

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 Gurunathan, 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 (16 395 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 144¹ suggest that a vaccine to prevent acquisition of HIV infection is possible.¹ 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.¹ 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,¹ 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.² 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.³ A notable outcome in RV 144 was the absence

Lancet Infect Dis 2012;
12: 531–37

Published Online
May 30, 2012
DOI:10.1016/S1473-
3099(12)70088-9

See [Comment](#) page 499

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 Gurunathan MD, J Tartaglia PhD); Fred Hutchinson Cancer Research Center, Seattle, WA, USA (P Gilbert PhD); EMMS 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.¹ Most of these non-human-primate studies used intravenous or non-physiological, high-dose mucosal challenge doses of virus. Non-human-primate challenge studies^{3,4} 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.⁵⁻⁷

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.^{8,9} 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.¹

We previously reported¹ 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.¹

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.¹ 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.¹

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

Download English Version:

<https://daneshyari.com/en/article/3411174>

Download Persian Version:

<https://daneshyari.com/article/3411174>

[Daneshyari.com](https://daneshyari.com)