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Merlin L. Robb

*US Military HIV Research Program*

Supachai Rerks-Ngarm

*Ministry of Public Health*

Sorachai Nitayaphan

*Thai Army*

Punnee Pitisuttithum

*Vaccine Trials Centre*

Jaranit Kaewkungwal

*Mahidol University*

*See next page for additional authors*

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## Authors

Merlin L. Robb, Supachai Rerks-Ngarm, Sorachai Nitayaphan, Punnee Pitisuttithum, Jaranit Kaewkungwal, Prayura Kunasol, Chirasak Khamboonruang, Prasert Thongcharoen, Patricia Morgan, Michael Benenson, Robert M. Paris, Joseph Chiu, Elizabeth Adams, Donald Francis, Sanjay Gurunathan, Jim Tartaglia, Peter Gilbert, Don Stablein, Nelson L. Michael, and Jerome H. Kim

# Risk behaviour and time as covariates for efficacy of the HIV vaccine regimen ALVAC-HIV (vCP1521) and AIDSVAX B/E: a post-hoc analysis of the Thai phase 3 efficacy trial RV 144



Merlin L Robb, Supachai Rerks-Ngarm, Sorachai Nitayaphan, Punnee Pitisuttithum, Jaranit Kaewkungwal, Prayura Kunasol, Chirasak Khamboonruang, Prasert Thongcharoen, Patricia Morgan, Michael Benenson, Robert M Paris, Joseph Chiu, Elizabeth Adams, Donald Francis, Sanjay Gurnathan, Jim Tartaglia, Peter Gilbert, Don Stablein, Nelson L Michael, Jerome H Kim

## Summary

**Background** The Thai phase 3 HIV vaccine trial RV 144 showed modest efficacy of a vaccine against HIV acquisition. Baseline variables of age, sex, marital status, and risk did not modify vaccine efficacy. We did a post-hoc analysis of the trial's data to investigate behavioural risk and efficacy every 6 months after vaccination.

**Methods** RV 144 was a randomised, multicentre, double-blind, placebo-controlled efficacy trial testing the combination of the HIV vaccines ALVAC-HIV (vCP1521) and AIDSVAX B/E to prevent HIV infection or reduce setpoint viral load. Male and female volunteers aged 18–30 years were recruited from the community. In this post-hoc analysis of the modified intention-to-treat population (16395 participants), HIV risk behaviour was assessed with a self-administered questionnaire at the time of initial vaccination in the trial and every 6 months thereafter for 3 years. We classified participants' behaviour as low, medium, or high risk. Both the acquisition endpoint and the early viral-load endpoint were examined for interactions with risk status over time and temporal effects after vaccination. Multiple proportional hazards regression models with treatment and time-varying risk covariates were analysed.

**Findings** Risk of acquisition of HIV was low in each risk group, but 9187 (58.2%) participants reported higher-risk behaviour at least once during the study. Participants classified as high or increasing risk at least once during follow-up were compared with those who maintained low-risk or medium-risk behaviour as a time-varying covariate, and the interaction of risk status and acquisition efficacy was significant ( $p=0.01$ ), with greater benefit in low-risk individuals. Vaccine efficacy seemed to peak early—cumulative vaccine efficacy was estimated to be 60.5% (95% CI 22–80) through the 12 months after initial vaccination—and declined quickly. Vaccination did not seem to affect viral load in either early or late infections.

**Interpretation** Future HIV vaccine trials should recognise potential interactions between challenge intensity and risk heterogeneity in both population and treatment effects. The regimen tested in the RV 144 phase 3 trial might benefit from extended immunisation schedules.

**Funding** US Army Medical Research and Materiel Command and Division of AIDS, National Institute of Allergy and Infectious Disease, National Institutes of Health.

## Introduction

The results of the phase 3 Thai HIV vaccine trial RV 144<sup>1</sup> suggest that a vaccine to prevent acquisition of HIV infection is possible.<sup>1</sup> Although the efficacy was modest and insufficient to warrant licensure, the study provided both insights and opportunities for future investigations into prevention of HIV acquisition. The investigators of the trial reported two salient, hypothesis-generating findings: efficacy seemed greatest in participants at lower risk for HIV infection compared with the study-defined high-risk participants, and efficacy seemed maximum early after administration, but decreased with time.

By contrast with previous efficacy trials for HIV vaccines, the investigators of RV 144 enrolled mainly heterosexual people from a population with low prevalence of HIV.<sup>1</sup> Most sexual encounters in RV 144 were unlikely to be associated with risk of HIV transmission. Few incident cases in the study were from

well defined high-risk groups such as sex workers, homosexual and bisexual men, or injecting drug users. The study was not designed to assess risk-stratified efficacy rates and no significant interaction between baseline risk and efficacy was noted,<sup>1</sup> although estimated vaccine efficacy was greater than 40% in the low-risk groups at baseline, and less than 5% in high-risk participants. In other diseases, sufficient challenge doses can overwhelm vaccine-induced protective immune responses.<sup>2</sup> The modest success noted in RV 144 could be because of low viral challenge encountered in the study population.

Results of non-human-primate challenge studies with high-dose, intravenous simian immunodeficiency virus (SIV) and pathogenic simian HIV have suggested that protection from infection is not feasible, but a favourable modification of early viral burden and clinical outcome is achievable.<sup>1</sup> A notable outcome in RV 144 was the absence

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US Military HIV Research Program, Division of Retrovirology, Walter Reed Army Institute of Research, Rockville, MD, USA (M L Robb MD, N L Michael MD, J H Kim MD); Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand (S Rerks-Ngarm MD, P Kunasol MD, C Khamboonruang MD, Prof P Thongcharoen MD); Thai (S Nitayaphan MD) and US Army (P Morgan MS, M Benenson MD) Components, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; Vaccine Trials Centre (Prof P Pitisuttithum MD) and Data Management Unit (J Kaewkungwal PhD), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; Biophics, Bangkok, Thailand (J Kaewkungwal); Henry Jackson Foundation, Rockville, MD, USA (P Morgan, M Benenson); Walter Reed Army Medical Center, Washington, DC, USA (R M Paris MD); National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA (J Chiu MD, E Adams MD); Global Solutions for Infectious Diseases, South San Francisco, CA, USA (D Francis MD); Sanofi Pasteur, Swiftwater, PA, USA (S Gurnathan MD, J Tartaglia PhD); Fred Hutchinson Cancer Research Center, Seattle, WA, USA (P Gilbert PhD); EMMES Corporation, Rockville, MD, USA (D Stablein PhD); and US Army Medical Materiel Development Activity, Fort Detrick, MD, USA (J H Kim)

Correspondence to:  
Dr Jerome H Kim, 1600 E Gude  
Drive, Rockville, MD 20850, USA  
jkim@hivresearch.org

of an effect on viral load in vaccine recipients.<sup>1</sup> Most of these non-human-primate studies used intravenous or non-physiological, high-dose mucosal challenge doses of virus. Non-human-primate challenge studies<sup>3,4</sup> with repeat, low-dose mucosal challenge with SIV after vaccination have shown protection from acquisition with no or variable effect on viral load or clinical outcome in animals with breakthrough infection. These findings are consistent with the notion that available vaccines against SIV and simian HIV afford a reduction in acquisition risk in repeat, low-dose mucosal challenge experiments that more closely model human transmucosal risk. Taken together, these findings also suggest that the immune responses associated with protection from infection are mostly distinct from those needed for reduction of viraemia and improved clinical outcome, and are similar to the results of a summary of data from human trials of breakthrough infections with the ALVAC-protein boost regimen and an SIV non-human-primate challenge study.<sup>5-7</sup>

The RV 144 study was designed to acquire endpoints over 3.5 years after initial vaccination in more than 16 000 volunteers with 90% statistical power to address the acquisition objective of 50% efficacy. This population size and extended follow-up was needed because of the ten-fold reduction in yearly HIV incidence in Thailand as a consequence of a vigorous public health campaign for prevention of HIV/AIDS.<sup>8,9</sup> The trial was not designed to define time-dependent effects. Nevertheless, the data suggest that efficacy fell during the extended observation period, although this finding was not significant.<sup>1</sup>

We previously reported<sup>1</sup> that baseline behavioural risk characteristics were balanced by treatment group and associated with different placebo group transmission rates ranging from 0.227 per 100 person-years in the low-risk group to 0.364 per 100 person-years in the high-risk group ( $p=0.005$ , adjusted for treatment). However, estimates of vaccine efficacy were not significantly different when compared by baseline behavioural risk covariate or any other parameter assessed, including sex, age, and baseline partnership status.<sup>1</sup>

We aimed to further explore, in a post-hoc analysis, the interaction of risk behaviour and efficacy during the full course of the study and examine time-dependent estimates of efficacy to guide the design of future efficacy trials for HIV vaccines.

## Methods

### Study design and participants

The main study methods and results including the screening, enrolment, and retention data by group have been published previously.<sup>1</sup> Briefly, RV 144 was a randomised, multicentre, double-blind, placebo-controlled efficacy trial testing the combination of the HIV vaccines ALVAC-HIV (vCP1521) and AIDSVAX B/E to prevent HIV infection or reduce setpoint viral load. Male and female volunteers aged 18–30 years were recruited from the community irrespective of HIV risk

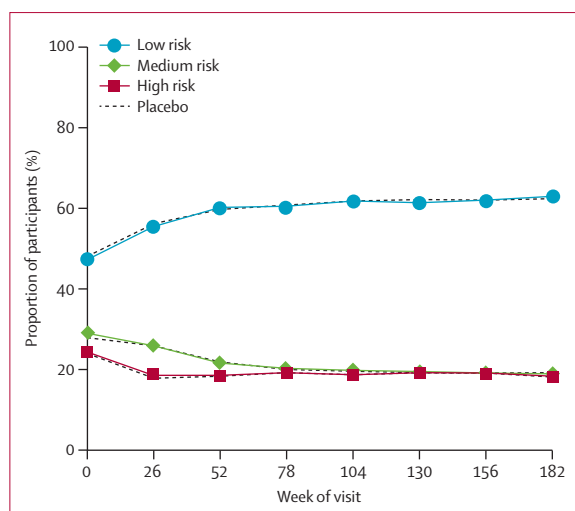
through a separate screening protocol. Volunteers received a trial information briefing and gave written informed consent for participation in the screening protocol. HIV testing was done, and a follow-up visit at one of the eight clinical research sites was scheduled for 2–3 weeks later.

### Procedures

Volunteers returned for follow-up after the screening visit, were informed of their HIV test results and, if seronegative, written informed consent for participation in the trial was obtained and vaccinations begun. The protocol was reviewed and approved by the Ethical Committees of the Ministry of Public Health, the Royal Thai Army, Mahidol University, and the Human Subjects Research Review Board of the US Army Medical Research and Materiel Command.

Vaccinations were given over 24 weeks. The ALVAC-HIV (vCP1521) or placebo prime was given in the left arm at weeks 0, 4, 12, and 24. Boosting with AIDSVAX B/E or placebo was given in the right arm at weeks 12 and 24. The volunteers were followed up with HIV testing (with appropriate counselling before and after the test) every 6 months for 3 years. Plasma samples for HIV-1 diagnostics were taken at 0 weeks and 24 weeks, and every 6 months during the follow-up phase. Research staff provided education about reduction of risky behaviours during each vaccination and post-test counselling visit. The scheme for clinical trial conduct from screening to treatment and analysis allocation is published elsewhere.<sup>1</sup>

Assessment of HIV risk behaviour within the preceding 6 months was done at baseline, 24 weeks, and each 6 month follow-up visit with a self-administered questionnaire. Volunteers had to classify whether their everyday behaviour placed them at risk for HIV infection. The questionnaire then identified specific risk behaviours for HIV acquisition. At each visit, participants were classified as high risk if in the past 6 months they met one of the following criteria: reported that their behaviour placed them at risk for HIV; had shared needles when injecting drugs; had two or more sexual partners; had an HIV-positive sexual partner; had not used a condom during their last sexual contact (if this sexual contact had been within the past 6 months) with a sex worker, casual partner, same-sex partner, drug-injecting partner, or partner with several partners; had symptoms of a sexually transmitted infection; had used injecting drugs while in prison; or were employed at baseline as prostitutes or in the restaurants and bars where commercial sex transactions were commonly organised. Volunteers were deemed low risk if, in the previous 6 months, they perceived their behaviour did not place them at risk of HIV infection; had no or one sexual partner and no sex with sex workers, casual partners, same-sex partners, HIV-positive partners, drug-injecting partners, or partners with many partners; or had not been in prison



**Figure 1: Proportion of participants in each risk category over time**

Participants were classified as low, medium, or high risk on the basis of questionnaires administered at baseline and every six months thereafter for 3.5 years.

and reported no symptoms of sexually transmitted infections. The moderate risk category contained people with neither low nor high risk—eg, an individual with a single partner who was a sex worker, injecting drug user, same-sex partner, or casual partner, but had used condoms at the last sexual encounter. Individuals who did not answer an item on the risk questionnaire but were otherwise inconsistent with the high-risk profile were classified as moderate risk. The risk score categories were devised from baseline responses through use of combined-group infection results in a blinded fashion. The terms high, moderate, and low are relative to each other within this population and do not equate to typical definitions in high-risk cohorts.

### Statistical analysis

Seven volunteers with prevalent infection at baseline were excluded, and the modified intention-to-treat population was used for the analyses (16 395). To account for missing data because of people leaving the study early, we estimated the proportion of individuals with identified risk characteristics with the product-limit survival method. Multiple proportional hazards regression models with treatment and time-varying risk covariates were analysed. Efficacy was higher in participants reporting low or medium risk at baseline than in those reporting high-risk behaviours at baseline. Taking all reported behaviours over time into consideration, participants with risk classified as high or ever increasing by the time-varying covariate model were compared with those who had low or medium risk at entry and throughout the study. Vaccine efficacy was also assessed for maximum degree of risk reported during the study and risk degree reported in the study before seroconversion. Vaccine efficacy estimates from the

	Baseline n (%)	Ever n (%)
Everyday behaviour puts at risk	1620 (9.9%)	5613 (36.1%)
Needle sharing	133 (0.8%)	1250 (8.2%)
Two to four sex partners	1034 (6.3%)	2745 (17.5%)
More than four sex partners	205 (1.3%)	502 (3.2%)
No condom with casual partner	936 (5.7%)	2490 (15.9%)
No condom with sex-worker partner	62 (0.4%)	291 (1.9%)
No condom with same-sex partner	169 (1.0%)	429 (2.7%)
Condom with HIV-positive partner	227 (1.4%)	597 (3.8%)
No condom with HIV-positive partner	29 (0.2%)	143 (0.9%)
No condom with injecting drug user partner	18 (0.1%)	97 (0.6%)
No condom with many sex partners	258 (1.6%)	753 (4.8%)
Symptoms of sexually transmitted infection	479 (2.9%)	1613 (10.4%)
Injecting drug use while in prison	38 (0.2%)	181 (1.2%)
Occupation as sex worker*	86 (0.5%)	..
Works in bar or restaurant where commercial sex transactions happen*	470 (2.9%)	..
Total number of people in at least one high-risk category	3945 (24.1%)	9187 (58.2%)

\*Data collection at baseline only.

**Table 1: Behavioural risk indicators for HIV infection at baseline and ever reported during the study**

	Vaccine			Placebo			Efficacy†
	Events (n)	% infected	SE	Events (n)	% infected	SE	
6 months	5	0.06%	0.028%	11	0.14%	0.042%	54.5%
12 months	12	0.15%	0.044%	30	0.38%	0.069%	59.9%
18 months	24	0.31%	0.063%	43	0.55%	0.083%	44.0%
24 months	32	0.41%	0.072%	50	0.64%	0.090%	35.7%
30 months	37	0.48%	0.078%	58	0.74%	0.097%	36.0%
36 months	45	0.58%	0.086%	65	0.84%	0.103%	30.4%
42 months	51	0.68%	0.096%	74	0.96%	0.111%	29.2%

\*Vaccine efficacy=100×(1-% vaccine infection/% placebo infection). †Figures calculated before rounding.

**Table 2: Cumulative vaccine efficacy\* at 6 month intervals for the modified intention-to-treat population determined from Kaplan-Meier infection rates**

Kaplan-Meier infection estimates were calculated every 6 months. A non-parametric estimate of the relative hazard function and confidence intervals were calculated.<sup>10</sup> Descriptive statistics were generated and pointwise Wilcoxon tests of viral load were done. Two-tailed p values are reported.

### Role of the funding source

ALVAC-HIV (vCP1521) and ALVAC placebo were supplied by the manufacturer, Sanofi Pasteur. AIDSVAX and AIDSVAX placebo (VaxGen) were purchased by the Division of AIDS, National Institute of Allergy and Infectious Diseases, for the purpose of this trial. The US Army Medical Research and Materiel Command participated fully in data collection, determination of the analysis plan, and interpretation of data. The National Institute of Allergy and Infectious Diseases also participated in analysis and data interpretation. The corresponding author had full access to all the data in the

study and had final responsibility for the decision to submit for publication (each of the partners had the opportunity to comment).

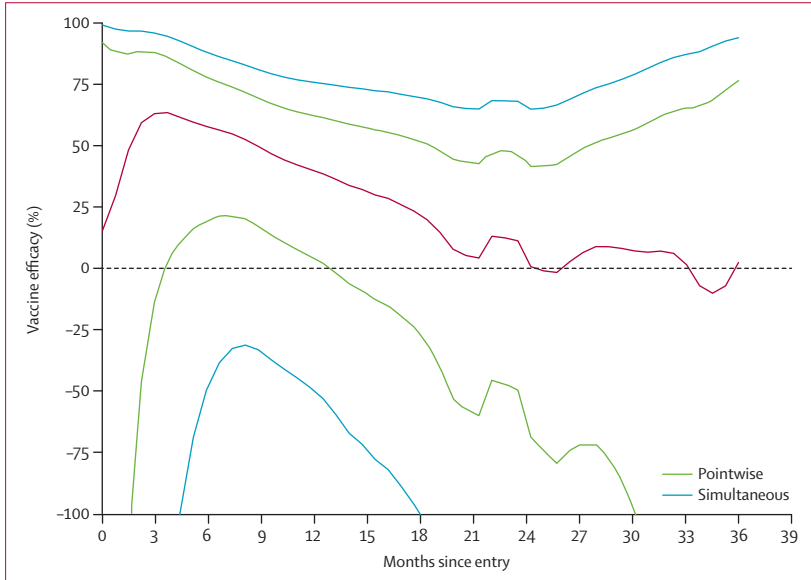
**Results**

The proportion of participants classified as low risk increased, and the numbers in the medium and high risk

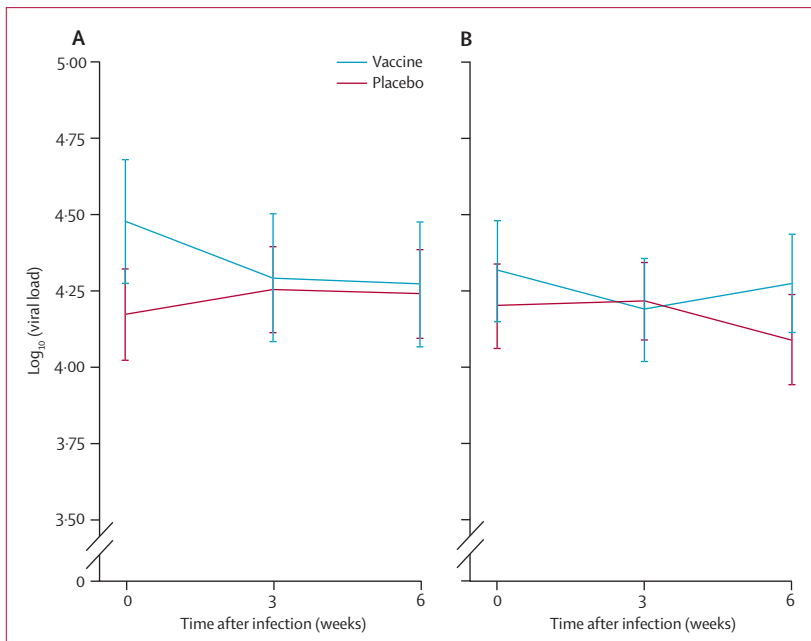
categories fell, during the first 52 weeks of the study, and remained stable thereafter (figure 1). The distribution of risk for both overall category and individual risk items (data not shown) between treatment groups was balanced. Condom use was stable during the study for all partner types. The proportions of men and women in each risk category were similar (data not shown).

Participants could skip a question or report “I don’t know or I am not sure”, and these response rates fell as the study progressed. For example, 1218 of 16 373 (7.4%) respondents declined to answer the question about injecting drug use with needle sharing at study entry, but at the end of the study 303 of 14794 (2.0%) declined to answer, with a small corresponding increase in reported rates both affirming and denying this behaviour over time. 105 (34.7%) of the participants who did not answer at the end of the trial also did not answer this question at baseline. Although the rates for individual and overall risk category did not systematically increase over time, the number of people who reported a high-risk factor at least once increased (table 1). Treatment groups did not differ in risk categories at baseline or with time. At baseline, more people in the placebo group had seven of the 15 risk characteristics than in the intervention group, with a maximum excess risk disparity of 18 participants. More people in the vaccine group had the other eight risk characteristics. 5613 (36%) of participants reported a self-assessment of high-risk behaviour at least once during the study. Generally, all other specific risk items were far less common than self-reporting of risk. Taken together, the proportion of participants self-classified or assigned to the high-risk group on the basis of specific responses rose from 24.1% at entry to 58.2% when including all timepoints in the study (table 1). The number of HIV infections was similar in baseline high-risk (45) and low-risk participants (46) despite different transmission rates because low-risk participants were more common at baseline. However, most infections (84) were identified in participants who reported high-risk behaviour at baseline or during at least one subsequent visit. An additional 39 HIV infections were diagnosed in participants who initially reported low-risk (n=28, 14 vaccine and 14 placebo) or medium-risk behaviour (11, five vaccine and six placebo) and subsequently reported at least one period of higher-risk behaviour. The interaction of risk with vaccine efficacy was significant (p=0.01) between participants reporting high-risk or increased-risk behaviour at least once and those reporting medium risk or low risk throughout the study on a time-varying basis. The vaccine efficacy estimate for participants who maintained low or medium risk from entry throughout the entire study was 68% (95% CI 34–84, p=0.002). We noted little vaccine effect for the high-risk group (vaccine efficacy 5%, 95% CI –46 to 38).

Although we identified an interaction with risk, the most important risk behaviours for HIV transmission contributed little to the findings of RV 144. For example, although injecting drug use with needle sharing was



**Figure 2: Vaccine efficacy point estimates over time**  
Vaccine efficacy rates are given over time (red line) with 95% pointwise CIs (green line) and 95% simultaneous CIs (blue line).



**Figure 3: Viral load for vaccine and placebo groups**  
Viral loads measured after infection are plotted for vaccine and placebo groups restricted to those who acquired HIV within 600 days of first vaccination (A) or after 600 days (B). 0 weeks is time of diagnosis of HIV infection. Error bars show the SE.



commonly reported ( $n=1250$  [8.2%]), only five (two vaccine and three placebo) HIV infections were reported in this group. In men reporting sex with men, only 16 HIV infections were noted (eight vaccine and eight placebo).

Vaccine efficacy fell at each interval (table 2), with endpoint ascertainment after 12 months, but the interaction of time from first immunisation and outcome was not significant ( $p=0.36$ ).<sup>1</sup> Nevertheless, the early timepoint efficacy estimates reported after completion of the vaccine series were substantially greater than those at conclusion of the study—vaccine efficacy was 54.5% at 6 months and 59.9% at 12 months compared with 29.2% at 42 months. The transmission rate for the placebo group varied modestly from 0.38 per 100 person years in year one to 0.26 per 100 person years in the final year of the investigation. In proportional hazards models that specified the log hazard ratio (vaccine vs placebo) as various smooth functions of time (linear, log-linear, quadratic, and piece-wise cubic polynomials in three or four segments), results were generally consistent with efficacy, which was most clearly evident early and declined from the second year of follow-up to the end of the study (data not shown). A non-parametric analysis gave a similar result, with early instantaneous hazards efficacy falling to 0 by 18 months (figure 2).

In an additional post-hoc analysis we assessed the relation between timing of infection and viral load. The viral-load endpoint was the average of three samples acquired during the first 6 weeks after serodiagnosis of HIV infection. This endpoint was assessed for acquisition events arising within 600 days of initial vaccination (a period with high efficacy rate estimates) separately from events reported after this period when efficacy fell. We detected no difference in viral load at any timepoint after infection or in mean early viral load (the co-primary endpoint) between the vaccine and placebo groups when segregated by proximity to vaccination (figure 3). The effect of vaccine on viral load did not differ either by baseline risk group or in participants classified as high risk or increased compared with baseline risk.

## Discussion

Vaccine efficacy in the RV 144 trial was unrelated to baseline variables including risk assessment (panel). The risk assessment variable is significant with respect to outcome when considered over the course of the study. Further, the efficacy estimate was highest in the first 6 months after completion of vaccination and fell rapidly.

Risk of infection is a complex, compound estimate of several effects but can be simply assessed.<sup>11</sup> Aggregate risk of infection is a function of donor challenge (eg, risk that source is HIV positive, viral load, presence of cofactors including sexually transmitted infections and bleeding), recipient susceptibility (eg, genetically defined host characteristics, route of infection, presence of cofactors), and frequency of exposure.

### Panel: Research in context

#### Systematic review

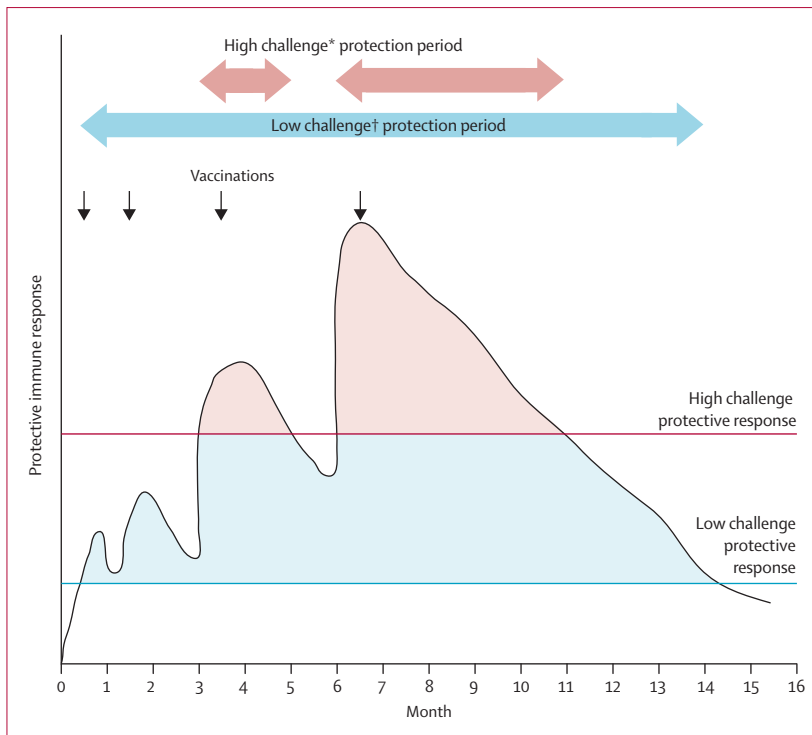
We systematically searched PubMed with the search terms “vaccine efficacy”, “HIV vaccine trial”, and “HIV vaccine clinical study” for HIV vaccine efficacy trials published in English to identify all randomised controlled trials with behavioural data and a positive outcome. We did not identify any previous studies of HIV vaccines showing efficacy. There was no restriction on dates of publication.

#### Interpretation

The efficacy and benefit noted in RV 144, which enrolled a population with a low incidence of HIV infection, fell quickly after 12 months and accrued mainly to participants who did not report or perceive themselves to show traditional HIV risk behaviours. Future studies will need to account for participant risk and temporal effects. This pox-protein prime boost regimen might show improved efficacy with extended boosts.

For example, HIV infection in individuals with deletions of *CCR5* are uncommon, but if they are exposed frequently the cumulative probability of encountering someone infected with the X4 virus mitigates the protective benefit of this element of genetic resistance.<sup>12</sup> Furthermore, data from human vaccine and challenge experiments provide convincing evidence that induction of protective immunity can be overcome with a single sufficiently large challenge.<sup>2</sup> In non-human primate studies, to reproducibly and efficiently overcome infectious challenge doses and routes seems to need an immune response that is unachievable for the current generation of vaccines. In Vax003, a trial<sup>13</sup> that used AIDSVAX B/E in Thai injecting drug users, the absence of efficacy might have been because of the stringency of intravenous challenge when compared with the intravaginal and intrarectal routes. This stringency could be because of the circumvention of mucosal barriers and related genetic bottlenecks or the avoidance of vaccine-associated immune responses at mucosal sites. Several lines of evidence<sup>14–16</sup> suggest that the challenge experienced by injecting drug users is higher in magnitude and genetic diversity than both that faced by non-injecting-drug users and that faced by people infected by a non-intravenous route. Possibly, human vaccines tested in efficacy trials thus far provided only modest time-sensitive reduction in host susceptibility that was undone by the aggregate transmission challenge intensity.

Vaccine-induced immune responses can reasonably be assumed to be independent of volunteer risk status. The absence of efficacy in high-risk participants in RV 144 could be because of either the higher challenge per exposure or more frequent exposure, or both, compared with low-risk participants, with participants infected if the threshold exposure occurred when immune responses were inadequate to contain the virus (figure 4). By contrast, the population maintaining low risk throughout the study



**Figure 4: Interaction of challenge intensity and vaccine efficacy**

The black line shows the scale of protective vaccine-induced immunity, which rises after each immunisation and falls subsequently with time. \*High challenge=high dose or frequency. †Low challenge=low dose and frequency.

(in whom efficacy was noted) probably have fewer and possibly less challenging exposures than the high-risk group (figure 4). Frequency and route of exposure, and cofactors such as sexually transmitted infections are the basis for consideration of the different degrees of challenge intensity<sup>17,18</sup> and, correspondingly, the different magnitudes of vaccine-induced immunity needed to achieve protection against HIV infection. Furthermore, we can deduce that vaccine-induced responses must be both high in magnitude and sustained to achieve similar efficacy in high-intensity challenge populations. Figure 4 shows a modest, time-limited protective immune response (as reported in RV 144) and suggests an additional boost or other augmentation of immune response would improve efficacy for all risk categories.

A second possibility assumes a more complex model in which different immune responses protect against high-risk and low-risk challenges (eg, responses might occur in different mucosal compartments); the differential decay of these protective responses could explain the early protective effect seen in RV 144. Correlation of immune responses induced by the ALVAC-HIV and AIDSVAX B/E regimen to the temporal pattern of protection will be crucial to guide future vaccine development.

Many researchers think that most HIV vaccines under development will not prevent acquisition of HIV infection because they do not stimulate production of neutralising antibodies.<sup>19,20</sup> A more realistic goal for vaccine

development is thought to be induction of T-cell immunity to reduce early viral load and slow disease progression, as has been noted in high-dose challenge studies in non-human primates<sup>21–23</sup> and inferred from studies of elite controllers and long-term non-progressors infected with HIV.<sup>24</sup> Despite the apparent absence of neutralising antibodies against primary HIV isolates or broadly neutralising activity, the ALVAC prime and AIDSVAX boost reduced acquisition by 31.2% at 42 months.<sup>1</sup> This regimen did not reduce early viral load even when examined in the period shortly after vaccination when anti-acquisition efficacy seems highest. This result is consistent with the notion that efficacy against acquisition requires a different set of immune effectors from those needed for reduction in viral load and altered prognosis.

Haynes and colleagues<sup>25</sup> reported that IgG against a conformational glycoprotein 120 V1V2 epitope was inversely correlated with infection in RV 144. These data prompted Barouch and co-workers<sup>7</sup> to look for anti-V2 responses in non-human primates vaccinated with adenovirus type 26 and modified-vaccinia-ankara vectored SIV inserts; anti-(SIV)V2 responses were inversely correlated with infection risk. These findings raise additional hypotheses related to the potential decay of immune responses in the plasma or mucosal compartments.

The value of a vaccine affording modest protection in low-challenge-intensity settings as a public health intervention is questionable, but some researchers argue that such a vaccine might be cost effective in the Thai setting.<sup>26,27</sup> Nevertheless, the value of protection against human-to-human transmission of HIV cannot be underestimated. Further elucidation of the nature of protection afforded in more permissive settings could allow optimisation of vaccine strategies to achieve qualitatively and quantitatively superior vaccines with expanded efficacy. Our data should be carefully considered in terms of the inherent risks of a post-hoc analysis and are intended to identify subjects deserving further consideration in future efficacy trials. The questions raised by the data from RV 144 are probably more important to the future of HIV vaccine development than are the primary findings of the trial. Among these issues, the temporal nature of protection and the interaction with risk should be studied in more detail in HIV vaccine trials.

#### Contributors

MLR, JHK, DS, and NLM wrote the report and contributed to study design and management and data analysis. PG contributed to data analysis and Article preparation. SR-N, SN, PP, JK, PK, CK, PT, PM, MB, RP, JC, and EA contributed to study design and execution, and collection and analysis of primary trial data and risk information. DF, SG, and JT are representatives of the manufacturers of the products studied and were involved in study design and oversight and data analysis and interpretation.

#### Conflicts of interest

SG and JT are employees of Sanofi Pasteur, the commercial manufacturer of ALVAC. All other authors declare that they have no conflicts of interest.



### Acknowledgments

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