



# Revisiting the Correlate of Reduced HIV Infection Risk in the Rv144 Vaccine Trial

 Susan Zolla-Pazner,<sup>a</sup> Peter B. Gilbert<sup>b</sup>

<sup>a</sup>Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA

<sup>b</sup>Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center and Department of Biostatistics, University of Washington, Seattle, Washington, USA

**ABSTRACT** The RV144 vaccine trial is the only clinical study to have shown a modest but statistically significant decrease in HIV infection risk. RV144 and the subsequent studies identifying the level of V1V2-specific antibodies as a correlate of reduced infection risk are still controversial despite many papers supporting and expanding the initial study. We address these controversies and summarize active-immunization and passive-immunization experiments in nonhuman primates that support the initial finding.

**KEYWORDS** HIV, V1V2 domain, vaccine, antibodies, immune correlates

The RV144 human vaccine trial has, from its inception to the present day, been the subject of controversy (1–4). Nonetheless, it is widely recognized to have been the only human HIV vaccine trial to show a statistically significant reduction in the HIV infection rate, thus generating a data-based hypothesis for how a vaccine could reduce infection in humans.

Since the announcement of the modest but significant decrease in HIV infection in recipients of the RV144 regimen (immunization with recombinant canarypox and two gp120 proteins [5]) and the description of the level of V1V2-specific antibodies as a correlate of reduced risk (CoR) of HIV infection (6), a plethora of papers have been published that support and expand the initial study (7–14). Despite this, there is continuing controversy about the reliability and veracity of RV144 results (3, 4, 15). Here we address issues contributing to the skepticism about the results of RV144.

Desrosiers (4) surmised that the difference in HIV acquisition rates in the vaccine recipients versus the placebo recipients was due to a sudden nonlinear increase in acquisition in the placebo arm within the first year of the trial, i.e., a “bunching” of the placebo infections. This statement refers to the 30 infection events registered in a time interval of ~1 to 2 weeks which might suggest that “bunching” caused the spurious inference of positive vaccine efficacy (VE) (Fig. 1). However, the “bunching” is due to the fact that trial participants were followed at 6-month intervals and that the relevant points in Fig. 1 are the midpoints between the last negative and the first positive HIV assays (5); thus, the “bunching” simply reflects the midpoint between the 6-month and 12-month visits for those placebo recipients who became infected during this period. Similar “bunching” is seen for the five infections in the vaccine group (Fig. 1). Moreover, the “bunching” had no bearing on the inference of VE because alternative analyses gave similar results. For example, an estimate of VE based on a VE analysis comparing the cumulative probabilities of HIV infection over the whole 42-month follow-up period (5) gives results similar to that given by a proportional-hazards model analysis over the same follow-up period (10). Moreover, for all HIV-1 VE trials, VE results were essentially the same whether using estimated infection dates or infection diagnosis dates. For an example, see Hammer et al. (16).

In response to a discussion of the statistical methods used to analyze the RV144

**Citation** Zolla-Pazner S, Gilbert PB. 2019. Revisiting the correlate of reduced HIV infection risk in the RV144 vaccine trial. *J Virol* 93:e00629-19. <https://doi.org/10.1128/JVI.00629-19>.

**Editor** Viviana Simon, Icahn School of Medicine at Mount Sinai

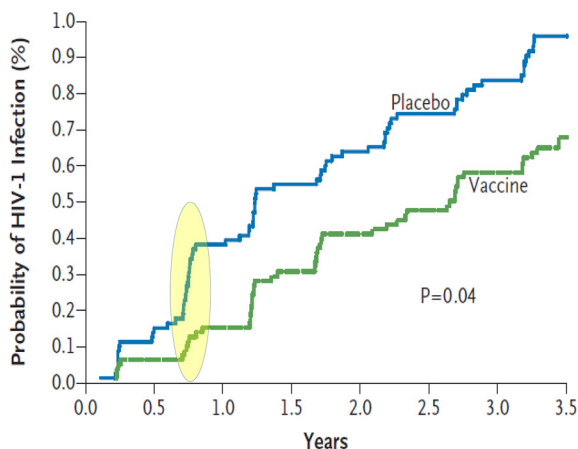
**Copyright** © 2019 American Society for Microbiology. All Rights Reserved.

Address correspondence to Susan Zolla-Pazner, Susan.Zolla-Pazner@mssm.edu.

*The views expressed in this article do not necessarily reflect the views of the journal or of ASM.*

**Accepted manuscript posted online** 12 June 2019

**Published** 13 August 2019



No. at Risk		Years			
Placebo	8198	7775	7643	7441	7325
Vaccine	8197	7797	7665	7471	7347
Cumulative No. of Infections					
Placebo		30	50	65	74
Vaccine		12	32	45	51

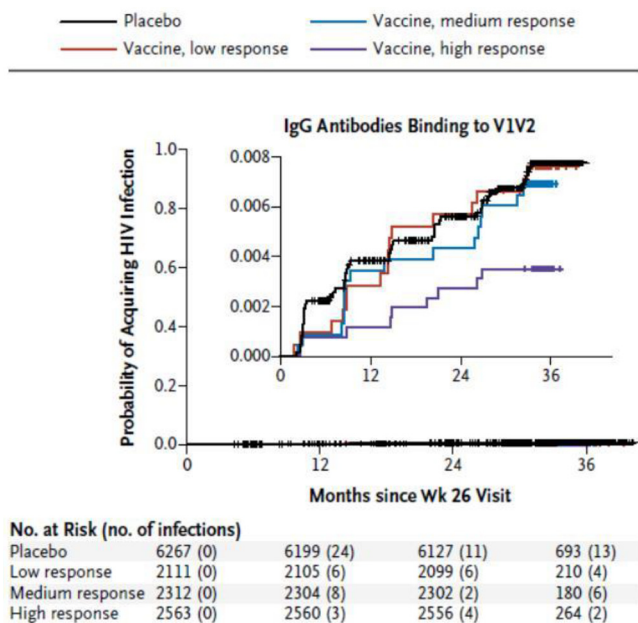
**FIG 1** The Kaplan-Meier cumulative acquisition rates of infection according to the modified intention-to-treat analysis. (Adapted from reference 28 with permission of the publisher.) Rather than representing “an anomalous nonlinear increase in acquisition in the placebo group in the first year of the trial” (4), the yellow ellipse highlights the midpoints between the 6-month and 12-month visits for the placebo recipients and vaccine recipients who became infected during the first 6 to 12 months of the trial.

study (17), Desrosiers stated that “the chance for no efficacy in the [RV144] trial was  $\geq 22\%$ , i.e., there was a less than 78% chance that there was protective efficacy... [This is] hardly a ringing endorsement” (4). However, given that HIV accounts for a massive burden of morbidity and mortality and that there is no direct evidence of even partial efficacy with any other HIV-1 vaccine, a 78% chance that the vaccine partially worked fulfils test-of-concept criteria for success as defined in other studies (18–21).

Criticism of the conclusions concerning the observed virus sieving effect in RV144 is based on a misinterpretation of the data: Desrosiers wrote that “amino acids present at positions 169 and 181 in the envelope were preferentially associated with HIV-1 acquisition in the vaccine arm compared to the placebo... Unfortunately the amino acid at position 169 in the vaccine was lysine and it was lysine at this position that was preferentially acquired in the vaccine group compared to the placebo group” (4). In fact, the opposite is true: the lysine at position 169 (K169) was preferentially acquired in the placebo group compared to the vaccine group, with 57/66 (86%) of infected placebo recipients having a K169 virus compared to 30/43 (70%) of infected vaccine recipients having a K169 virus. This resulted in a VE of 48% ( $P = 0.0036$ ) for viruses with K169 in contrast to an absence of statistically significant VE when there was a mismatch at K169 (11). Conversely, K169 was replaced with amino acids other than lysine in 9/66 (14%) of infected placebo recipients, whereas K169 was replaced by residues other than lysine in 13/43 (30%) breakthrough viruses from infected vaccine recipients. Additionally, a recent reanalysis showed a 7.2-fold-greater VE for K169 versus non-K169 viruses at 12 months after the first vaccination ( $P$  value for VE,  $<0.05$ ) (22).

The sieving effect also supported the antibody studies. Sera from RV144 vaccine recipients drawn 6 months after the first vaccination showed a drastic reduction in the mean binding response to V2 peptides in which K169 was replaced with V169, indicating that a substantial proportion of vaccine recipients mounted an antibody response that targeted K169 (14), the residue identified in sieve analysis performed by Rolland et al. (11). Additionally, the specificity of V2-specific monoclonal antibodies derived from recipients of the RV144 vaccine regimen targeted a V2 epitope that included K169 (8).

The independent inverse CoR in RV144 was identified as high levels of antibodies



**FIG 2** Estimated cumulative HIV-1 incidence curves from placebo recipients and from vaccine recipients with low, medium, and high IgG antibody responses showing specific binding to the V1V2<sub>CaseA2</sub>-gp70 fusion protein. (Adapted from reference 19 with permission of the publisher.)

reactive with the V1V2<sub>CaseA2</sub>-gp70 fusion protein (6, 13, 14), and, using a different technology, a CoR in RV144 was also identified by interrogating plasma reactivity with V2 peptides (7, 14). Thus, “technical issues” did not influence the identification of the CoR as suggested in one critique (4). An additional critique was that median enzyme-linked immunosorbent assay (ELISA) values for V1V2 antibodies were similar for infected and uninfected vaccine recipients. In fact, the CoR was identified as a difference in risk of infection between vaccine recipients with high and low anti-V1V2 antibody levels ( $P = 0.02$ ) (Fig. 2), so median values played no role.

While the data supporting the interpretation of efficacy of the ALVAC/gp120 vaccine regimen tested in RV144 have grown in the years since publication of the clinical trial results, note that (i) conclusions from the initial RV144 correlates study were described as a correlate of reduced risk rather than of protection (6); (ii) a correlate of protection is difficult to validate in human efficacy trials since the number and frequency of exposures to infection are unknown and since statistical analyses that directly assess correlates of protection in humans require assumptions that are not fully verifiable; (iii) “the immune correlates study generated the *hypothesis* that V1V2 antibodies may have contributed to protection against HIV-1 infection” (6); (iv) the sieve analysis provided “evidence that vaccine-induced V2 responses *plausibly* had a role in the partial protection conferred by the RV144 regimen” (11); (v) while the sources of evidence for CoRs specific to regions of Env are concentrated in V1V2, there are suggestions that antibodies to other epitopes, such as C1 in gp120, may be important (23); and (vi) there is no reason to think that other vaccine-induced antibodies as well as cellular immune activities will not and have not played a role in control or prevention of infection. In fact, several studies, including the original case-control report, have indicated that antiviral activities mediated via the Fc fragment of antibodies (antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement activation) may have played a role in the reduced rate of infection in RV144 (6, 24–26) and similar findings have been published in terms of the involvement of Fc-mediated antiviral modalities in prevention and control of disease in other studies in humans and nonhuman primates (NHPs) (27–31).

As noted, the RV144 correlates study was “designed to be hypothesis-generating

and sensitive for discovering strong correlates of infection risk" (6). In the years since the publication of the analysis of the RV144 immune correlates, the RV144-generated hypothesis that V1V2-specific antibodies were involved in reduced HIV infection risk has been tested repeatedly in NHPs (32). To date, there have been seven published studies showing that delivery of various vaccines led to protection, control, and/or delayed infection of simian immunodeficiency virus (SIV) mac251 (SIV<sub>mac251</sub>), SIV<sub>smE660r</sub> and simian-human immunodeficiency virus (SHIV) 1157ipEL-p (SHIV<sub>1157ipEL-p</sub>) (33–39). In addition, passive immunization of NHPs with a human V2i-specific MAb, 830A, followed by challenge with SHIV<sub>BaL</sub> resulted in reduced plasma and peripheral blood mononuclear cell virus levels and decreased viral DNA levels in lymphoid tissues compared to controls, although too few animals remained uninfected to achieve significance with respect to reducing the risk of infection (40). These NHP studies support the hypothesis generated by the RV144 data and indicate that it is imperative that the RV144 results not be dismissed.

In this context, it is relevant that there are two large proof-of-concept clinical trials of HIV vaccines currently in progress. The first, HVTN 702, is testing a vaccine consisting of a recombinant ALVAC (carrying a clade C gp120 gene as well as clade B *gag* and *pro* genes) and two gp120 Env proteins from clade C strains (TV1 and 1086) adjuvanted with MF59 (<https://clinicaltrials.gov/ct2/show/NCT02968849>). A second trial, HVTN 705, is testing a vaccine consisting of recombinant adenovirus 26 (Ad26.Mos4 expressing bioinformatically optimized global mosaic antigens designed to expand immunological coverage of HIV-1 M group viruses) and an aluminum-adjuvanted clade C Env gp140 protein (<https://clinicaltrials.gov/ct2/show/NCT03060629>). While the HVTN 702 vaccine regimen is more similar to the RV144 vaccine regimen than to that in HVTN 705, the former differs significantly from RV144 in many respects, including the *env* gene in the vector, the Env proteins, and the adjuvant. Given the differences in vaccine regimens, if either or both of these trials result in a significant reduction of HIV infection rates, the CoR(s) could be the same as or different from those identified in RV144 since different vaccines may work via different mechanisms. Similarly, if one or neither results in significant reduction in infection risk, the results may have little bearing on the RV144 findings.

Thus, the RV144 results need to be further tested in human vaccine trials that replicate the regimen of RV144 and in NHP studies that can provide direct (rather than correlative) data representing the role played and the mechanisms by which V1V2 antibodies impact infection with HIV, SIV, and SHIV.

## ACKNOWLEDGMENTS

This report was supported in part by an NIH program grant, P01 AI100151. Partial support for S.Z-P. was also provided by the Icahn School of Medicine at Mount Sinai.

## REFERENCES

- Burton DR, Desrosiers RC, Doms RW, Koff WC, Kwong PD, Moore JP, Nabel GJ, Sodroski J, Wilson IA, Wyatt RT. 2004. HIV vaccine design and the neutralizing antibody problem. *Nat Immunol* 5:233–236. <https://doi.org/10.1038/ni0304-233>.
- Cohen J. 2009. HIV/AIDS research. Beyond Thailand: making sense of a qualified AIDS vaccine "success". *Science* 326:652–653. <https://doi.org/10.1126/science.326.652>.
- Cohen J. 2009. Unrevealed analysis weakens claim of AIDS vaccine "success". *Sci Insider*, vol 362.
- Desrosiers RC. 2017. Protection against HIV acquisition in the RV144 trial. *J Virol* 91:e00905-17.
- Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, Prensri N, Namwat C, de Souza M, Adams E, Benenson M, Gurunathan S, Tartaglia J, McNeil JG, Francis DP, Stablein D, Bix DL, Chunsuttiwat S, Khamboonruang C, Thongcharoen P, Robb ML, Michael NL, Kunasol P, Kim JH. 2009. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 361:2209–2220. <https://doi.org/10.1056/NEJMoa0908492>.
- Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, Alam SM, Evans DT, Montefiori DC, Karnasuta C, Sutthent R, Liao H-X, DeVico AL, Lewis GK, Williams C, Pinter A, Fong Y, Janes H, DeCamp A, Huang Y, Rao M, Billings E, Karasavvas N, Robb ML, Ngauy V, de Souza MS, Paris R, Ferrari G, Bailer RT, Soderberg KA, Andrews C, Berman PW, Frahm N, De Rosa SC, Alpert MD, Yates NL, Shen X, Koup RA, Pitisuttithum P, Kaewkungwal J, Nitayaphan S, Rerks-Ngarm S, Michael NL, Kim JH. 2012. Immune correlates analysis of the ALVAC-AIDSVAX HIV-1 vaccine efficacy trial. *N Engl J Med* 366:1275–1286. <https://doi.org/10.1056/NEJMoa1113425>.
- Gottardo R, Bailer RT, Korber BT, Gnanakaran S, Phillips J, Shen X, Tomaras GD, Turk E, Imholte G, Eckler L, Wenschuh H, Zerweck J, Greene K, Gao H, Berman PW, Francis D, Sinangil F, Lee C, Nitayaphan S, Rerks-Ngarm S, Kaewkungwal J, Pitisuttithum P, Tartaglia J, Robb ML, Michael NL, Kim JH, Zolla-Pazner S, Haynes BF, Mascola JR, Self S, Gilbert P, Montefiori DC. 2013. 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* 8:e75665. <https://doi.org/10.1371/journal.pone.0075665>.
- Liao H-X, Bonsignori M, Alam SM, McLellan JS, Tomaras GD, Moody MA, Kozink DM, Hwang K-K, Chen X, Tsao C-Y, Liu P, Lu X, Parks RJ, Montefiori DC, Ferrari G, Pollara J, Rao M, Peachman KK, Santra S, Letvin NL,



- Karasavvas N, Yang Z-Y, Dai K, Pancera M, Gorman J, Wiehe K, Nicely NI, Rerks-Ngarm S, Nitayaphan S, Kaewkungwal J, Pitisuttithum P, Tartaglia J, Sinangil F, Kim JH, Michael NL, Kepler TB, Kwong PD, Mascola JR, Nabel GJ, Pinter A, Zolla-Pazner S, Haynes BF. 2013. Vaccine induction of antibodies against a structurally heterogeneous site of immune pressure within HIV-1 envelope protein variable regions 1 and 2. *Immunity* 38: 176–186. <https://doi.org/10.1016/j.immuni.2012.11.011>.
9. Perez LG, Martinez DR, deCamp AC, Pinter A, Berman PW, Francis D, Sinangil F, Lee C, Greene K, Gao H, Nitayaphan S, Rerks-Ngarm S, Kaewkungwal J, Pitisuttithum P, Tartaglia J, O'Connell RJ, Robb ML, Michael NL, Kim JH, Gilbert P, Montefiori DC. 2017. V1V2-specific complement activating serum IgG as a correlate of reduced HIV-1 infection risk in RV144. *PLoS One* 12:e0180720. <https://doi.org/10.1371/journal.pone.0180720>.
  10. Robb ML, Rerks-Ngarm S, Nitayaphan S, Pitisuttithum P, Kaewkungwal J, Kulasol P, Khamboonruang C, Thongcharoen P, Morgan P, Benenson M, Paris RM, Chiu J, Adams E, Francis D, Gurnathan S, Tartaglia J, Gilbert P, Stablein D, Michael NL, Kim JH. 2012. 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. *Lancet Infect Dis* 12:531–537. [https://doi.org/10.1016/S1473-3099\(12\)70088-9](https://doi.org/10.1016/S1473-3099(12)70088-9).
  11. Rolland M, Edlefsen PT, Larsen BB, Tovanabutra S, Sanders-Buell E, Hertz T, deCamp AC, Carrico C, Menis S, Margaret CA, Ahmed H, Juraska M, Chen L, Konopa P, Nariya S, Stoddard JN, Wong K, Zhao H, Deng W, Maust BS, Bose M, Howell S, Bates A, Lazzaro M, O'Sullivan A, Lei E, Bradfield A, Ibitamuno G, Assawadarachai V, O'Connell RJ, deSouza MS, Nitayaphan S, Rerks-Ngarm S, Robb ML, McLellan JS, Georgiev I, Kwong PD, Carlson JM, Michael NL, Schief WR, Gilbert PB, Mullins JI, Kim JH. 2012. Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2. *Nature* 490:417–420. <https://doi.org/10.1038/nature11519>.
  12. Yates NL, Liao HX, Fong Y, deCamp A, Vandergrift NA, Williams WT, Alam SM, Ferrari G, Yang ZY, Seaton KE, Berman PW, Alpert MD, Evans DT, O'Connell RJ, Francis D, Sinangil F, Lee C, Nitayaphan S, Rerks-Ngarm S, Kaewkungwal J, Pitisuttithum P, Tartaglia J, Pinter A, Zolla-Pazner S, Gilbert PB, Nabel GJ, Michael NL, Kim JH, Montefiori DC, Haynes BF, Tomaras GD. 2014. Vaccine-induced Env V1-V2 IgG3 correlates with lower HIV-1 infection risk and declines soon after vaccination. *Sci Transl Med* 6:228ra239.
  13. Zolla-Pazner S, deCamp A, Gilbert PB, Williams C, Yates NL, Williams WT, Howington R, Fong Y, Morris DE, Soderberg KA, Irene C, Reichman C, Pinter A, Parks R, Pitisuttithum P, Kaewkungwal J, Rerks-Ngarm S, Nitayaphan S, Andrews C, O'Connell RJ, Yang Z-y, Nabel GJ, Kim JH, Michael NL, Montefiori DC, Liao H-X, Haynes BF, Tomaras GD. 2014. Vaccine-induced IgG antibodies to V1V2 regions of multiple HIV-1 subtypes correlate with decreased risk of HIV-1 infection. *PLoS One* 9:e87572. <https://doi.org/10.1371/journal.pone.0087572>.
  14. Zolla-Pazner S, deCamp AC, Cardozo T, Karasavvas N, Gottardo R, Williams C, Morris DE, Tomaras G, Rao M, Billings E, Berman P, Shen X, Andrews C, O'Connell RJ, Ngaug V, Nitayaphan S, de Souza M, Korber B, Koup R, Bailor RT, Mascola JR, Pinter A, Montefiori D, Haynes BF, Robb ML, Rerks-Ngarm S, Michael NL, Gilbert PB, Kim JH. 2013. Analysis of V2 antibody responses induced in vaccinees in the ALVAC/AIDSVAX HIV-1 vaccine efficacy trial. *PLoS One* 8:e53629. <https://doi.org/10.1371/journal.pone.0053629>.
  15. Klasse PJ, Moore JP. 2012. Good CoP, bad CoP? Interrogating the immune responses to primate lentiviral vaccines. *Retrovirology* 9:80. <https://doi.org/10.1186/1742-4690-9-80>.
  16. Hammer SM, Sobieszczyk ME, Janes H, Karuna ST, Mulligan MJ, Grove D, Koblin BA, Buchbinder SP, Keefer MC, Tomaras GD, Frahm N, Hural J, Anude C, Graham BS, Enama ME, Adams E, DeJesus E, Novak RM, Frank I, Bentley C, Ramirez S, Fu R, Koup RA, Mascola JR, Nabel GJ, Montefiori DC, Kublin J, McElrath MJ, Corey L, Gilbert PB, Team HS. 2013. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med* 369: 2083–2092. <https://doi.org/10.1056/NEJMoa1310566>.
  17. Gilbert P, Wang M, Wrin T, Petropoulos C, Gurwith M, Sinangil F, D'Souza P, Rodriguez-Chavez IR, DeCamp A, Giganti M, Berman PW, Self SG, Montefiori DC. 2010. Magnitude and breadth of a nonprotective neutralizing antibody response in an efficacy trial of a candidate HIV-1 gp120 vaccine. *J Infect Dis* 202:595–605. <https://doi.org/10.1086/654816>.
  18. Fleming TR, Richardson BA. 2004. Some design issues in trials of microbicides for the prevention of HIV infection. *J Infect Dis* 190:666–674. <https://doi.org/10.1086/422603>.
  19. Gilbert PB. 2010. Some design issues in phase 2B vs phase 3 prevention trials for testing efficacy of products or concepts. *Stat Med* 29: 1061–1071. <https://doi.org/10.1002/sim.3676>.
  20. Rida W, Fast P, Hoff R, Fleming T. 1997. Intermediate-size trials for the evaluation of HIV vaccine candidates: a workshop summary. *J Acquir Immune Defic Syndr Hum Retrovirol* 16:195–203. <https://doi.org/10.1097/00042560-199711010-00009>.
  21. Sabchareon A, Wallace D, Sirivichayukul C, Limkittikul K, Chanthavanich P, Suvannadabba S, Jiwariyavej V, Dulyachai W, Pengsaa K, Wartel LA, Moureau A, Saville M, Bouckennooghe A, Viviani S, Tornieporth NG, Tang J. 2012. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *Lancet* 380:1559–1567. [https://doi.org/10.1016/S0140-6736\(12\)61428-7](https://doi.org/10.1016/S0140-6736(12)61428-7).
  22. Benkeser D, Gilbert P, Carone M. 2018. Estimating and testing vaccine sieve effects using machine learning. *J Amer Stat Assoc* 104:863–880. <https://doi.org/10.1080/01621459.2018.1529594>.
  23. Pollara J, Bonsignori M, Moody MA, Liu P, Alam SM, Hwang K-K, Gurley TC, Kozink DM, Armand LC, Marshall DJ, Whitesides JF, Kaewkungwal J, Nitayaphan S, Pitisuttithum P, Rerks-Ngarm S, Robb ML, O'Connell RJ, Kim JH, Michael NL, Montefiori DC, Tomaras GD, Liao H-X, Haynes BF, Ferrari G. 2014. HIV-1 vaccine-induced C1 and V2 Env-specific antibodies synergize for increased antiviral activities. *J Virol* 88:7715–7726. <https://doi.org/10.1128/JVI.00156-14>.
  24. Chung AW, Ghebremichael M, Robinson H, Brown E, Choi I, Lane S, Dugast AS, Schoen MK, Rolland M, Suscovich TJ, Mahan AE, Liao L, Streeck H, Andrews C, Rerks-Ngarm S, Nitayaphan S, de Souza MS, Kaewkungwal J, Pitisuttithum P, Francis D, Michael NL, Kim JH, Bailey-Kellogg C, Ackerman ME, Alter G. 2014. Polyfunctional Fc-effector profiles mediated by IgG subclass selection distinguish RV144 and VAX003 vaccines. *Sci Transl Med* 6:228–238.
  25. Chung AW, Kumar MP, Arnold KB, Yu WH, Schoen MK, Dunphy LJ, Suscovich TJ, Frahm N, Linde C, Mahan AE, Hoffner M, Streeck H, Ackerman ME, McElrath MJ, Schuitemaker H, Pau MG, Baden LR, Kim JH, Michael NL, Barouch DH, Lauffenburger DA, Alter G. 2015. Dissecting polyclonal vaccine-induced humoral immunity against HIV using systems serology. *Cell* 163:988–998. <https://doi.org/10.1016/j.cell.2015.10.027>.
  26. Li SS, Gilbert PB, Tomaras GD, Kijak G, Ferrari G, Thomas R, Pyo C-W, Zolla-Pazner S, Montefiori D, Liao H-X, Nabel G, Pinter A, Evans DT, Gottardo R, Dai JY, Janes H, Morris D, Fong Y, Edlefsen PT, Li F, Frahm N, Alpert MD, Prentice H, Rerks-Ngarm S, Pitisuttithum P, Kaewkungwal J, Nitayaphan S, Robb ML, O'Connell RJ, Haynes BF, Michael NL, Kim JH, McElrath MJ, Geraghty DE. 2014. Fc gamma IIC polymorphisms associate with HIV-1 vaccine protection in RV144 trial. *J Clin Invest* 124:3879–3890. <https://doi.org/10.1172/JCI75539>.
  27. Alpert MD, Harvey JD, Lauer WA, Reeves RK, Piatak M, Jr, Carville A, Mansfield KG, Lifson JD, Li W, Desrosiers RC, Johnson RP, Evans DT. 2012. ADCC develops over time during persistent infection with live-attenuated SIV and is associated with complete protection against SIV(mac)251 challenge. *PLoS Pathog* 8:e1002890. <https://doi.org/10.1371/journal.ppat.1002890>.
  28. Barouch DH, Stephenson KE, Borducchi EN, Smith K, Stanley K, McNally AG, Liu J, Abbink P, Maxfield LF, Seaman MS, Dugast AS, Alter G, Ferguson M, Li W, Earl PL, Moss B, Giorgi EE, Szinger JJ, Eller LA, Billings EA, Rao M, Tovanabutra S, Sanders-Buell E, Weijtens M, Pau MG, Schuitemaker H, Robb ML, Kim JH, Korber BT, Michael NL. 2013. Protective efficacy of a global HIV-1 mosaic vaccine against heterologous SHIV challenges in rhesus monkeys. *Cell* 155:531–539. <https://doi.org/10.1016/j.cell.2013.09.061>.
  29. Forthal DN, Gilbert PB, Landucci G, Phan T. 2007. Recombinant gp120 vaccine-induced antibodies inhibit clinical strains of HIV-1 in the presence of fc receptor-bearing effector cells and correlate inversely with HIV infection rate. *J Immunol* 178:6596–6603. <https://doi.org/10.4049/jimmunol.178.10.6596>.
  30. Forthal DN, Moog C. 2009. Fc receptor-mediated antiviral antibodies. *Curr Opin HIV AIDS* 4:388–393. <https://doi.org/10.1097/COH.0b013e32832f0a89>.
  31. Vargas-Inchaustegui DA, Robert-Guroff M. 2013. Fc receptor-mediated immune responses: new tools but increased complexity in HIV prevention. *Curr HIV Res* 11:407–420. <https://doi.org/10.2174/1570162X113116660063>.
  32. Zolla-Pazner S, Alvarez R, Kong XP, Weiss S. 1 July 2019, posting date. Vaccine-induced V1V2-specific antibodies control and or protect against

- infection with HIV, SIV and SHIV. *Curr Opin HIV AIDS* <https://doi.org/10.1097/COH.0000000000000551>.
33. Barouch DH, Liu J, Li H, Maxfield LF, Abbink P, Lynch DM, Iampietro MJ, SanMiguel A, Seaman MS, Ferrari G, Forthal DN, Ourmanov I, Hirsch VM, Carville A, Mansfield KG, Stablein D, Pau MG, Schuitemaker H, Sadoff JC, Billings EA, Rao M, Robb ML, Kim JH, Marovich MA, Goudsmit J, Michael NL. 2012. Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys. *Nature* 482:89–93. <https://doi.org/10.1038/nature10766>.
  34. Gordon SN, Doster MN, Kines RC, Keele BF, Brocca-Cofano E, Guan Y, Pegu P, Liyanage NP, Vaccari M, Cuburu N, Buck CB, Ferrari G, Montefiori D, Piatak M, Jr, Lifson JD, Xenophontos AM, Venzon D, Robert-Guroff M, Graham BS, Lowy DR, Schiller JT, Franchini G. 2014. Antibody to the gp120 V1/V2 loops and CD4+ and CD8+ T cell responses in protection from SIVmac251 vaginal acquisition and persistent viremia. *J Immunol* 193:6172–6183. <https://doi.org/10.4049/jimmunol.1401504>.
  35. Malherbe DC, Mendy J, Vang L, Barnette PT, Reed J, Lakhashe SK, Owuor J, Gach JS, Legasse AW, Axthelm MK, LaBranche CC, Montefiori D, Forthal DN, Park B, Wilson JM, McLinden JH, Xiang J, Stapleton JT, Sacha JB, Haynes BF, Liao HX, Ruprecht RM, Smith J, Gurwith M, Haigwood NL, Alexander J. 2018. Combination adenovirus and protein vaccines prevent infection or reduce viral burden after heterologous clade C simian-human immunodeficiency virus mucosal challenge. *J Virol* 92:e01092-17.
  36. Pegu P, Vaccari M, Gordon S, Keele BF, Doster M, Guan Y, Ferrari G, Pal R, Ferrari MG, Whitney S, Hudacik L, Billings E, Rao M, Montefiori D, Tomaras G, Alam SM, Fenizia C, Lifson JD, Stablein D, Tartaglia J, Michael N, Kim J, Venzon D, Franchini G. 2013. Antibodies with high avidity to the gp120 envelope protein in protection from simian immunodeficiency virus SIV(mac251) acquisition in an immunization regimen that mimics the RV-144 Thai trial. *J Virol* 87:1708–1719. <https://doi.org/10.1128/JVI.02544-12>.
  37. Roederer M, Keele BF, Schmidt SD, Mason RD, Welles HC, Fischer W, LaBranche C, Foulds KE, Louder MK, Yang ZY, Todd JP, Buzby AP, Mach LV, Shen L, Seaton KE, Ward BM, Bailer RT, Gottardo R, Gu W, Ferrari G, Alam SM, Denny TN, Montefiori DC, Tomaras GD, Korber BT, Nason MC, Seder RA, Koup RA, Letvin NL, Rao SS, Nabel GJ, Mascola JR. 2014. Immunological and virological mechanisms of vaccine-mediated protection against SIV and HIV. *Nature* 505:502–508. <https://doi.org/10.1038/nature12893>.
  38. Singh S, Ramirez-Salazar EG, Doueiri R, Valentin A, Rosati M, Hu X, Keele BF, Shen X, Tomaras GD, Ferrari G, LaBranche C, Montefiori DC, Das J, Alter G, Trinh HV, Hamlin C, Rao M, Dayton F, Bear J, Chowdhury B, Alicea C, Lifson JD, Broderick KE, Sardesai NY, Sivananthan SJ, Fox CB, Reed SG, Venzon DJ, Hirsch VM, Pavlakis GN, Felber BK. 2018. Control of heterologous simian immunodeficiency virus SIVsmE660 infection by DNA and protein coimmunization regimens combined with different Toll-like-receptor-4-based adjuvants in macaques. *J Virol* 92:e00281-18.
  39. Vaccari M, Gordon SN, Fourati S, Schifanella L, Liyanage NPM, Cameron M, Keele BF, Shen X, Tomaras GD, Billings E, Rao M, Chung AW, Dowell KG, Bailey-Kellogg C, Brown EP, Ackerman ME, Vargas-Inchaustegui DA, Whitney S, Doster MN, Binello N, Pegu P, Montefiori DC, Foulds K, Quinn DS, Donaldson M, Liang F, Loré K, Roederer M, Koup RA, McDermott A, Ma Z-M, Miller CJ, Phan TB, Forthal DN, Blackburn M, Caccuri F, Bissa M, Ferrari G, Kalyanaraman V, Ferrari MG, Thompson D, Robert-Guroff M, Ratto-Kim S, Kim JH, Michael NL, Phogat S, Barnett SW, Tartaglia J, Venzon D, Stablein DM, et al. 2016. Adjuvant-dependent innate and adaptive immune signatures of risk of SIV acquisition. *Nat Med* 22: 762–770. <https://doi.org/10.1038/nm.4105>.
  40. Hessel AD, Philip B, Shilpi P, Sutton W, Liu L, Liuzhe L, Xiang-Peng K, Nancy LH, Miroslaw KG. 2018. Tight control of SHIV BaL.P4 challenge in rhesus macaques co-immunized with DNA and protein HIV vaccine regimen, abstr OA09.04. *Abstr HIV Res Prevent*, Madrid, Spain.