in infected individuals in Thailand. The RV144 trial was sufficiently powered to test the primary end point: protection from HIV acquisition.
- Prior to the RV144 trial, two other Phase III efficacy trials for HIV vaccines were conducted and have conferred no protection from HIV acquisition. The first was based on the rationale of inducing mainly antibodies using recombinant gp120 (VaxGene trial); the second was based on the rationale of eliciting high levels of CD8⁺ T-cell responses to the HIV Gag and Nef antigens using a recombinant replication-defective adenovirus-5 that did not contain the envelope gene.
- The rationale of the RV144 trial was to combine vaccine modalities able to elicit CD8⁺ and CD4⁺ T cells and antibody responses to HIV. The population chosen to test the combination of these vaccines consisted mainly of heterosexual men and women living in two Thailand provinces, with known HIV incidence and with adequate infrastructures for conducting a large trial.
- The RV144 trial results demonstrated a significant protection from HIV acquisition (31.2%) in a 3-year follow-up.
- While the result of the RV144 trial has raised some skepticism, it has also raised hope in others that perhaps the combination of antibodies with functions other than the neutralization of cell-free virus and T-cell response may be sufficient to inhibit HIV infection at the mucosal port of entry.
- Thus, further efforts to improve the immunogenicity of these or similar vaccines are warranted at present. Hopefully, a well-orchestrated use of an animal model will help in the development of more effective vaccines for HIV.

Box 1.**HIV/AIDS in Thailand.**

- People living with HIV: 610,000 (range: 410,000–880,000)
- Percentage of adults aged 15 to 49 years with HIV/AIDS: 1.4 (range: 0.9–2.1)
- Women aged 15 years and over living with HIV: 250,000 (range: 170,000–360,000)
- Ratio of male:female 15–24-year olds in 2007 with HIV/AIDS: 1.2:1.2
- Deaths due to AIDS: 31,000 (range: 17,000–48,000)

Data from [102].

Table 1.

Summary of ALVAC-based vaccine studies in animal models.

Vaccine regimen	Antigen	Animal model	Outcome (protected/total challenged)	Ref.
ALVAC-HIV-1 vCP250	HIV gag, gp120 and protease	Chimpanzees	One out of two	[70]
ALVAC-HIV-2	HIV-2 gag, pol and env	Rhesus macaques	None out of three	[43]
ALVAC-HIV-2/gp160 boost	HIV-2 gag, pol and env + gp160 protein	Rhesus macaques	Two out of five	[66]
ALVAC-HIV-1/Env subunit boost	HIV-1 gag, pol and env + HIV-1 T-helper V3 peptide or gp160 protein	Rhesus macaques	One out of two	[71]
ALVAC-HIV-2	HIV-2 gag, pol and env	Cynomolgus monkeys	None out of four	[48]
ALVAC-HIV-2/gp120	HIV-2 gag, pol and env + gp120 protein	Cynomolgus monkeys	Two out of four	[48]
ALVAC-HIV-2/Env subunit boost	HIV-2 gag, pol and env + gp120 or V3 peptide	Cynomolgus monkeys	Two out of six	[48]
ALVAC-SIV-gpe	SIV gag, pol and env	Rhesus macaques	Decreased viral load	[45]
ALVAC-SIV-gpe	SIV gag, pol and env	Infant rhesus macaques	Reduced viremia in immunized group	[65]
ALVAC-HIV-gpe (vCP250 or vCP1420)	HIV gag, pol and gp120 protein or HIV-1 gag, pol and gp160	Rhesus macaques (SIV challenge)	Decreased viral load in blood and mucosal sites and protection from CD4 T-cell loss	[45]

Env: Envelope protein; gp: Glycoprotein; gpe: Gag, pol and env; SIV: Simian immunodeficiency virus; vCP: Virus recombinant Canarypox.

Table 2.
Summary of clinical trials in humans, involving use of ALVAC or AIDSVAX vaccine.

Vaccine	HIV subtype	Administered (month)	Clinical trial phase	Start date	Location of trial	Ref.
AIDSVAX B (HIV-1 MN gp120)/bivalent AIDSVAX B/E (HIV-1 MN gp120/A244 gp120)	B	0, 1 and 6	I	December 1998	USA	[72]
ALVAC-HIV (vCP125)/AIDSVAX (HIV-1 SF-2 gp120)	B	0, 1, 9 and 12	I	NA	USA	[22]
ALVAC-HIV (vCP205)	B	0, 1, 3 and 6	I	February 1999	Uganda	[73]
ALVAC-HIV (vCP205)	B	0, 1, 3 and 6	I	NA	USA	[25]
ALVAC-HIV (vCP1452) and/or HIV lipopeptides (LIPO-5)	B	4–6 immunizations in 6 months	I/II	January 2004	USA	[74]
ALVAC-HIV (vCP1521)/AIDSVAX B/E (HIV-1 MN gp120/A244 gp120)	B/E	0, 1, 3 and 6	I/II	NA	Thailand	[27,53]
ALVAC-HIV (vCP205) and/or AIDSVAX (HIV-1 SF-2 gp120)	B/B	0, 1, 3 and 6	II	May 1997	USA	[25]
AIDSVAX B/E (HIV-1 MN and A244 rgp120)	B/E	0, 1, 6, 12, 18, 24 and 30	III	March 1999	Thailand	[20]
AIDSVAX B/B (HIV-1 MN and GNE8 gp120)	B	0, 1, 6, 12, 18, 24 and 30	III	NA	USA, Canada, The Netherlands and Puerto Rico	[75]
ALVAC-HIV (vCP1521)/AIDSVAX B/E (HIV-1 MN gp120/A244 gp120)	B/E	0, 1, 3 and 6	III	October 2003	Thailand	[12]

AIDSVAX: Experimental HIV vaccine, which was developed and trialed by VaxGen; gp: Glycoprotein; NA: Not applicable.