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HIV Vaccine Research and Discovery in the NHP model: a unified theory in acquisition prevention and control of SIV infection

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Abstract

Purpose of the review—Here we highlight the latest advances in HIV vaccine concepts that will expand our knowledge on how to elicit effective acquisition-prevention and/or control of SIV replication in the NHP model.

Recent findings—In the context of the promising analyses from the RV144 Thai Trial and the effective control of SIV replication exerted by rhCMV-(SIV) elicited EM CD8 T cells, the HIV field has recently shifted toward vaccine concepts that combine protection from acquisition with effective control of SIV replication. Current studies in the NHP model have demonstrated the efficacy of HIV-neutralizing antibodies via passive transfer, the potential importance of the CD4 Tfh subset, the ability to effectively model the RV144 vaccine trial and the capacity of an Ad26 prime and MVA boost to elicit Env-specific antibody and cellular responses that both limit acquisition and control heterologous SIVmac251 challenge.

Summary—The latest work in the NHP model suggests that the next generation HIV-1 vaccines should aim to provoke a comprehensive adaptive immune response for both prevention of SIV acquisition as well as control of replication in breakthrough infection.

Keywords

NHP model; vaccines; SIV

Introduction

Over the last 30 years the quest for an HIV vaccine has taken us on a journey from classical empirical vaccine strategies to approaches employing sophisticated structural biology and virally vectored vaccines. Since the first clinical HIV vaccine candidate was evaluated in 1987 there have been nearly 100 clinical vaccine trials and thousands of willing volunteers. Many, if not all, of these vaccine approaches were initially tested in non-human primates (NHPs) prior to advancement into humans(1). In general, SIV and chimeric HIV/SIV (or SHIV) challenge models are used to test immunogenicity and efficacy of vaccine strategies

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designed to principally elicit T cell or antibody responses, respectively. The NHP model has also been employed extensively to investigate SIV pathogenesis and questions of immunological importance, which have directly advanced the design of prototype HIV vaccines. A key point remains that the selection of challenge viruses and the challenge methodologies are pivotal in the interpretation of NHP challenge studies. The field has evolved from challenging NHP with large doses of cloned viruses, to lower dose swarm based mucosal challenges with SIVmac251 or SIVsmE660 to more accurately recapitulate human HIV acquisition and infection. Furthermore, this strategy permits simultaneous analysis of SIV specific T cell and antibody responses after vaccination and challenge. For example, it has recently been demonstrated that the SIVsmE660 quasi-species is comprised of more neutralization sensitive viruses as compared to SIVmac251 or SIVmac239, emphasizing the significance of the challenge virus in NHP model analysis (2). As highlighted in Table 1, the evolution of the NHP challenge model has informed HIV vaccine development decisions, and continued development will lead to more effective products entering the clinical pipeline. However, until an absolute correlate of immunity is defined or a vaccine regimen proves effective in clinical trials and iterative studies are conducted in a relevant NHP model, (like those NHP studies highlighted below) there will be continued debate on the interpretation of data, SIV challenge virus and routes of infection in relation to human clinical vaccine trials.

Nevertheless, two significant vaccine studies have established that a HIV vaccine is possible, one performed in the NHP model and the other a large-scale clinical trial. These studies have strongly influenced the field in demonstrating efficacy either by eliciting HIV Env-specific antibodies or high frequency effector memory (EM) CD8 T cells(18, 19).

Antibodies are a crucial component for protection from HIV/SIV infection

The much deliberated RV144 Thai HIV vaccine trial, involved the establishment of a functional HIV-specific antibody response that blocked the ability of the virus to infect target cells at the site of exposure, thereby resulting in ‘sterilizing protection’. Results from this trial demonstrated modest protection from acquisition (31.2%, $p=0.04$) in humans, and this effect strongly correlated with antibody responses directed towards the Env-V1/V2 loop of HIV(20, 21). These intriguing data challenged the common conception that antibody-mediated neutralization was required to confer protection (21, 22), an interesting conclusion for the vaccine field considering the challenges ahead for inducing broadly neutralizing antibodies (bNab). Exactly how non-neutralizing antibodies mediated effects on acquisition in the RV144 vaccine trial is the subject of discussion and reviewed in detail (21, 23-25), but the NHP model provides an opportunity to address hypotheses regarding the mechanisms behind protection. However, modeling the modest protective vaccine effect of RV144 in NHP is problematic, requiring a large number of NHPs coupled with a suitable virus challenge regimen designed to limit the number of transmitted virus variants and an optimized repeated intra-rectal challenge (26). Recently, Pegu and colleagues performed a pilot study that mimicked the RV144 regimen in a small number of NHP with a SIVmac251 optimized repeated challenge regimen. Three of eleven NHP immunized with ALVAC-SIV/gp120 remained uninfected after 5 SIVmac251 challenge doses(8). Consistent with RV144 recipients, NHPs in this pilot study had no appreciable SIV specific CD4 or CD8 T cell

activity yet uninfected NHP demonstrated high avidity binding for the Env-V1/V2 loop with no associated antibody dependent cellular cytotoxicity (ADCC) activity. Consequently, an adequately powered NHP study is underway to confirm this interesting result and address the role of non-neutralizing antibody in protection from acquisition.

Nevertheless, empirically developed vaccines for common viral diseases, such as influenza, afford protection by eliciting neutralizing antibody(27). In the past few years, highly potent and broadly neutralizing antibodies (bNabs) capable of neutralizing the majority of circulating strains of HIV-1 have been identified from HIV infected individuals. The bNabs target four major components of the viral spike (CD4bs, V1/V2, glycan-V3 and MPER)(28). Design of immunogens capable of eliciting bNabs is complex and challenging, especially in light of the extraordinarily high levels of somatic hypermutation observed in these antibodies(29). It remains unclear if HIV Env-antibodies elicited during vaccination can reproduce the same degree of affinity maturation, especially in comparison with a currently licensed influenza vaccination regimen (30). Therefore, alternative strategies for delivery of bNabs are now being considered and evaluated in NHP. Direct vectored-mediated gene transfer of bNabs into muscle tissue allows the continued secretion of the desired antibody into the bloodstream(31, 32). Whether this strategy will deliver a long lasting optimal concentration of bNabs remains to be determined. In the interim, passive immunization of bNabs by intravenous transfer into NHP followed by subsequent mucosal SHIV challenge evaluates the serum concentration and potential efficacy of bNabs. Broadly neutralizing antibodies such as b12, 2G12, 4E10 and 2F5 can all confer protection against mucosal SHIV challenge in NHP models(33-36). A recent study by Moldt and colleagues showed that passive immunization with a highly potent bNab-PGT121 (glycan-V3 specific) completely protected all 5 NHP against SHIV_{SF162P3} challenge at an average serum concentration of 15µg/ml, significantly lower than previously reported for other bNabs (37, 38) (Fig. 1). If potent bNabs can indeed be efficacious at low concentrations, they could be delivered singly or as combination therapy(28, 39), perhaps limiting the pathways of viral escape. Moreover, it has been shown that passive immunization with low levels of 2G12 reduces viral load in newborn macaques(40), thereby highlighting the prospects for an additional, cost effective therapeutic strategy to combat mother to child transmission.

For an effective HIV-Env immunogen to mediate protection by the induction of neutralizing antibodies, it will most likely require the generation of Env-specific antibodies with exceptional levels of somatic mutation and long complementary determining regions in the heavy chain (CDRH3s), which are hallmarks of currently identified HIV-bNabs(29). Although there may be no way to induce long CDR3H3 loops solely by vaccination since they are formed by recombination events (41), the problem of extensive affinity maturation is another hurdle unique in current vaccine designs. For example, multiple studies have demonstrated that Influenza vaccination elicits vaccine-induced antibodies with mutation rates in the V-gene that are about the same, or slightly higher as non-specific memory B cells (5%) (30, 42). However, CD4 binding site-specific bNab, VRC01 demonstrates a mutation rate around 30%(43).

How are these affinity matured antibodies generated? Specialized CD4 T follicular helper cells (T_{FH}) are intimately associated with B cell differentiation and survival signals in the

germinal centers(44, 45). Also, CD4 T_{FH} cells promote somatic mutation (46), isotype switching and generation of high affinity memory B and plasma cells (47, 48). The possibility of eliciting antigen-specific T_{FH} in the context of vaccination has yet to be fully explored or realized. Interestingly, most current vaccine designs tested in NHP and in clinical trials are down-selected for the ability to elicit IFN γ and/or IL-2 responses, which potentially inhibit CD4 T_{FH} cells(45, 49). So what is currently known about the role of CD4 T_{FH} in NHP and clinical models? During chronic SIV and HIV infection, T_{FH} cells accumulate in lymphoid tissues (50, 51). This accumulation may promote the generation of high affinity and broadly reactive antibodies, and studies have observed a correlation between the frequency of T_{FH} cells and the production of IgG antibodies during chronic infection (50, 51). It is, however, very important to understand the potential risk of increasing the frequency of T_{FH} cells. This study by Petrovas and colleagues observed that T_{FH} cells were the major targets of SIV infection during the acute phase of infection, although there was not a demonstrable relationship between SIV infection and the frequency of T_{FH} cells in the chronic phase of infection. Although the importance of T_{FH} cells for B cell help is clear, it is still unclear whether the accumulation of T_{FH} cells during the chronic phase of HIV/ SIV infection drives B cell dysfunction, or if accumulation of T_{FH} cells, especially HIV-specific T_{FH} cells, contribute to antibody responses. Further studies in NHP are ongoing to determine the contribution of antigen-specific CD4 T_{FH} cells toward eliciting bNabs. For future vaccine studies, it will be important to investigate whether it will be scientifically pragmatic to track T_{FH} cells in the peripheral blood of humans and NHPs. There is currently much discussion regarding which cell markers define T_{FH} or T_{FH}-like cells in peripheral blood and whether those T_{FH}-like cells are representative of germinal center TFH cell responses; however, studies have indicated that antigen-specific T_{FH}-like cells can be detected in human blood(52, 53). Quite recently Salah-Eddine Bentebibel et al. showed that antigen-specific T_{FH}-like detected in the periphery associated with protective antibody responses after seasonal flu vaccination, suggesting this population may be useful for the evaluation of vaccine efficacy although further research is still required in this area(54).

CD8 T cells are a crucial component for control of HIV/SIV infection

Analyses of immune correlates in the RV144 vaccine trial and the failure of the Merck STEP trial have shifted the field of HIV vaccine design from CD8 T cell based vaccines to vaccines that induce Env-specific antibodies and prevent HIV acquisition (21, 43, 55). However, epitope specific CD8 T cells remain essential in the initial reduction of virus load and subsequent control following HIV and SIV infection, especially in HIV and SIV long-term controllers (56). Few NHP studies have demonstrated significant control of virus load following SIV challenge (3, 57). In general, older studies were not powered to observe differences in acquisition, despite having SIV-Env included in the regimen. But an evaluation of DNA prime followed by replication incompetent recombinant Ad5 (rAd5) boost vaccine by Letvin and colleagues was powered to address both acquisition-prevention and SIV viral control(12). These animals were challenged with either SIVsmE660 or SIVmac251, and a reduction in acquisition of SIVsmE660 infection correlated with robust Env-specific CD4 T cells responses, neutralizing antibody activity and innate genetic

factors. Among SIVsmE660-infected animals, peak viral loads were reduced by approximately 1 log and associated with CD8 T cell responses. SIV-specific effector memory (EM) CD8 T cells, which display strong virus inhibitory activity (VIA), were associated with this SIVsmE660 control in vitro (58). In-vivo, EM CD8 T cells reside in peripheral lymphoid and mucosal tissue with the capacity to rapidly proliferate, and have been strongly associated with early virus control in NHP receiving rhCMV vector (19, 59). In this rhCMV vector study, EM CD8 T cells also exerted persistent control of viral recrudescence in the absence of SIV Env-specific antibody. Extrapolation of the specific CD8 T cell epitopes involved in control of SIVmac239 replication, for other viral vector insert design, is difficult because rhCMV generates persistent high-frequency SIV-specific EM CD8 T cells that target different epitopes as compared to natural SIV infection or vaccination with rAd5 encoding the same genes (60).

While Env-specific CD8 T cell responses have found to be associated with higher HIV viremia in people (61), HIV Gag-specific CD8 T cell responses are consistently associated with effective control of viremia, especially when restricted by protective MHC class I molecules (61, 62). In a recent study, it has been shown that CD8 T cell cytotoxic capacity is strongly associated with disease outcome in SIV-infected NHPs and potentially in vaccines (58, 63). Although, further defining the characteristics of effective T cell epitopes restricted by class I molecules associated with slow or non-progression of HIV or SIV could possibly enlighten vaccine mediated CD8 control for future vaccine design (64).

Unified adaptive immune response approach to HIV Vaccine design

Recently, Barouch and colleagues extensively analyzed both humoral and cellular responses in the NHP immunized with a rAd26/MVA prime boost vector-based vaccine expressing SIVsmE543 Gag, Pol and Env antigens (3). They observed an 80% or greater reduction in the per-exposure probability of low dose intra-rectal heterologous SIVmac251 challenge that correlated with Env-specific antibody. Interestingly, the central memory (CM) or EM CD8 T cell responses did not correlate with this protection from acquisition. Yet, in the same study, NHP with break-through SIV replication after rAd26/MVA vaccination developed robust SIV specific CD4 and CD8 responses and reduced virus replication by >2 logs. Based on these studies, arAd26 vector expressing HIV-Env has advanced to clinical evaluation eliciting promising immunogenicity results (65, 66). Similar findings were recently generated by Patel et al using a different vaccine regimen (67). In this study rhesus macaques received DNA vectors expressing SIVmac239 followed by inactivated SIVmac239 viral particles (AT-2), effectively targeting both arms of the immune system. After challenge with neutralization-sensitive SIVsmE660, 2 of the 8 co-immunized monkeys were protected from acquisition that correlated with mucosal Env-specific antibody. Furthermore, 73% of total vaccinated NHP that became infected controlled virus replication to low levels, and this control was associated with SIV-specific CD8 T cell responses.

Given this finding and other data now available, vector based HIV vaccine designs will include an HIV-Env component to reduce acquisition (8, 68) although additional components that potentially mediate vaccine control of HIV replication remain to be defined. As the current pipeline of vaccine candidates near the clinic, there will be a

requirement for induction of Env-specific antibodies to reduce acquisition, and the activation of CD8 T cells to reduce virus replication, in a similar manner to rAd26/MVA approach in NHP challenge studies, and these compound effects will be an essential requirement for new vaccines.

Conclusion

HIV vaccines that are currently undergoing large-scale clinical evaluation were originally designed to contain viral components best suited to elicit T cell responses, although the majority included HIV-Env antigens. The unexpected outcome and correlates analyses of the RV144 Thai vaccine trial has prompted intense HIV-acquisition correlate evaluations and scrutiny of responses elicited by the HIV-Env components of the vaccines. It is clear that prototype HIV vaccines under evaluation in the NHP will ostensibly utilize viral vector delivery platforms delivered as homologous prime and boost or in heterologous combinations with DNA or protein constructs. Current road blocks in vaccine development are the delivery-method or elicitation of bNabs that demonstrate high rates of somatic hypermutation, as well as the safety considerations of novel viral vectors such as human CMV. Ideally a successful HIV vaccine will develop robust antigen specific CD4 T_{FH} T cells that will help induce and maintain a functional antibody response while also activating only the most effective antigen-specific CD8 response. Most importantly, these new vaccines will need to be tested in a well-designed and sufficiently powered NHP studies in order to best test candidates for large-scale clinical trials in humans.

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References

1. Berman PW, Murthy KK, Wrin T, et al. Protection of MN-rgp120-immunized chimpanzees from heterologous infection with a primary isolate of human immunodeficiency virus type 1. *The Journal of infectious diseases*. 1996 Jan; 173(1):52–9. [PubMed: 8537682]
2. Lopker M, Easlick J, Sterrett S, et al. Heterogeneity in neutralization sensitivity of viruses comprising the SIVsmE660 isolate and vaccine challenge stock. *Journal of virology*. 2013 Mar 6.
- 3**. Barouch DH, Liu J, Li H, et al. Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys. *Nature*. 2012 Feb 2; 482(7383):89–93. This article demonstrates that adenovirus vector-based vaccines can provide protection against viral acquisition in a mucosal challenge model, and that inclusion of Env was required for this protective effect. These studies highlight both the role that non-neutralizing antibodies may play in infection prevention, as well as Env-specific CD4 EM responses in virologic control. [PubMed: 22217938]
4. Barouch DH, Klasse PJ, Dufour J, et al. Macaque studies of vaccine and microbicide combinations for preventing HIV-1 sexual transmission. *Proceedings of the National Academy of Sciences of the United States of America*. 2012 May 29; 109(22):8694–8. [PubMed: 22586094]
5. Schell JB, Rose NF, Bahl K, et al. Significant protection against high-dose simian immunodeficiency virus challenge conferred by a new prime-boost vaccine regimen. *Journal of virology*. 2011 Jun; 85(12):5764–72. [PubMed: 21490100]
6. Lai L, Kwa SF, Kozlowski PA, et al. SIVmac239 MVA vaccine with and without a DNA prime, similar prevention of infection by a repeated dose SIVsmE660 challenge despite different immune responses. *Vaccine*. 2012 Feb 21; 30(9):1737–45. [PubMed: 22178526]

7. Matano T, Kobayashi M, Igarashi H, et al. Cytotoxic T lymphocyte-based control of simian immunodeficiency virus replication in a preclinical AIDS vaccine trial. *The Journal of experimental medicine*. 2004 Jun 21; 199(12):1709–18. [PubMed: 15210746]
- 8*. Pegu P, Vaccari M, Gordon S, et al. Antibodies with High Avidity to the gp120 Envelope Protein in Protection from Simian Immunodeficiency Virus SIVmac251 Acquisition in an Immunization Regimen That Mimics the RV-144 Thai Trial. *Journal of virology*. 2013 Feb; 87(3):1708–19. This study establishes that vaccinating non-human primates with the RV144-trial ALVAC-SIV/gp120 regimen mimics the results seen in humans (slightly lower viral acquisition in vaccinees that correlates with high-avidity gp120-directed antibodies). This research validates this NHP model as useful for future mechanistic studies into how the protection is afforded. [PubMed: 23175374]
9. Pal R, Venzon D, Santra S, et al. Systemic immunization with an ALVAC-HIV-1/protein boost vaccine strategy protects rhesus macaques from CD4+ T-cell loss and reduces both systemic and mucosal simian-human immunodeficiency virus SHIVKU2 RNA levels. *Journal of virology*. 2006 Apr; 80(8):3732–42. [PubMed: 16571790]
10. Cox JH, Ferrari MG, Earl P, et al. Inclusion of a CRF01_AE HIV envelope protein boost with a DNA/MVA prime-boost vaccine: Impact on humoral and cellular immunogenicity and viral load reduction after SHIV-E challenge. *Vaccine*. 2012 Feb 27; 30(10):1830–40. [PubMed: 22234262]
11. Stevceva L, Alvarez X, Lackner AA, et al. Both mucosal and systemic routes of immunization with the live, attenuated NYVAC/simian immunodeficiency virus SIV(gpe) recombinant vaccine result in gag-specific CD8(+) T-cell responses in mucosal tissues of macaques. *Journal of virology*. 2002 Nov; 76(22):11659–76. [PubMed: 12388726]
12. Letvin NL, Rao SS, Montefiori DC, et al. Immune and Genetic Correlates of Vaccine Protection Against Mucosal Infection by SIV in Monkeys. *Science translational medicine*. 2011 May 4.3(81): 81ra36. Epub 2011/05/06. eng.
13. Letvin NL, Mascola JR, Sun Y, et al. Preserved CD4+ central memory T cells and survival in vaccinated SIV-challenged monkeys. *Science*. 2006 Jun 9; 312(5779):1530–3. [PubMed: 16763152]
14. Shiver JW, Fu TM, Chen L, et al. Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. *Nature*. 2002 Jan 17; 415(6869):331–5. [PubMed: 11797011]
15. Reynolds MR, Weiler AM, Piaskowski SM, et al. A trivalent recombinant Ad5 gag/pol/nef vaccine fails to protect rhesus macaques from infection or control virus replication after a limiting-dose heterologous SIV challenge. *Vaccine*. 2012 Jun 22; 30(30):4465–75. [PubMed: 22569124]
16. Casimiro DR, Wang F, Schleif WA, et al. Attenuation of simian immunodeficiency virus SIVmac239 infection by prophylactic immunization with dna and recombinant adenoviral vaccine vectors expressing Gag. *Journal of virology*. 2005 Dec; 79(24):15547–55. [PubMed: 16306625]
17. Qureshi H, Ma ZM, Huang Y, et al. Low-dose penile SIVmac251 exposure of rhesus macaques infected with adenovirus type 5 (Ad5) and then immunized with a replication-defective Ad5-based SIV gag/pol/nef vaccine recapitulates the results of the phase IIb step trial of a similar HIV-1 vaccine. *Journal of virology*. 2012 Feb; 86(4):2239–50. [PubMed: 22156519]
18. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *The New England journal of medicine*. 2009 Dec 3; 361(23): 2209–20. [PubMed: 19843557]
19. Hansen SG, Vieville C, Whizin N, et al. Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge. *Nature medicine*. 2009 Mar; 15(3):293–9. Epub 2009/02/17. eng.
20. Rolland M, Edlefsen PT, Larsen BB, et al. Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2. *Nature*. 2012 Oct 18; 490(7420):417–20. [PubMed: 22960785]
21. Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. *The New England journal of medicine*. 2012 Apr 5; 366(14):1275–86. [PubMed: 22475592]
22. Page M, Stebbings R, Berry N, et al. Heterologous protection elicited by candidate monomeric recombinant HIV-1 gp120 vaccine in the absence of cross neutralising antibodies in a macaque model. *Retrovirology*. 2012; 9:56. [PubMed: 22799593]

23. Robinson HL. Non-neutralizing antibodies in prevention of HIV infection. Expert opinion on biological therapy. 2013 Feb; 13(2):197–207. [PubMed: 23130709]
24. Madhavi V, Kent SJ, Stratov I. HIV-specific antibody-dependent cellular cytotoxicity: a novel vaccine modality. Expert review of clinical immunology. 2012 Nov; 8(8):767–74. [PubMed: 23167688]
25. Liao HX, Bonsignori M, Alam SM, et al. Vaccine Induction of Antibodies against a Structurally Heterogeneous Site of Immune Pressure within HIV-1 Envelope Protein Variable Regions 1 and 2. Immunity. 2013 Jan 8.
26. Vaccari M, Keele BF, Bosinger SE, et al. Protection afforded by an HIV vaccine candidate in macaques dependent on the dose of SIVmac251 challenge exposure. Journal of virology. 2013 Jan 16.
27. Plotkin SA. Correlates of protection induced by vaccination. Clinical and vaccine immunology : CVI. 2010 Jul; 17(7):1055–65. [PubMed: 20463105]
28. Kwong PD, Mascola JR. Human antibodies that neutralize HIV-1: identification, structures, and B cell ontogenies. Immunity. 2012 Sep 21; 37(3):412–25. Epub 2012/09/25. eng. [PubMed: 22999947]
29. Haynes BF, Kelsoe G, Harrison SC, Kepler TB. B-cell-lineage immunogen design in vaccine development with HIV-1 as a case study. Nature biotechnology. 2012 May; 30(5):423–33.
30. Moody MA, Zhang R, Walter EB, et al. H3N2 influenza infection elicits more cross-reactive and less clonally expanded anti-hemagglutinin antibodies than influenza vaccination. PloS one. 2011; 6(10):e25797. [PubMed: 22039424]
31. Balazs AB, Chen J, Hong CM, et al. Antibody-based protection against HIV infection by vectored immunoprophylaxis. Nature. 2012 Jan 5; 481(7379):81–4. [PubMed: 22139420]
32. Johnson PR, Schnepf BC, Zhang J, et al. Vector-mediated gene transfer engenders long-lived neutralizing activity and protection against SIV infection in monkeys. Nature medicine. 2009 Aug; 15(8):901–6.
33. Hessel AJ, Pognard P, Hunter M, et al. Effective, low-titer antibody protection against low-dose repeated mucosal SHIV challenge in macaques. Nature medicine. 2009 Aug; 15(8):951–4. Epub 2009/06/16. eng.
34. Hessel AJ, Rakasz EG, Tehrani DM, et al. Broadly neutralizing monoclonal antibodies 2F5 and 4E10 directed against the human immunodeficiency virus type 1 gp41 membrane-proximal external region protect against mucosal challenge by simian-human immunodeficiency virus SHIVBa-L. Journal of virology. 2010 Feb; 84(3):1302–13. Epub 2009/11/13. eng. [PubMed: 19906907]
35. Mascola JR, Stiegler G, VanCott TC, et al. Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies. Nature medicine. 2000 Feb; 6(2):207–10. Epub 2000/02/02. eng.
36. Parren PW, Marx PA, Hessel AJ, et al. Antibody protects macaques against vaginal challenge with a pathogenic R5 simian/human immunodeficiency virus at serum levels giving complete neutralization in vitro. Journal of virology. 2001 Sep; 75(17):8340–7. Epub 2001/08/03. eng. [PubMed: 11483779]
- 37*. Moldt B, Rakasz EG, Schultz N, et al. Highly potent HIV-specific antibody neutralization in vitro translates into effective protection against mucosal SHIV challenge in vivo. Proceedings of the National Academy of Sciences of the United States of America. 2012 Nov 13; 109(46):18921–5. Epub 2012/10/27. eng. This article validates that the relative potency of neutralizing activity *in vitro* translates into relatively more potent protection in a passive immunization SHIV challenge model. This conclusion suggests that lower doses of highly potent antibodies may still be clinically effective. [PubMed: 23100539]
38. Walker LM, Huber M, Doores KJ, et al. Broad neutralization coverage of HIV by multiple highly potent antibodies. Nature. 2011 Sep 22; 477(7365):466–70. [PubMed: 21849977]
39. Klein F, Halper-Stromberg A, Horwitz JA, et al. HIV therapy by a combination of broadly neutralizing antibodies in humanized mice. Nature. 2012 Dec 6; 492(7427):118–22. [PubMed: 23103874]

40. Ng CT, Jaworski JP, Jayaraman P, et al. Passive neutralizing antibody controls SHIV viremia and enhances B cell responses in infant macaques. *Nature medicine*. 2010 Oct; 16(10):1117–9. Epub 2010/10/05. eng.
41. Briney BS, Willis JR, Crowe JE Jr. Human peripheral blood antibodies with long HCDR3s are established primarily at original recombination using a limited subset of germline genes. *PloS one*. 2012; 7(5):e36750. [PubMed: 22590602]
42. Li GM, Chiu C, Wrammert J, et al. Pandemic H1N1 influenza vaccine induces a recall response in humans that favors broadly cross-reactive memory B cells. *Proceedings of the National Academy of Sciences of the United States of America*. 2012 Jun 5; 109(23):9047–52. [PubMed: 22615367]
43. Kwong PD, Mascola JR, Nabel GJ. The changing face of HIV vaccine research. *J Int AIDS Soc*. 2012; 15(2):17407. [PubMed: 22789610]
44. Ramiscal RR, Vinuesa CG. T-cell subsets in the germinal center. *Immunological reviews*. 2013 Mar; 252(1):146–55. [PubMed: 23405902]
45. Streeck H, D'Souza PM, Littman DR, Crotty S. Harnessing CD4+ T cell responses in HIV vaccine. *Nature medicine*. 2013; 19:143–9. Epub 06 February 2013.
46. Reinhardt RL, Liang HE, Locksley RM. Cytokine-secreting follicular T cells shape the antibody repertoire. *Nature immunology*. 2009 Apr; 10(4):385–93. [PubMed: 19252490]
47. Crotty S. Follicular helper CD4 T cells (TFH). *Annu Rev Immunol*. 2010 Apr 23; 29:621–63. Epub 2011/02/15. eng. [PubMed: 21314428]
48. Nutt SL, Tarlinton DM. Germinal center B and follicular helper T cells: siblings, cousins or just good friends? *Nature immunology*. 2011 Jun; 12(6):472–7. Epub 2011/07/09. eng. [PubMed: 21739669]
49. Ballesteros-Tato A, Leon B, Graf BA, et al. Interleukin-2 inhibits germinal center formation by limiting T follicular helper cell differentiation. *Immunity*. 2012 May 25; 36(5):847–56. [PubMed: 22464171]
- 50*. Petrovas C, Yamamoto T, Gerner MY, et al. CD4 T follicular helper cell dynamics during SIV infection. *J Clin Invest*. 2012 Sep 4; 122(9):3281–94. Epub 2012/08/28. eng. This study establishes characteristics of T_{FH} cells in non-human primates during SIV infection. This research validated this NHP model as useful to see the relationship between B cells and T_{FH} cells. [PubMed: 22922258]
51. Lindqvist M, van Lunzen J, Soghoian DZ, et al. Expansion of HIV-specific T follicular helper cells in chronic HIV infection. *J Clin Invest*. 2012 Sep 4; 122(9):3271–80. Epub 2012/08/28. eng. [PubMed: 22922259]
52. Pallikkuth S, Parmigiani A, Silva SY, et al. Impaired peripheral blood T-follicular helper cell function in HIV-infected nonresponders to the 2009 H1N1/09 vaccine. *Blood*. 2012 Aug 2; 120(5):985–93. [PubMed: 22692510]
53. Morita R, Schmitt N, Bentebibel SE, et al. Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. *Immunity*. 2011 Jan 28; 34(1):108–21. [PubMed: 21215658]
54. Bentebibel SE, Lopez S, Obermoser G, et al. Induction of ICOS+CXCR3+CXCR5+ TH Cells Correlates with Antibody Responses to Influenza Vaccination. *Science translational medicine*. 2013 Mar 13; 5(176):176ra32.
55. 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 Nov 29; 372(9653):1881–93. [PubMed: 19012954]
56. McDermott AB, Koup RA. CD8(+) T cells in preventing HIV infection and disease. *Aids*. 2012 Jun 19; 26(10):1281–92. [PubMed: 22441256]
57. Winstone N, Wilson AJ, Morrow G, et al. Enhanced control of pathogenic Simian immunodeficiency virus SIVmac239 replication in macaques immunized with an interleukin-12 plasmid and a DNA prime-viral vector boost vaccine regimen. *Journal of virology*. 2011 Sep; 85(18):9578–87. Epub 2011/07/08. eng. [PubMed: 21734035]
58. Yamamoto T, Johnson MJ, Price DA, et al. Virus inhibition activity of effector memory CD8(+) T cells determines simian immunodeficiency virus load in vaccinated monkeys after vaccine

- breakthrough infection. *Journal of virology*. 2012 May; 86(10):5877–84. Epub 2012/03/16. eng. [PubMed: 22419810]
59. Ahlers JD, Belyakov IM. Memories that last forever: strategies for optimizing vaccine T-cell memory. *Blood*. 2010 Mar 4; 115(9):1678–89. [PubMed: 19903895]
 60. Hansen SG, Ford JC, Lewis MS, et al. Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. *Nature*. 2011 May 26; 473(7348):523–7. Epub 2011/05/13. eng. [PubMed: 21562493]
 61. Kiepiela P, Ngumbela K, Thobakgale C, et al. CD8+ T-cell responses to different HIV proteins have discordant associations with viral load. *Nature medicine*. 2007 Jan; 13(1):46–53.
 62. Stephenson KE, Li H, Walker BD, et al. Gag-specific cellular immunity determines in vitro viral inhibition and in vivo virologic control following simian immunodeficiency virus challenges of vaccinated rhesus monkeys. *Journal of virology*. 2012 Sep; 86(18):9583–9. [PubMed: 22761379]
 63. Mendoza D, Migueles SA, Rood JE, et al. Cytotoxic Capacity of SIV-Specific CD8(+) T Cells against Primary Autologous Targets Correlates with Immune Control in SIV-Infected Rhesus Macaques. *PLoS pathogens*. 2013 Feb.9(2):e1003195. [PubMed: 23468632]
 64. Mudd PA, Martins MA, Ericson AJ, et al. Vaccine-induced CD8+ T cells control AIDS virus replication. *Nature*. 2012 Nov 1; 491(7422):129–33. Epub 2012/10/02. eng. [PubMed: 23023123]
 65. Barouch DH, Liu J, Peter L, et al. Characterization of Humoral and Cellular Immune Responses Elicited by a Recombinant Adenovirus Serotype 26 HIV-1 Env Vaccine in Healthy Adults (IPCAVD 001). *The Journal of infectious diseases*. 2013 Jan; 207(2):248–56. [PubMed: 23125443]
 66. Baden LR, Walsh SR, Seaman MS, et al. First-in-Human Evaluation of the Safety and Immunogenicity of a Recombinant Adenovirus Serotype 26 HIV-1 Env Vaccine (IPCAVD 001). *The Journal of infectious diseases*. 2013 Jan; 207(2):240–7. [PubMed: 23125444]
 67. Patel V, Jalah R, Kulkarni V, et al. DNA and virus particle vaccination protects against acquisition and confers control of viremia upon heterologous simian immunodeficiency virus challenge. *Proceedings of the National Academy of Sciences of the United States of America*. 2013 Feb 19; 110(8):2975–80. [PubMed: 23359688]
 68. Flatz L, Cheng C, Wang L, et al. Gene-based vaccination with a mismatched envelope protects against simian immunodeficiency virus infection in nonhuman primates. *Journal of virology*. 2012 Aug; 86(15):7760–70. [PubMed: 22593152]

Key points

- Broadly neutralizing antibodies have yet to be induced by a vaccine, so current studies have focused on passive immunization as well as vectored-delivery methods.
- One group has successfully modeled the RV144 vaccine trial for the use in future vaccine studies.
- The use of a rAd26/MVA prime-boost has shown promise in eliciting Env-specific antibody and cellular responses that limit acquisition and control heterologous SIVmac251 challenge.

Fig 1. Broadly neutralizing antibodies used in passive immunization studies

A glycosylated gp120 model of the HIV viral spike derived from (28) highlights five antibodies that have been used in passive transfer studies in NHP. The epitopes of these antibodies are indicated by color: CD4bs in red, V3 in blue and membrane-proximal region (MPER) in cyan. Average serum concentration of each mAb in protected animals before is indicated as well as the dose-model and challenge strain.

Table 1

Phase	Trial ID	Status	Strategy Prime/Boost	NHP challenge virus
I	Ad26.ENVA.01	Ongoing	Viral Vector – Adeno	SIVmac251 [3■]
I	Ad5HVR48.ENVA.01	Ongoing	Viral Vector – Adeno	SHIV-SF162P3 [4]
I	HVTN 087	Ongoing	DNA/Viral Vector – VSV	SIVsmE660 [5]
I	HVTN 090	Ongoing	Viral Vector – VSV	SIVsmE660 [5]
I	HVTN 094	Ongoing	DNA/Viral Vector – Pox	SIVsmE660 [6]
I	IAVI B003	Ongoing	Viral Vector – Adeno/Viral Vector – Adeno	SIVmac251 [3■]
I	IAVI B004	Ongoing	DNA/Viral Vector – Adeno	SIV/DeltaB670 [6]
I	IAVI S001	Ongoing	Viral Vector – Replicating/Viral Vector – Adeno	SIVmac239 [7]
I	RV 306	Scheduled	Viral Vector – Pox/Protein	SIVmac251 [8■]; SHIV KU2 [9]
I	RV 328	Scheduled	Protein	SIVmac251 [8■]; SHIV KU2 [9]
I	RV262	Ongoing	DNA/Viral Vector – Pox	SHIV-E [10]
Ib	HVTN 078	Ongoing	Viral Vector – Pox/Viral Vector – Adeno	SIVmac251 [11]
II	RV 305	Ongoing	Viral Vector – Pox/Protein	SIVmac251 [8■]; SHIV KU2 [9]
Iib	HVTN 505	Ongoing	DNA/Viral Vector – Adeno	SIVmac251 [12,13]; SIVsmE660 [12]
II	AVEG 202/HIVNET 014	Completed	Viral Vector – Pox/Protein	SIVmac251 [11]
II	HIVNET 026	Completed	Viral Vector – Pox/Protein	SIVmac251 [11]
II	HVTN 203	Completed	Viral Vector – Pox/Protein	HIV SF2 [1]; SIVmac251 [11]
II	V520-023	Terminated	Viral Vector – Adeno/Viral Vector – Adeno	SHIV89.6P [14]; SIVsmE660 [15]; SIVmac239 [16]; SIVmac251 [17]
III	RV 144	Completed	Viral Vector – Pox/Protein	SIVmac251 [8■]; SHIV KU2 [9]
III	VAX 003	Completed	Protein	SIVmac251 [8■]; SHIV KU2 [9]
III	VAX 004	Completed	Protein	HIV SF2[1]

NHP, nonhuman primates; VSV, vesicular stomatitis Indiana virus.