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A tale of four studies: HIV vaccine immunogenicity and efficacy in clinical trials

Susan Zolla-Pazner, Nelson L Michael, Jerome H Kim

Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA (Prof S Zolla-Pazner PhD); Center for Infectious Diseases Research, Walter Reed Army Institute of Research, Silver Spring, MD, USA (N L Michael MD); International Vaccine Institute, Seoul, South Korea (J H Kim MD)

Abstract

The advanced-phase HIV prevention vaccine trials done in South Africa (HVTN 702) and in Thailand (RV144), which both investigated canarypox vectors and adjuvanted gp120 proteins, gave rise to different results. The South African trial did not find vaccine efficacy, whereas the Thai trial had modest, but statistically significant, success with the modified intention-to-treat analysis prespecified in the protocols of both studies. An understanding of the differences between the studies is required to avoid the possible, but erroneous, conclusion that the results from the South African trial negatively affect the results of the Thai trial.

Introduction

The phase 2b/3 HVTN 702 clinical trial¹ constitutes the sixth completed human active HIV immunisation vaccine trial that did not show efficacy. Of these six studies—VAX003,² VAX004,³ STEP,⁴ Phambili/HVTN 503,⁵ HVTN 505,⁶ and HVTN 702—three were not efficacious (STEP, Phambili/HVTN 503, and HVTN 505) and were stopped by the Data and Safety Monitoring Boards due to apparent excess of infections in the vaccine recipients or because futility was declared.

The HVTN 702 study in South Africa was modelled on, but did not replicate, the RV144 clinical vaccine trial,⁷ which was the only study that produced a modest, but statistically significant, reduction in HIV infection rate using the modified intention-to-treat analysis prespecified in the trial protocol. To understand the different results of RV144 and HVTN 702, it is important to compare them with two other trials that used the same immunogens, HVTN 097⁸ and HVTN 100 (table).⁹

Correspondence to: Prof Susan Zolla-Pazner, Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA, susan.zolla-pazner@mssm.edu.

Contributors

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Declaration of interests

We declare no competing interests.

Phase 2b/3 trial RV144 and phase 1b trial HVTN 097

RV144 used three immunogens—a recombinant canarypox, ALVAC (vCP1521 carrying *env gp120*, clade AE, strain 92TH023); and AIDSVAX (composed of gp120 proteins from clade B, strain MN and circulating recombinant form CRF01_AE, strain A244). Each gp120 protein was modified by an N-terminal 11 amino acid deletion and the addition of a herpes simplex virus gD protein-derived tag. Alum was used as an adjuvant. This regimen is abbreviated as P_{AE/B}/alum (table).

RV144 consisted of giving ALVAC at weeks 0 and 4, and then ALVAC and AIDSVAX at weeks 12 and 24. The study was done in Thailand and resulted in a vaccine efficacy of 31.2% (p=0.04).⁷ An analysis of six primary variables, measured with specimens from infected and uninfected vaccine recipients, identified a single independent correlate of reduced risk—a robust antibody response to the V1V2 domain of gp120.^{10–12} Subsequent studies identified several variables as secondary correlates of reduced risk (panel), and viral sieve analysis of breakthrough virus sequences suggested that mutations in V2 were associated with an increased risk of infection in participants who had received the vaccine.¹⁶

The immunogenicity of the P_{AE/B}/alum RV144 regimen was subsequently tested in the HVTN 097 study in South Africa (table). An analysis of the immune responses in HVTN 097 found that South African participants had a higher concentration of IgG antibodies recognising the V1V2 region of gp120 than RV144 participants in Thailand had, and participants in the HVTN 097 trial had a significantly higher titre of antibodies specific for V1V2 epitopes from clade B and clade C.⁸ Antibody-dependent cell-mediated cytotoxic activity was statistically similar in HVTN 097 and RV144. Although there were differences in some of the immune responses in participants from South Africa who received the vaccine versus in participants from Thailand (especially with respect to higher T-cell responses in the Thai participants), the results indicated that, in terms of immunogenicity, the RV144 vaccine regimen was as good as, or better, in the South African trial than in Thai trial.

Phase 1/2 trial HVTN 100 and phase 2b/3 trial HVTN 702

Subsequently, HVTN 100 was initiated to investigate the immunogenicity of clade C immunogens that were modelled on, but different from, those used in RV144. The recombinant canarypox used in HVTN 100 contained the *gp120 env* gene of clade C, strain ZM96, rather than the *gp120 env* gene of clade AE, strain 92TH023, that was used in RV144. In HVTN 100, the protein immunogens consisted of gp120 proteins with the N-terminal deletion from clade C strains, TV1 and 1086 (without the herpes simplex virus-derived gD tags), rather than the clade B and clade AE gD-tagged gp120 proteins with the N-terminal deletion used in RV144. Another difference was the use of MF59 as an adjuvant in HVTN 100, rather than alum used in RV144 and HVTN 097 (the HVTN 100 and HVTN 702 regimens are abbreviated as P_C/MF59; table). The HVTN 100 study was done to define the immunogenicity of the P_C/MF59 regimen and to generate a go or no-go decision to proceed with a future phase 2b/3 study in South Africa, where the most prevalent infecting

HIV subtype is clade C. The phase 2b/3 HVTN 702 study used the same P_C/MF59 regimen that was used in HVTN 100 (table).

Comparisons of the related but dissimilar vaccine trials

The decision to proceed with the phase 2b/3 HVTN 702 study was based on four prespecified immunological criteria: the gp120-specific IgG antibody response rate, the gp120-specific IgG antibody magnitude, the CD4 T-cell response rate to the ZM96 Env protein, and the V1V2-specific antibody response rate.⁹ None of these criteria coincided with any of the primary or secondary correlates of reduced risk identified in RV144 (panel). The independent primary correlate of reduced risk in RV144, elevated magnitude of anti-V1V2 antibodies, was not used.

HVTN 702 began in 2016, and the planned end was in 2022; however, in February, 2020, the US National Institutes of Health announced that the study had been stopped by the US Data and Safety Monitoring Board on the basis of findings during an interim review that indicated that the regimen did not prevent HIV infection.^{1,18}

A comparison of the immunogenicity of the HVTN 100 P_C/MF59 regimen versus the RV144 P_{AE/B}/alum regimen was published by Bekker and colleagues.⁹ The immune profiles in these two studies were distinct, with the HVTN 100 P_C/MF59 regimen inducing higher CD4 T-cell responses and anti-gp120 binding antibodies, but a lower clade C anti-V1V2 IgG response rate, than the P_{AE/B}/alum regimen used in RV144 and HVTN 097. Subsequently, another study was published comparing immunological responses in RV144, HVTN 097, and HVTN 100.¹⁹ This study explored multivariate binding antibodies and T-cell response patterns elicited by P_{AE/B}/alum and P_C/MF59. The bivariate CD4 T-cell and anti-V1V2 IgG1 and IgG3 antibody response patterns were similar in the RV144 and HVTN 097 P_{AE/B}/alum trials, irrespective of the countries where the studies were done; these patterns were significantly different in individuals receiving the HVTN 100 P_C/MF59 regimen.

The finding that the P_C/MF59 HVTN 702 regimen did not prevent HIV infection raises the important question of why this vaccine did not provide even the modest positive result achieved with the P_{AE/B}/alum RV144 regimen. As noted, there were many differences between the RV144 and HVTN 702 clinical trials, any one of which—or any combination of which—could account for the different outcomes. For example, the *env gp120* genes in the recombinant canarypox immunogens in the studies were different; the gp120 proteins used were different; the subtypes of the proteins used in RV144 and HVTN 097 were from clades B and AE and were tagged with gD, whereas the proteins used in HVTN 100 and HVTN 702 were from clade C HIV strains and were not gD-tagged; the adjuvants were different, with alum used in RV144 and HVTN 097 and MF59 used in HVTN 100 and HVTN 702, a difference that, according to non-human primate studies, could have contributed to the low efficacy in HVTN 702;²⁰ there were changes in the number of booster doses, from two in RV144 to four in HVTN 702, which could have induced changes in non-neutralising, functional antibodies, as shown in studies with AIDSVAX B/E gp120;^{14,21} HIV incidence was more than ten times higher in the South African population than in the Thai populations;^{22,23} the HLA backgrounds of the studies' populations differed;^{24–26}

the prevalence of genital inflammatory diseases among women from South African and Thailand differed, which might have contributed to the release from the genetic bottleneck for infecting virions due to inflammatory genital lesions;^{27–30} and the seropositivity prevalence of herpes simplex virus type 2 differed between South Africa and Thailand, hence the risk of genitourinary disease (independent of chlamydia and bacterial vaginosis) was different.^{30,31}

As detailed immunological, viral, and genetic data of the participants in HVTN 702 become available, it is anticipated that these findings will be compared with the extensive published data from RV144 and will, hopefully, illuminate the reasons for the different outcomes. Given the multiple variables in these studies, it would be erroneous to conclude that the negative results from HVTN 702 have any bearing on the conclusions reached as a result of the data generated in RV144.

Despite the fact that HVTN 702 did not show efficacy, this study is a valuable addition to data that will contribute to the development of an efficacious vaccine. Correlates of reduced infection rates can be identified even if vaccine trials do not result in clinical efficacy. Although a DNA and adenovirus vaccine regimen (HVTN 505) did not show HIV vaccine efficacy, correlates of reduced risk of HIV infection were nonetheless identified when comparing infected with uninfected vaccine recipients. These correlates included antibody-dependent cellular phagocytosis, antibody-mediated Fc-gamma receptor recruitment, polyfunctional CD4 and CD8 T cells, and anti-Env IgG3 antibodies.³² Similarly, although HVTN 702 failed to provide statistically significant protection from HIV infection, it might yet reveal immune responses that correlate with decreased risk of infection.

HIV vaccine trials—whether or not clinically effective—are providing valuable data for designing vaccines that will successfully reduce the incidence of HIV infection. The urgent need to continue with clinical vaccine studies is underscored by the valuable information that can only be generated by such trials.

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References

1. Gray GE, Bekker LG, Laher F, et al. Vaccine efficacy of ALVAC-HIV and bivalent subtype C gp120-MF59 in adults. *N Engl J Med* 2021; 384: 1089–100. [PubMed: 33761206]
2. Pitisuttithum P, Gilbert P, Gurwith M, et al. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. *J Infect Dis* 2006; 194: 1661–71. [PubMed: 17109337]
3. Gilbert PB, Peterson ML, Follmann D, et al. Correlation between immunologic responses to a recombinant glycoprotein 120 vaccine and incidence of HIV-1 infection in a phase 3 HIV-1 preventive vaccine trial. *J Infect Dis* 2005; 191: 666–77. [PubMed: 15688279]

4. Buchbinder SP, Mehrotra DV, Duerr A, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet* 2008; 372: 1881–93. [PubMed: 19012954]
5. Gray GE, Allen M, Moodie Z, et al. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. *Lancet Infect Dis* 2011; 11: 507–15. [PubMed: 21570355]
6. Hammer SM, Sobieszczyk ME, Janes H, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med* 2013; 369: 2083–92. [PubMed: 24099601]
7. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009; 361: 2209–20. [PubMed: 19843557]
8. Gray GE, Huang Y, Grunenberg N, et al. Immune correlates of the Thai RV144 HIV vaccine regimen in South Africa. *Sci Transl Med* 2019; 11: eaax1880. [PubMed: 31534016]
9. Bekker LG, Moodie Z, Grunenberg N, et al. Subtype C ALVAC-HIV and bivalent subtype C gp120/MF59 HIV-1 vaccine in low-risk, HIV-uninfected, South African adults: a phase 1/2 trial. *Lancet HIV* 2018; 5: e366–78. [PubMed: 29898870]
10. Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. *N Engl J Med* 2012; 366: 1275–86. [PubMed: 22475592]
11. Zolla-Pazner S, deCamp AC, Cardozo T, et al. Analysis of V2 antibody responses induced in vaccinees in the ALVAC/AIDSVAX HIV-1 vaccine efficacy trial. *PLoS One* 2013; 8: e53629. [PubMed: 23349725]
12. Zolla-Pazner S, deCamp A, Gilbert PB, et al. Vaccine-induced IgG antibodies to V1V2 regions of multiple HIV-1 subtypes correlate with decreased risk of HIV-1 infection. *PLoS One* 2014; 9: e87572. [PubMed: 24504509]
13. Gottardo R, Bailer RT, Korber BT, et al. Plasma IgG to linear epitopes in the V2 and V3 regions of HIV-1 gp120 correlate with a reduced risk of infection in the RV144 vaccine efficacy trial. *PLoS One* 2013; 8: e75665. [PubMed: 24086607]
14. Chung AW, Ghebremichael M, Robinson H, et al. Polyfunctional Fc-effector profiles mediated by IgG subclass selection distinguish RV144 and VAX003 vaccines. *Sci Transl Med* 2014; 6: 228ra38.
15. Yates NL, Liao HX, Fong Y, et al. Vaccine-induced Env V1-V2 IgG3 correlates with lower HIV-1 infection risk and declines soon after vaccination. *Sci Transl Med* 2014; 6: 228ra39.
16. Gartland AJ, Li S, McNevin J, et al. Analysis of HLA A*02 association with vaccine efficacy in the RV144 HIV-1 vaccine trial. *J Virol* 2014; 88: 8242–55. [PubMed: 24829343]
17. Rolland M, Edlefsen PT, Larsen BB, et al. Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2. *Nature* 2012; 490: 417–20. [PubMed: 22960785]
18. Cohen J. Combo of two HIV vaccines fails its big test. *Science* 2020; 367: 611–12. [PubMed: 32029605]
19. Zhao LP, Fiore-Gartland A, Carpp LN, et al. Landscapes of binding antibody and T-cell responses to pox-protein HIV vaccines in Thais and South Africans. *PLoS One* 2020; 15: e0226803. [PubMed: 31999736]
20. Vaccari M, Gordon SN, Fourati S, et al. Adjuvant-dependent innate and adaptive immune signatures of risk of SIVmac251 acquisition. *Nat Med* 2016; 22: 762–70. [PubMed: 27239761]
21. Pitisuttithum P, Nitayaphan S, Chariyalertsak S, et al. Late boosting of the RV144 regimen with AIDSVAX B/E and ALVAC-HIV in HIV-uninfected Thai volunteers: a double-blind, randomised controlled trial. *Lancet HIV* 2020; 7: e238–48. [PubMed: 32035516]
22. Vandormael A, Akullian A, Siedner M, de Oliveira T, Bärnighausen T, Tanser F. Declines in HIV incidence among men and women in a South African population-based cohort. *Nat Commun* 2019; 10: 5482. [PubMed: 31792217]
23. Robb ML, Eller LA, Kibuuka H, et al. Prospective study of acute HIV-1 infection in adults in east Africa and Thailand. *N Engl J Med* 2016; 374: 2120–30. [PubMed: 27192360]
24. Tshabalala M, Mellet J, Pepper MS. Human leukocyte antigen diversity: a southern African perspective. *J Immunol Res* 2015; 2015: 746151. [PubMed: 26347896]
25. Hurley CK, Kempenich J, Wadsworth K, et al. Common, intermediate and well-documented HLA alleles in world populations: CIWD version 3.0.0. *HLA* 2020; 95: 516–31. [PubMed: 31970929]

26. Gandhi RT, Bosch RJ, Rangsri R, et al. HLA class I alleles associated with mortality in Thai military recruits with HIV-1 CRF01_AE infection. *AIDS Res Hum Retroviruses* 2016; 32: 44–49. [PubMed: 26383907]
27. Sivro A, Schuetz A, Sheward D, et al. Integrin $\alpha_4\beta_7$ expression on peripheral blood CD4⁺ T cells predicts HIV acquisition and disease progression outcomes. *Sci Transl Med* 2018; 10: eaam6354. [PubMed: 29367348]
28. Haaland RE, Hawkins PA, Salazar-Gonzalez J, et al. Inflammatory genital infections mitigate a severe genetic bottleneck in heterosexual transmission of subtype A and C HIV-1. *PLoS Pathog* 2009; 5: e1000274. [PubMed: 19165325]
29. Tunthanathip P, Lolekha R, Bollen LJ, et al. Indicators for sexual HIV transmission risk among people in Thailand attending HIV care: the importance of positive prevention. *Sex Transm Infect* 2009; 85: 36–41. [PubMed: 18927180]
30. Looker KJ, Welton NJ, Sabin KM, et al. Global and regional estimates of the contribution of herpes simplex virus type 2 infection to HIV incidence: a population attributable fraction analysis using published epidemiological data. *Lancet Infect Dis* 2020; 20: 240–49. [PubMed: 31753763]
31. Kouyoumjian SP, Heijnen M, Chaabna K, et al. Global population-level association between herpes simplex virus 2 prevalence and HIV prevalence. *AIDS* 2018; 32: 1343–52. [PubMed: 29794495]
32. Neidich SD, Fong Y, Li SS, et al. Antibody Fc effector functions and IgG3 associate with decreased HIV-1 risk. *J Clin Invest* 2019; 129: 4838–49. [PubMed: 31589165]

Panel: RV144 correlates of reduced risk of HIV infection**Primary variables**

- Elevated magnitude of IgG antibodies binding to gp70 V1V2 (clade B, strain caseA2)^{10–12}

Secondary variables

- IgG antibodies binding to linear V2 peptides¹³
- IgG3 antibodies binding to gp70 V1V2^{14,15}
- Combination of low plasma anti-HIV-1 Env IgA antibodies and high levels of antibody-dependent cellular cytotoxicity¹⁰
- Combination of low plasma anti-HIV-1 Env IgA antibodies and binding avidity of Env-specific plasma IgG antibodies¹⁰
- Combination of low plasma anti-HIV-1 Env IgA antibodies and neutralising antibodies¹⁰
- Combination of low plasma anti-HIV-1 Env IgA antibodies and Env-specific CD4 T cells¹⁰
- HLA-A*02 positivity¹⁶

Table:

Design of clinical trials using recombinant canarypox and protein immunogens

	Prime	Protein boost	Adjuvant	Location	Description	Participants	Efficacy
RV144 ⁷ P _{AE/B} / alum	Recombinant canarypox (ALVAC; vCP1521) containing HIV-1 <i>gag</i> (clade B LAI), <i>pro</i> (clade B LAI), <i>env</i> (gp120 AE 92TH023), and <i>gp41</i> (clade B LAI) transmembrane anchor	AIDSVAX (gp120 [*] clade B, strain MN, with gD tag and gp120 [*] clade AE, strain A244, with gD tag)	Alum	Thailand	Phase 2b/3; efficacy; double-blind, placebo-controlled (n=16 402)	HIV uninfected adults 18–30 years of age, regardless of HIV risk	31.2% (p=0.04)
HVTN 097 ⁸ P _{AE/B} / alum	Recombinant canarypox (ALVAC-vCP1521) containing HIV-1 <i>gag</i> (clade B LAI), <i>pro</i> (clade B LAI), <i>env</i> (gp120 AE 92TH023), and <i>gp41</i> (clade B LAI) transmembrane anchor	AIDSVAX (gp120 [*] clade B, strain MN, with gD tag and gp120 [*] clade AE, strain A244, with gD tag)	Alum	South Africa	Phase 1b; immunogenicity; double-blind, placebo-controlled (n=100)	HIV uninfected adults 18–35 years of age	NA
HVTN 100 ⁹ P _C / MF59	Recombinant canarypox (ALVAC-vCP2438) containing HIV-1 <i>gag</i> (clade B LAI), <i>pro</i> (clade B LAI), <i>env</i> (gp120; clade ZM96.C), and <i>gp41</i> (clade B LAI) transmembrane anchor	gp120 [*] clade C, strain TV1, and gp120 [*] clade C, strain 1086 (no gD tag)	MF59	South Africa	Phase 1/2; immunogenicity; double-blind, placebo-controlled (n=252)	HIV uninfected adults 18–40 years of age at low risk of acquiring HIV	NA
HVTN 702 ¹ P _C / MF59	Recombinant canarypox (ALVAC-vCP2438) containing HIV-1 <i>gag</i> (clade B LAI), <i>pro</i> (clade B LAI), <i>env</i> (gp120; clade ZM96.C), and <i>gp41</i> (clade B LAI) transmembrane anchor	gp120 [*] clade C, strain TV1, and gp120 [*] clade C, strain 1086 (no gD tag)	MF59	South Africa	Phase 2b/3; efficacy; double-blind, placebo-controlled (n=5404)	HIV uninfected adults 18–35 years of age who are sexually active	None

* With N-terminal 11 amino acid deletion. NA=not applicable.