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Novel directions in HIV-1 vaccines revealed from clinical trials

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Abstract

Purpose of review—Considerable HIV-1 vaccine development efforts have been deployed over the past decade. Put into perspective, the results from efficacy trials and the identification of correlates of risk have opened large and unforeseen avenues for vaccine development.

Recent findings—The Thai efficacy trial, RV144, provided the first evidence that HIV-1 vaccine protection against HIV-1 acquisition could be achieved. The correlate of risk analysis showed that IgG antibodies against the gp120 V2 loop inversely correlated with decreased risk of infection, while Env-specific IgA directly correlated with risk. Further clinical trials will focus on testing new envelope subunit proteins formulated with adjuvants capable of inducing higher and more durable functional antibody responses (both binding and broadly neutralizing antibodies). Moreover, vector-based vaccine regimens that can induce cell-mediated immune responses in addition to humoral responses remain a priority.

Summary—Future efficacy trials will focus on prevention of HIV-1 transmission in heterosexual population in Africa and men who have sex with men in Asia. The recent successes leading to novel directions in HIV-1 vaccine development are a result of collaboration and commitment among vaccine manufacturers, funders, scientists and civil society stakeholders. Sustained and broad collaborative efforts are required to advance new vaccine strategies for higher levels of efficacy.

Keywords

HIV-1; vaccine; correlates; clinical trial; efficacy

Introduction

Globally, 34.0 million people were living with HIV-1 at the end of 2011. Sub-Saharan Africa remains most severely affected, accounting for 69% of the people living with HIV-1 worldwide. The number of newly infected people and the AIDS-related mortality continue

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to fall [1]. Despite this incremental and fragile success, the development of a cost-effective preventive HIV-1 vaccine remains among the best hopes for controlling the HIV-1/AIDS pandemic [2,3]. In 2009, vaccine efficacy against HIV-1 acquisition was demonstrated in humans for the first time. This breakthrough finding has opened unprecedented avenues to accelerating the development of a vaccine suitable for licensure. Our paper reviews the main advances and challenges.

Lessons learnt from clinical trials

Experimental preventive HIV-1 vaccines have been administered to over 44,000 human volunteers in over 187 separate trials since 1987, tested mostly in Phase I/II clinical trials. The different HIV-1 vaccine approaches along with their scientific and programmatic challenges have been reviewed elsewhere [2,4–9]. Table 1 lists the combinations, route and mode of administration of vaccine concepts tested more recently in Phase I/II trials, while Table 2 summarizes their main immunogenicity findings.

A key goal for an effective HIV-1 vaccine is to induce responses that differ qualitatively, quantitatively, or both from that induced by natural infection [73]. Phase I/II trials provides fundamental information about safety and immunogenicity, but not about the relevance of those immune responses to protective efficacy. In the absence of a link to sufficient efficacy endpoints, flurries of new vaccine concepts have aimed at inducing immune responses of uncertain relevance.

Modern assessments have revealed that the majority of successfully licensed vaccines protect through elicitation of protective antibodies [74–77]. It has been postulated that with our limited current knowledge on correlates of protection, induction of both humoral and cell-mediated immune responses are important to combat HIV-1 in the peripheral compartment and in the mucosal tissues, the entry point of the virus [78]. These considerations led to develop vaccine strategies such as the concept of ‘prime-boost’ vaccination aiming at inducing and augmenting both types of responses [79–81]. Innate immune activation has also been a desired addition and new systems biology tools have become available to provide a framework to compare immune signatures that might predict subsequent HIV-1-specific immune responses induced by vaccines [82,83*].

Safety

The vast majority of candidate vaccines were generally safe and well tolerated, including those delivered using new modes (Biojector and electroporation) and routes (intravaginal, nasal, oral) of administration. While there have been regional differences, background morbidity of healthy participants at low risk for HIV-1 infection selected for Phase I/II trials has not posed an obstacle to clinical trial conduct and interpretation [84]. The RV144 prime-boost regimen tested for efficacy (ALVAC-HIV, vCP1521 and gp120 in alum, AIDSVAX B/E) exhibited a remarkable safety profile in more than 8000 Thai vaccinees [19]. ALVAC-HIV (vCP1521) was also been found to be safe in infants born to HIV-1-infected mothers [85].

Following the Step trial (HVTN 502) outcome in 2007, in which Ad5 vector-based vaccinees were at higher risk of HIV acquisition than placebo recipients, concerns were raised about the use of new vectors, in particular adenovirus-based vectors. In subjects with pre-existing Ad5-specific neutralizing antibody (NAb) titers, a greater number of HIV-1 infections occurred in vaccinees. Post-hoc multivariate analysis suggested that the greatest increased risk was in men who had pre-existing Ad5-NAb and were uncircumcised [86]. The vaccine-associated risk waned with time from vaccination [87]. The increased HIV-1 infection rate observed among uncircumcised men was not supported by a behavioral explanation [88]. The presence of Ad5-NAb was not linked to the risk of HIV-1 acquisition among unvaccinated populations at elevated risk of HIV-1 infection [89]. Anti-vector immunity differed qualitatively in Ad5 seropositive participants who became HIV-infected compared to uninfected controls; Ad5 seropositive participants who later acquired HIV had lower neutralizing antibodies to capsid. Moreover, Ad35 seropositivity was decreased in HIV-infected subjects compared with uninfected controls, while seroprevalence for other serotypes including Ad14, Ad28 and Ad41 was similar in both groups [90]. Given the unclear significance of these findings, close monitoring of such events is warranted in future efficacy trials with recombinant adenovirus vectors.

Increasing interest in potent adjuvants administered systemically or mucosally to bolster immune responses, has introduced other safety concerns. Following administration of a polyvalent DNA prime-protein boost HIV-1 vaccine formulated with QS21, two subjects developed strong delayed-type hypersensitivity reactions with cutaneous leukocytoclastic vasculitis and Henoch-Schonlein purpura [91]. Although such events are rare, safety and tolerability needs to be carefully monitored following the administration of adjuvanted proteins in prime-boost regimens.

Another concern, unrelated to safety, is the potential social harm that comes from vaccine-induced seropositivity (VISP) in uninfected vaccinees. The use of vaccines expressing several HIV-1 proteins, as well as HIV-1 envelope subunit proteins formulated with adjuvants, has led to an increasing proportion of vaccinated individuals testing HIV-1 positive with routine diagnostic tests. This has raised growing concern in communities targeted for HIV-1 vaccination and with health authorities regarding the differentiation of VISP from true HIV-1 infection [92]. For example, more than 80% of volunteers vaccinated with an adjuvanted envelope subunit protein still tested HIV-1 positive 8 years post vaccination [93]. Although Western Blot and nucleic acid tests may allow this differentiation, the development of cheaper and easier-to-run antibody-based diagnostic tests able to differentiate VISP from HIV-1 infection is actively pursued [94–96].

Correlates of risk: Lessons from Phase IIB and III Trials

Table 3 summarizes the completed and ongoing clinical efficacy trials. The detailed analysis of vaccine-elicited immune responses, virus sieve analysis of breakthrough infections and host genetics have all provided invaluable information into potentially protective immune responses, regardless of outcome. Each of these trials underpins the current rationale for planned HIV-1 vaccine trials.

The Vax003 and Vax004 trials evaluated the efficacy of recombinant HIV-1 gp120 proteins. They have provided important insights into vaccine-elicited immune responses and the potential bar that needs to be overcome for further HIV-1 vaccine efficacy studies. In Vax004, higher NAb responses to an easy-to-neutralize virus (MN) corresponded with lower risk of infection in the vaccine group. Evidence of low-level NAb responses against more-difficult-to-neutralize viruses suggests that level and breadth were not sufficient for protection [119]. However, other studies reported that antibody-dependent cellular virus inhibition (ADCVI) corresponded with a decreased HIV-1 infection rate [120] suggesting that beneficial immune responses did not reach sufficient magnitude to impact the outcome of the trial. Host genetics may have also played a role in the vaccinee outcome. While there was no evidence of increased HIV acquisition in vaccinees relative to placebo recipients, there has been suggestion that the vaccine may have increased the likelihood of acquiring HIV-1 infection in low-behavioral risk individuals with the Fcγ receptor IIIa genotype [121].

RV144 is the only HIV-1 vaccine efficacy trial to date that has demonstrated vaccine efficacy, with a modest level of protection of 31% [97]. Humoral responses were the predominant immune response in this trial, along with vaccine-elicited CD4+ T-cell responses [98,99]. A case-control study showed that IgG antibodies to the V1/V2 region of HIV-1 gp120 correlated with decreased risk of infection [100–102] while IgA antibodies to the envelope correlated with decreased vaccine efficacy in the vaccine group.

Follow-up studies further supported the role of V2-specific immunity in vaccine efficacy with evidence of a virus sieve effect in infected vaccine recipients at this gp120 region [103]. Additionally, monoclonal antibodies generated from RV144 vaccine recipients targeted a critical residue in V2 (K169), thus providing evidence that vaccine-induced antibodies could potentially mediate a virus sieve effect. These V2-specific antibodies can mediate ADCC, neutralization and low-level virus capture [126,127]. These studies do not prove whether the V2 IgG response was a mechanistic or non-mechanistic correlate [128*]. They however generate new hypotheses to test in further efficacy clinical trials; namely, is there a functional role for V2-specific IgG antibodies or are they merely a marker of another functional immune response?

The plasma IgA antibody combined with the lack of knowledge of whether mucosal immune responses were elicited by vaccination has led to renewed interest in understanding the different forms of IgA and their potentially protective functions. Several RV144 follow-up studies as well as new vaccine studies are now collecting mucosal samples to probe these questions and determine the functional properties of vaccine-elicited IgA responses. In RV144, in the presence of low vaccine-elicited IgA responses, either ADCC or NAb responses correlated with decreased risk of infection. ADCC responses were predominantly directed to the C1 conformational region of gp120 [129–131] although other epitope specificities (i.e., V2) also contributed to the overall response [126]. Another hypothesis is that C1 region Env-specific IgA could block C1-specific IgG effector function due to their ability to bind to different Fc receptors on effector cells. We recently demonstrated that IgA antibodies elicited by RV144 could block C1 region-specific IgG-mediated ADCC (via natural killer cells) [132]. These findings indicate that the study of Fc receptor-mediated

antibody function will be important in the evaluation of HIV-1 vaccines. In addition, there is a remaining open question as to whether V2 antibodies might block the gp120-α4β7 interaction and contribute at least partially to the protective effect against HIV-1 sexual transmission [133].

Despite the 31% protective efficacy observed in RV144 and the lack of protection in Vax003, NAb responses were lower in RV144 as compared to Vax003 [99*]. The interpretation of these findings between the two trials remains difficult, as the route of HIV-1 transmission (heterosexual vs. IDU) was radically different. In previous clinical studies, it was found that gp120 induced high levels of Env-specific IgG4 antibodies [134] while ALVAC (vCP1452) prime and gp120 MN in alum boost elicited lower IgG4 relative to IgG1 and IgG3 antibodies [134]. Antigen-specific IgG3 antibodies have been associated with control of the pathogen and clinical protection in several infectious diseases [136,137]. A comparative study of IgG subclasses between RV144 and Vax003 may provide additional clues to mechanisms of vaccine protection.

The Step (HVTN502) [108] and Phambili (HVTN503) [116] studies were the first human efficacy trials of a T-cell-based HIV-1 vaccine. Despite an absence of vaccine efficacy, there was evidence of vaccine-elicited immune pressure on the founder virus [109]. This virus sieve analysis suggests that there were vaccine-elicited T-cell responses potentially not picked up by the IFN-γ ELISpot assays and that vaccine elicited Gag- and Nef-specific CD8+ T cells [110] applied pressure to the virus resulting in specific escape mutations in those with specific HLA alleles. Moreover vaccinees with HLA alleles associated with HIV-1 control had a significantly lower mean viral load over time [138]. Interestingly, the most highly conserved epitopes were detected at a lower frequency, suggesting that stronger responses to conserved sequences may be as important as breadth for protection [139]. Very recently, HVTN 505 was stopped for futility, showing no efficacy and no statistically significant effect on viral load as well as a non-significant increase in the number of HIV infections among vaccine recipients compared to the placebo group (Table 3). Similarly, a recent follow-up analysis of HVTN503 participants suggests a non-significant increased rate of HIV infection in the vaccinees compared to placebo recipients [117]. Further analysis is needed to better understand the immunogenicity of the HVTN505 and HVTN503 vaccines and how these results might inform the development of other adenoviruses vectors.

New directions

Table 4 shows some of the clinical trials planned within the next 5 years based on lessons learned from recent trials.

One of the main objectives for future vaccines is to counter HIV-1 variability. Several groups are focused on designing novel envelope immunogens capable of inducing broadly NAb [140–143]. This work is being based on study of envelope structure and host-pathogen interactions aimed at guiding the immune response toward the vulnerable sites on the envelope. Improvement of existing envelope immunogens to elicit higher levels of V2 antibodies is an approach suggested by antigenicity studies of the envelope used in RV144. These studies demonstrated that certain epitopes were better exposed as a result of a non-

HIV-1 sequence inserted into the HIV-1 envelope and likely led to the elicitation of antibody epitope specificities in RV144 [144]. Whether V2 antibodies elicited by various envelope immunogens are functional in a cross-clade manner and universal correlates of risk or just the 'tree hiding the forest' remains to be demonstrated. Vaccines utilizing a combination of consensus and transmitter-founder envelopes may be able to induce neutralizing responses with greater breadth and potency than single envelope immunogens [145]. Whether the induction of IgA blocking ADCC is a potential 'spine on the rose', and how to overcome it, also remains to be explored.

Mucosal IgA responses are elicited in acute HIV-1 infection but are focused predominantly on gp41 (and not gp120) and decline rapidly after the acute phase [146]. Several studies in non-human primates have reported the elicitation of mucosal immunity by different vaccine regimens [reviewed in 147]. Interestingly, a gp41-derived peptide formulated on virosomes protected macaques against SHIV challenge and elicited mucosal IgA and IgG antibodies in the protected animals [148]. The same vaccine administered in humans via systemic and mucosal routes elicited limited IgG and IgA antibodies in mucosal secretions [18]. Further clinical trials with mucosal sampling will provide additional insights in the ability of different vaccine regimens to elicit mucosal antibodies. Moreover, some emerging vaccine strategies aim at inducing long-lived memory B-cell responses.

Combination regimens using heterologous vectors in prime-boost and inserts aiming at broadening CD4+ and CD8+ T-cell responses such as mosaics [149] and conserved sequences [150] are promising avenues. Alternative vectors that might minimize or eliminate the presence of pre-existing anti-vector immunity [151] such as rare serotype human [152] and chimpanzee [153,154] adenovirus vectors as well as replication-competent vectors [155] are now in early clinical development (Table 4). It remains however uncertain how the recent outcomes of HVTN505 and HVTN503 may impact the use of adenovirus vectors in humans.

Unmet needs and opportunities

Significant efforts are currently focused on advancing efficacy trials in sub-saharan African with an emphasis on South Africa, due to the ongoing devastating subtype C HIV-1 epidemic. The HIV-1 subtype A epidemic also remains rampant in East Africa [156–158], which will demand similar efforts in the future. While heterosexual transmission predominates in sub-saharan Africa [159], an epidemic in men who have sex with men (MSM) is now expanding [160,161]. MSM will represent the predominant high-risk population for future HIV-1 vaccine efficacy trials in Asia [162–164]. The feasibility of efficacy testing in IDU is questionable due to the success of harm reduction programs [165] with decreasing HIV-1 incidence. The identification of low–intermediate-risk populations with predominant heterosexual transmission in Asia should however deserve heightened attention for the implementation of future efficacy trials [166].

Adaptive trial designs that would allow for the ongoing comparative evaluation of multiple vaccine concepts have been suggested as way to inform immune correlates analysis and enhance the efficiency of efficacy evaluation of HIV-1 vaccine candidates [167]. They may

also help address the complexities of evaluating the efficacy of multiple HIV prevention measures in combination [168,169].

Conclusion

Preventive HIV-1 vaccine clinical development is at a critical juncture due to the identification of correlates of HIV-1 infection risk from RV144. These findings have opened new avenues of research that were previously unforeseen and only made possible through the conduct of large-scale efficacy trials, in-depth analysis of immune response with modern laboratory assays, detailed statistical analysis and modeling, interdisciplinary teams, and strong international collaborations.

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References

1. UNAIDS. Report on the Global AIDS Epidemic. 2012
2. Kim JH, Rerks-Ngarm S, Excler JL, et al. HIV vaccines: lessons learned and the way forward. Curr Opin HIV AIDS. 2010; 5:428–434. [PubMed: 20978385]
3. Koff WC. Accelerating HIV vaccine development. Nature. 2010; 464:161–162. [PubMed: 20220821]
4. Barouch DH. Challenges in the development of an HIV-1 vaccine. Nature. 2008; 455:613–619. [PubMed: 18833271]
5. Johnston MI, Fauci AS. An HIV vaccine–challenges and prospects. N Engl J Med. 2008; 359:888–890. [PubMed: 18753644]
6. Fauci AS, Johnston MI, Dieffenbach CW, et al. HIV vaccine research: the way forward. Science. 2008; 321:530–532. [PubMed: 18653883]
7*. Koff WC. HIV vaccine development: Challenges and opportunities towards solving the HIV vaccine-neutralizing antibody problem. Vaccine. 2012; 30:4310–4315. Review of the progress and challenges of a vaccine inducing broadly neutralizing antibodies. [PubMed: 22100891]
8. O'Connell, RJ., Kim, JH., Corey, L., et al. Human Immunodeficiency Virus Vaccine Trials. In: Bushman, FD.Nabel, GJ., Swanstrom, R., editors. HIV: From Biology to Prevention and Treatment. Cold Spring Harbor Laboratory Press; Cold Spring Harbor, NY: 2012. p. 483-504.
9. Kublin JG, Morgan CA, Day TA, et al. HIV Vaccine Trials Network: activities and achievements of the first decade and beyond. Clin Investig (Lond). 2012; 2:245–254.
10. Launay O, Durier C, Desaint C, et al. Cellular immune responses induced with dose-sparing intradermal administration of HIV vaccine to HIV-uninfected volunteers in the ANRS VAC16 trial. PLoS One. 2007; 2(8):e725. [PubMed: 17712402]
11. Thiebaut R, Liquet B, Hocini H, et al. A New Method for Integrated Analysis Applied to Gene Expression and Cytokines Secretion in Response to LIPO-5 Vaccine in HIV-Negative Volunteers. AIDS Vaccine 2012, Boston MA, 9–12 September 2012. Retrovirology. 2012; 9(Suppl 2) P04.14.
12. Lewis DJ, Fraser CA, Mahmoud AN, Wiggins RC, Woodrow M, Cope A, et al. Phase I randomised clinical trial of an HIV-1(CN54), clade C, trimeric envelope vaccine candidate delivered vaginally. PLoS One. 2011; 6:e25165. [PubMed: 21984924]

13. Spearman P, Tomaras G, Montefiori D, et al. Rapid Development of Cross-Clade Neutralizing Antibody Responses After Clade B gp120/gp 140 Protein Priming And Clade C gp 140 Protein Boosting. AIDS Vaccine 2012, Boston MA, 9–12 September 2012. Retrovirology. 2012; 9(Suppl 2) P04.30 LB.
14. Ensoli B, Fiorelli V, Ensoli F, et al. The preventive phase I trial with the HIV-1 Tat-based vaccine. Vaccine. 2009; 28:371–378. [PubMed: 19879233]
15. Bellino S, Francavilla V, Longo O, et al. Parallel conduction of the phase I preventive and therapeutic trials based on the Tat vaccine candidate. Rev Recent Clin Trials. 2009; 4:195–204. [PubMed: 20028332]
16. Goepfert PA, Tomaras GD, Horton H, et al. Durable HIV-1 antibody and T-cell responses elicited by an adjuvanted multiprotein recombinant vaccine in uninfected human volunteers. Vaccine. 2007; 25:510–518. [PubMed: 17049679]
17. Leroux-Roels I, Koutsoukos M, Clement F, et al. Strong and persistent CD4+ T-cell response in healthy adults immunized with a candidate HIV-1 vaccine containing gp120, Nef and Tat antigens formulated in three Adjuvant Systems. Vaccine. 2010; 28:7016–7024. [PubMed: 20728522]
18. Leroux-Roels G, Maes C, Clement F, et al. Randomized Phase I: Safety, Immunogenicity and Mucosal Antiviral Activity in Young Healthy Women Vaccinated with HIV-1 Gp41 P1 Peptide on Virosomes. PLoS One. 2013; 8:e55438. [PubMed: 23437055]
19. Pitisuttithum P, Rerks-Ngarm S, Bussaratid V, et al. Safety and reactogenicity of canarypox ALVAC-HIV (vCP1521) and HIV-1 gp120 AIDSVAX B/E vaccination in an efficacy trial in Thailand. PLoS One. 2011; 6:e27837. [PubMed: 22205930]
20. Shao Y, Li T, Liu Y, et al. The safety and immunogenicity of HIV-1 vaccines based on DNA and replication competent vaccinia vector in Phase I clinical trial. Presented at: AIDS Vaccine 2010. Atlanta GA, USA, 28 September–1 October 2010. AIDS Res Hum Retroviruses. 2010; 26:A-1–A-184.
21. Vasan S, Schlesinger SJ, Chen Z, et al. Phase 1 safety and immunogenicity evaluation of ADMVA, a multigenic, modified vaccinia Ankara-HIV-1 B'/C candidate vaccine. PLoS One. 2010; 5:e8816. [PubMed: 20111599]
22. Ramanathan VD, Kumar M, Mahalingam J, et al. A phase 1 study to evaluate the safety and immunogenicity of a recombinant HIV type 1 subtype C-modified vaccinia Ankara virus vaccine candidate in Indian volunteers. AIDS Res Hum Retroviruses. 2009; 25:1107–1116. [PubMed: 19943789]
23. Currier JR, Ngauy V, de Souza MS, et al. Phase I safety and immunogenicity evaluation of MVA-CMDR, a multigenic, recombinant modified vaccinia Ankara-HIV-1 vaccine candidate. PLoS One. 2010; 5:e13983. [PubMed: 21085591]
24. Bart PA, Goodall R, Barber T, et al. EV01: a phase I trial in healthy HIV negative volunteers to evaluate a clade C HIV vaccine, NYVAC-C undertaken by the EuroVacc Consortium. Vaccine. 2008; 26:3153–3161. [PubMed: 18502002]
25. Catanzaro AT, Roederer M, Koup RA, et al. Phase I clinical evaluation of a six- plasmid multiclade HIV-1 DNA candidate vaccine. Vaccine. 2007; 25:4085–4092. [PubMed: 17391815]
26. Mulligan MJ, Russell ND, Celum C, et al. Excellent safety and tolerability of the human immunodeficiency virus type 1 pGA2/JS2 plasmid DNA priming vector vaccine in HIV type 1 uninfected adults. AIDS Res Hum Retroviruses. 2006; 22:678–683. [PubMed: 16831092]
27. Vasan S, Schlesinger SJ, Huang Y, et al. Phase 1 Safety and Immunogenicity Evaluation of ADVAX, a Multigenic, DNA-Based Clade C/B' HIV-1 Candidate Vaccine. PLoS One. 2010; 5:e8617. [PubMed: 20111582]
28. Vasan S, Hurley A, Schlesinger SJ, et al. In vivo electroporation enhances the immunogenicity of an HIV-1 DNA vaccine candidate in healthy volunteers. PLoS One. 2011; 6:e19252. [PubMed: 21603651]
29. Gorse GJ, Baden LR, Wecker M, et al. Safety and immunogenicity of cytotoxic T-lymphocyte poly-epitope, DNA plasmid (EP HIV-1090) vaccine in healthy, human immunodeficiency virus type 1 (HIV-1)-uninfected adults. Vaccine. 2008; 26:215–223. [PubMed: 18055072]

30. Jin X, Newman MJ, De-Rosa S, et al. A novel HIV T helper epitope-based vaccine elicits cytokine-secreting HIV-specific CD4+ T cells in a Phase I clinical trial in HIV-uninfected adults. Vaccine. 2009; 27:7080–7086. [PubMed: 19786145]
31. Wilson CC, Newman MJ, Livingston BD, et al. Clinical phase 1 testing of the safety and immunogenicity of an epitope-based DNA vaccine in human immunodeficiency virus type 1-infected subjects receiving highly active antiretroviral therapy. Clin Vaccine Immunol. 2008; 15:986–994. [PubMed: 18400976]
32. Kalams SA, Parker S, Jin X, et al. Safety and immunogenicity of an HIV-1 gag DNA vaccine with or without IL-12 and/or IL-15 plasmid cytokine adjuvant in healthy, HIV-1 uninfected adults. PLoS One. 2012; 7:e29231. [PubMed: 22242162]
33. Catanzaro AT, Koup RA, Roederer M, et al. Phase 1 safety and immunogenicity evaluation of a multiclade HIV-1 candidate vaccine delivered by a replication-defective recombinant adenovirus vector. J Infect Dis. 2006; 194:1638–1649. [PubMed: 17109335]
34. Priddy FH, Brown D, Kublin J, et al. Safety and immunogenicity of a replication-incompetent adenovirus type 5 HIV-1 clade B gag/pol/nef vaccine in healthy adults. Clin Infect Dis. 2008; 46:1769–1781. [PubMed: 18433307]
35. Keefer MC, Gilmour J, Hayes P, et al. A phase I double blind, placebo-controlled, randomized study of a multigenic HIV-1 adenovirus subtype 35 vector vaccine in healthy uninfected adults. PLoS One. 2012; 7:e41936. [PubMed: 22870265]
36. 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). J Infect Dis. 2013; 207:240–247. [PubMed: 23125444]
37. 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). J Infect Dis. 2013; 207:248–256. [PubMed: 23125443]
38. Mehendale S, van Lunzen J, Clumeck N, et al. A phase 1 study to evaluate the safety and immunogenicity of a recombinant HIV type 1 subtype C adeno-associated virus vaccine. AIDS Res Hum Retroviruses. 2008; 24:873–880. [PubMed: 18544020]
39. Mehendale S, Sahay S, Thakar M, et al. Safety and immunogenicity of tgAAC09, a recombinant adeno-associated virus type 2 HIV-1 subtype C vaccine in India. Indian J Med Res. 2010; 132:168–175. [PubMed: 20716817]
40. Vardas E, Kaleebu P, Bekker LG, et al. A phase 2 study to evaluate the safety and immunogenicity of a recombinant HIV type 1 vaccine based on adeno-associated virus. AIDS Res Hum Retroviruses. 2010; 26:933–942. [PubMed: 20666584]
41. Wecker M, Gilbert P, Russell N, et al. Phase I safety and immunogenicity evaluations of an alphavirus replicon HIV-1 subtype C gag vaccine in healthy HIV-1-uninfected adults. Clin Vaccine Immunol. 2012; 19:1651–1660. [PubMed: 22914365]
42. Fuchs JD, Frank I, Kochar N, et al. First-In-Human Phase I Clinical Trial Of A Recombinant Vesicular Stomatitis Virus (rVSV)-Based Preventive HIV-1 Vaccine. AIDS Vaccine 2012, Boston MA, 9–12 September 2012. Retrovirology. 2012; 9(Suppl 2) P01.27 LB.
43. Spearman P, Lally MA, Elizaga M, et al. A trimeric, V2-deleted HIV-1 envelope glycoprotein vaccine elicits potent neutralizing antibodies but limited breadth of neutralization in human volunteers. J Infect Dis. 2011; 203:1165–1173. [PubMed: 21451004]
44. Wang S, Kennedy JS, West K, et al. Cross-subtype antibody and cellular immune responses induced by a polyvalent DNA prime-protein boost HIV-1 vaccine in healthy human volunteers. Vaccine. 2008; 26:3947–3957. [PubMed: 18724414]
45. Kennedy JS, Co M, Green S, et al. The safety and tolerability of an HIV-1 DNA prime-protein boost vaccine (DP6-001) in healthy adult volunteers. Vaccine. 2008; 26:4420–4424. [PubMed: 18588934]
46. Goonetilleke N, Moore S, Dally L, et al. Induction of multifunctional human immunodeficiency virus type 1 (HIV-1)-specific T cells capable of proliferation in healthy subjects by using a prime-boost regimen of DNA- and modified vaccinia virus Ankara-vectored vaccines expressing HIV-1 Gag coupled to CD8+ T-cell epitopes. J Virol. 2006; 80:4717–4728. [PubMed: 16641265]

47. Cebere I, Dorrell L, McShane H, et al. Phase I clinical trial safety of DNA- and modified virus Ankara-vectored human immunodeficiency virus type 1 (HIV-1) vaccines administered alone and in a prime-boost regime to healthy HIV-1-uninfected volunteers. Vaccine. 2006; 24:417–425. [PubMed: 16176847]

48. Peters BS, Jaoko W, Vardas E, et al. Studies of a prophylactic HIV-1 vaccine candidate based on modified vaccinia virus Ankara (MVA) with and without DNA priming: effects of dosage and route on safety and immunogenicity. Vaccine. 2007; 25:2120–2127. [PubMed: 17250931]

49. Jaoko W, Nakwagala FN, Anzala O, et al. Safety and immunogenicity of recombinant low-dosage HIV-1 A vaccine candidates vectored by plasmid pTHr DNA or modified vaccinia virus Ankara (MVA) in humans in East Africa. Vaccine. 2008; 26:2788–2795. [PubMed: 18440674]

50. Guimarães-Walker A, Mackie N, McCormack S, et al. Lessons from IAVI-006, a phase I clinical trial to evaluate the safety and immunogenicity of the pTHr.HIVA DNA and MVA.HIVA vaccines in a prime-boost strategy to induce HIV-1 specific T-cell responses in healthy volunteers. Vaccine. 2008; 26:6671–6677. [PubMed: 18812202]

51. Sandstrom E, Nilsson C, Hejdeman B, et al. Broad immunogenicity of a multigene, multiclade HIV-1 DNA vaccine boosted with heterologous HIV-1 recombinant modified vaccinia virus Ankara. J Infect Dis. 2008; 198:1482–1490. [PubMed: 18808335]

52. Gudmundsdotter L, Nilsson C, Brave A, et al. Recombinant Modified Vaccinia Ankara (MVA) effectively boosts DNA-primed HIV-specific immune responses in humans despite pre-existing vaccinia immunity. Vaccine. 2009; 27:4468–4474. [PubMed: 19450644]

53. Aboud S, Nilsson C, Karlén K, et al. Strong HIV-specific CD4+ and CD8+ T-lymphocyte proliferative responses in healthy individuals immunized with an HIV-1 DNA vaccine and boosted with recombinant modified vaccinia virus ankara expressing HIV-1 genes. Clin Vaccine Immunol. 2010; 17:1124–1131. [PubMed: 20463104]

54. Bakari M, Aboud S, Nilsson C, et al. Broad and potent immune responses to a low dose intradermal HIV-1 DNA boosted with HIV-1 recombinant MVA among healthy adults in Tanzania. Vaccine. 2011; 29:8417–8428. [PubMed: 21864626]

55. Goepfert PA, Elizaga ML, Sato A, et al. Phase 1 safety and immunogenicity testing of DNA and recombinant modified vaccinia Ankara vaccines expressing HIV-1 virus-like particles. J Infect Dis. 2011; 203:610–619. [PubMed: 21282192]

56. Gorse GJ, Newman MJ, deCamp A, et al. DNA and modified vaccinia virus Ankara vaccines encoding multiple cytotoxic and helper T-lymphocyte epitopes of human immunodeficiency virus type 1 (HIV-1) are safe but weakly immunogenic in HIV-1-uninfected, vaccinia virus-naive adults. Clin Vaccine Immunol. 2012; 19:649–658. [PubMed: 22398243]

57. Kelleher AD, Puls RL, Bebbington M, et al. A randomized, placebo-controlled phase I trial of DNA prime, recombinant fowlpox virus boost prophylactic vaccine for HIV-1. AIDS. 2006; 20:294–297. [PubMed: 16511428]

58. Hemachandra A, Puls RL, Sirivichayakul S, et al. An HIV-1 clade A/E DNA prime, recombinant fowlpox virus boost vaccine is safe, but non-immunogenic in a randomized phase I/IIa trial in Thai volunteers at low risk of HIV infection. Hum Vaccin. 2010; 6:835–840. [PubMed: 20864808]

59. Harari A, Bart PA, Stohr W, et al. An HIV-1 clade C DNA prime, NYVAC boost vaccine regimen induces reliable, polyfunctional, and long-lasting T cell responses. J Exp Med. 2008; 205:63–77. [PubMed: 18195071]

60. McCormack S, Stöhr W, Barber T, et al. EV02: a Phase I trial to compare the safety and immunogenicity of HIV DNA-C prime-NYVAC-C boost to NYVAC-C alone. Vaccine. 2008; 26:3162–3174. [PubMed: 18502003]

61. Perreau M, Welles HC, Harari A, et al. DNA/NYVAC vaccine regimen induces HIV-specific CD4 and CD8 T-cell responses in intestinal mucosa. J Virol. 2011; 85:9854–9862. [PubMed: 21775454]

62. Montefiori DC, Huang Y, Karuna S, et al. rAd5/NYVAC-B is Superior to NYVAC-B/rAd5 and is Dependent on rAd5 Dose for Neutralizing Antibody Responses Against HIV-1. AIDS Vaccine 2012, Boston MA, 9–12 September 2012. Retrovirology. 2012; 9(Suppl 2) P04.25 LB.

63. Koup RA, Roederer M, Lamoreaux L, et al. Priming immunization with DNA augments immunogenicity of recombinant adenoviral vectors for both HIV-1 specific antibody and T-cell responses. PLoS One. 2010; 5:e9015. [PubMed: 20126394]

64. Kibuuka H, Kimutai R, Maboko L, et al. A phase 1/2 study of a multiclade HIV-1 DNA plasmid prime and recombinant adenovirus serotype 5 boost vaccine in HIV-Uninfected East Africans (RV 172). J Infect Dis. 2010; 201:600–607. [PubMed: 20078213]

65. Jaoko W, Karita E, Kayitenkore K, et al. Safety and Immunogenicity Study of Multiclade HIV-1 Adenoviral Vector Vaccine Alone or as Boost following a Multiclade HIV-1 DNA Vaccine in Africa. PLoS One. 2010; 5:e12873. [PubMed: 20877623]

66. Churchyard GJ, Morgan C, Adams E, et al. A phase IIA randomized clinical trial of a multiclade HIV-1 DNA prime followed by a multiclade rAd5 HIV-1 vaccine boost in healthy adults (HVTN204). PLoS One. 2011; 6:e21225. [PubMed: 21857901]

67. Koblin BA, Casapia M, Morgan C, et al. Safety and immunogenicity of an HIV adenoviral vector boost after DNA plasmid vaccine prime by route of administration: a randomized clinical trial. PLoS One. 2011; 6:e24517. [PubMed: 21931737]

68. Fuchs JD, Morgan C, Bart P, et al. DNA And Recombinant Adenovirus Serotype 35 And 5 Preventive HIV-1 Vaccines With Env A Inserts Elicit Cross-Clade Binding And V1V2 Antibodies. AIDS Vaccine 2012, Boston MA, 9–12 September 2012. Retrovirology. 2012; 9(Suppl 2) P04.29 LB.

69. Mpendo J, Bayingana R, Nanvubya A, et al. Tolerability and Acceptability of Electroporation During a Phase 1 Vaccine Trial at Two Sites in Uganda and Rwanda. AIDS Vaccine 2012, Boston MA, 9–12 September 2012. Retrovirology. 2012; 9(Suppl 2) P04.19.

70. Borthwick NJ, Ahmed T, Rose A, et al. Immunogenicity of a universal HIV-1 vaccine vectored by DNA, MVA and CHADV-63 in a Phase I/IIA clinical trial. AIDS Vaccine 2012, Boston MA, 9–12 September 2012. Retrovirology. 2012; 9(Suppl 2):P118.

71. Keefer MC, Frey SE, Elizaga M, et al. A phase I trial of preventive HIV vaccination with heterologous poxviral-vectors containing matching HIV-1 inserts in healthy HIV-uninfected subjects. Vaccine. 2011; 29:1948–1958. [PubMed: 21216311]

72. Walsh SR, Seaman MS, Grandpre LE, et al. Impact of anti-orthopoxvirus neutralizing antibodies induced by a heterologous prime-boost HIV-1 vaccine on insert-specific immune responses. Vaccine. 2012; 31:114–119. [PubMed: 23142302]

73. Nabel GJ, Fauci AS. Induction of unnatural immunity: prospects for a broadly protective universal influenza vaccine. Nat Med. 2010; 16:1389–1391. [PubMed: 21135852]

74. Qin L, Gilbert PB, Corey L, et al. A framework for assessing immunological correlates of protection in vaccine trials. J Infect Dis. 2007; 196:1304–1312. [PubMed: 17922394]

75. Plotkin SA. Vaccines: correlates of vaccine-induced immunity. Clin Infect Dis. 2008; 47:401–409. [PubMed: 18558875]

76. Plotkin SA, Plotkin SL. The development of vaccines: how the past led to the future. Nat Rev Microbiol. 2011; 9:889–893. [PubMed: 21963800]

77. Thakur A, Pedersen LE, Jungersen G. Immune markers and correlates of protection for vaccine induced immune responses. Vaccine. 2012; 30:4907–4920. [PubMed: 22658928]

78. Walker BD, Ahmed R, Plotkin S. Moving ahead an HIV vaccine: use both arms to beat HIV. Nat Med. 2011; 17:1194–1195. [PubMed: 21988996]

79. Excler JL, Plotkin S. The prime-boost concept applied to HIV preventive vaccines. AIDS. 1997; 11 (Suppl A):S127–S137. [PubMed: 9451976]

80. Tartaglia J, Excler JL, El Habib R, et al. Canarypox virus-based vaccines: prime-boost strategies to induce cell-mediated and humoral immunity against HIV. AIDS Res Hum Retroviruses. 1998; 14 (Suppl 3):S291–S298. [PubMed: 9814957]

81. Paris RM, Kim JH, Robb ML, Michael NL. Prime-boost immunization with poxvirus or adenovirus vectors as a strategy to develop a protective vaccine for HIV-1. Expert Rev Vaccines. 2010; 9:1055–1069. [PubMed: 20822348]

82. Zak DE, Aderem A. Overcoming limitations in the systems vaccinology approach: a pathway for accelerated HIV vaccine development. Curr Opin HIV AIDS. 2012; 7:58–63. [PubMed: 22156843]

83*. Zak DE, Andersen-Nissen E, Peterson ER, et al. Merck Ad5/HIV induces broad innate immune activation that predicts CD8+ T-cell responses but is attenuated by preexisting Ad5 immunity.

Proc Natl Acad Sci USA. 2012; 109:E3503–E3512. Evidence of systems biology predicting HIV vaccine-induced immune responses. [PubMed: 23151505]

84. Schmidt C, Smith C, Barin B, et al. Background morbidity in HIV vaccine trial participants from various geographic regions as assessed by unsolicited adverse events. Hum Vaccin Immunother. 2012; 8:630–638. [PubMed: 22634443]
85. Kintu K, Andrew P, Musoke P, et al. Feasibility and Safety of ALVAC-HIV vCP1521 Vaccine in HIV- exposed Infants in Uganda: Results from the First HIV Vaccine Trial in Infants in Africa. J Acquir Immune Defic Syndr. 2013; 63:1–8. [PubMed: 23221981]
86. D'Souza MP, Frahm N. Adenovirus 5 serotype vector-specific immunity and HIV-1 infection: a tale of T cells and antibodies. AIDS. 2010; 24:803–809. [PubMed: 20168203]
87. Duerr A, Huang Y, Buchbinder S, et al. Extended Follow-up Confirms Early Vaccine-Enhanced Risk of HIV Acquisition and Demonstrates Waning Effect Over Time Among Participants in a Randomized Trial of Recombinant Adenovirus HIV Vaccine (Step Study). J Infect Dis. 2012; 206:258–266. [PubMed: 22561365]
88. Koblin BA, Mayer KH, Noonan E, et al. Sexual Risk Behaviors, Circumcision Status, and Preexisting Immunity to Adenovirus Type 5 Among Men Who Have Sex With Men Participating in a Randomized HIV-1 Vaccine Efficacy Trial: Step Study. J Acquir Immune Defic Syndr. 2012; 60:405–413. [PubMed: 22421748]
89. Curlin ME, Cassis-Ghavami F, Magaret AS, et al. Serological immunity to adenovirus serotype 5 is not associated with risk of HIV infection: a case-control study. AIDS. 2011; 25:153–158. [PubMed: 21150554]
90. Cheng C, Wang L, Gall JG, et al. Decreased pre-existing Ad5 capsid and Ad35 neutralizing antibodies increase HIV-1 infection risk in the Step trial independent of vaccination. PLoS One. 2012; 7:e33969. [PubMed: 22496775]
91. Kennedy JS, Co M, Green S, et al. The safety and tolerability of an HIV-1 DNA prime-protein boost vaccine (DP6-001) in healthy adult volunteers. Vaccine. 2008; 26:4420–4424. [PubMed: 18588934]
92. Van Braeckel E, Koutsoukos M, Bourguignon P, et al. Vaccine-induced HIV seropositivity: a problem on the rise. J Clin Virol. 2011; 50:334–337. [PubMed: 21300566]
93. Silbermann B, Tod M, Desaint C, et al. Short communication: Long-term persistence of vaccine-induced HIV seropositivity among healthy volunteers. AIDS Res Hum Retroviruses. 2008; 24:1445–1448. [PubMed: 19000023]
94. Khurana S, Needham J, Park S, et al. Novel approach for differential diagnosis of HIV infections in the face of vaccine-generated antibodies: utility for detection of diverse HIV-1 subtypes. J Acquir Immune Defic Syndr. 2006; 43:304–312. [PubMed: 17019363]
95. Cooper CJ, Metch B, Dragavon J, et al. Vaccine-induced HIV seropositivity/reactivity in noninfected HIV vaccine recipients. JAMA. 2010; 304:275–283. [PubMed: 20639561]
96. Penezina O, Clapham D, Collins J, et al. New HIV Peptide-Based Immunoassay Resolves Vaccine-Induced Seropositivity in HIV Vaccine (Phase III) Trial Participants. AIDS Vaccine 2012, Boston MA, 9–12 September 2012. Retrovirology. 2012; 9(Suppl 2) P04.13.
97**. 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; 361:1–12. Seminal trial (RV144) showing for the first time that an HIV vaccine regimen can confer protection against HIV acquisition. [PubMed: 19528190]
98. de Souza MS, Ratto-Kim S, Chuenarom W, et al. The Thai phase III trial (RV144) vaccine regimen induces T cell responses that preferentially target epitopes within the V2 region of HIV-1 envelope. J Immunol. 2012; 188:5166–5176. [PubMed: 22529301]
99*. Montefiori DC, Karnasuta C, Huang Y, et al. Magnitude and Breadth of the Neutralizing Antibody Response in the RV144 and Vax003 HIV-1 Vaccine Efficacy Trials. J Infect Dis. 2012; 206:431–441. Comparative analysis of the neutralizing antibody response in two seminal antibody-based efficacy trials. [PubMed: 22634875]
100**. Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med. 2012; 366:1275–1286. Seminal study (RV144) identifying for the

first time correlates of risk (IgG V2 and IgA antibodies) for HIV acquisition. [PubMed: 22475592]

101. Karasavvas N, Billings E, Rao M, et al. The Thai Phase III HIV Type 1 Vaccine trial (RV144) regimen induces antibodies that target conserved regions within the V2 loop of gp120. AIDS Res Hum Retroviruses. 2012; 28:1444–1457. [PubMed: 23035746]
102. 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]
103**. Rolland M, Edlefsen PT, Larsen BB, et al. Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2. Nature. 2012; 490:417–420. Seminal paper supporting the role of gp120 V2 in protection in RV144. [PubMed: 22960785]
104. Gilbert PB, Berger JO, Stablein D, et al. Statistical interpretation of the RV144 HIV vaccine efficacy trial in Thailand: a case study for statistical issues in efficacy trials. J Infect Dis. 2011; 203:969–975. [PubMed: 21402548]
105*. Robb ML, Rerks-Ngarm S, Nitayaphan S, et al. 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. 2012; 12:531–537. Study demonstrating a greater vaccine benefit (efficacy) in low-risk individuals. [PubMed: 22652344]
106. Paris R, Bejrachandra S, Thongcharoen P, et al. HLA class II restriction of HIV-1 clade-specific neutralizing antibody responses in ethnic Thai recipients of the RV144 prime-boost vaccine combination of ALVAC-HIV and AIDSVAX(®) B/E. Vaccine. 2012; 30:832–836. [PubMed: 22085554]
107. Rerks-Ngarm S, Paris RM, Chunsutthiwat S, et al. Extended evaluation of the virologic, immunologic, and clinical course of volunteers who acquired HIV-1 infection in a phase III vaccine trial of ALVAC-HIV and AIDSVAX(R) B/E. J Infect Dis. 2013; 207:1195–205. [PubMed: 22837492]
108**. 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; 372:1881–1893. First efficacy trial of a T-cell-based vaccine that failed to confer protection. [PubMed: 19012954]
109. Rolland M, Tovanabutra S, deCamp AC, et al. Genetic impact of vaccination on breakthrough HIV-1 sequences from the STEP trial. Nat Med. 2011; 17:366–371. [PubMed: 21358627]
110. McElrath MJ, De Rosa SC, Moodie Z, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: a case-cohort analysis. Lancet. 2008; 372:1894–1905. [PubMed: 19012957]
111. O'Brien KL, Liu J, King SL, et al. Adenovirus-specific immunity after immunization with an Ad5 HIV-1 vaccine candidate in humans. Nat Med. 2009; 15:873–875. [PubMed: 19620961]
112. D'Souza MP, Frahm N. Adenovirus 5 serotype vector-specific immunity and HIV-1 infection: a tale of T cells and antibodies. AIDS. 2010; 24:803–809. [PubMed: 20168203]
113. Koblin BA, Mayer KH, Noonan E, et al. Sexual Risk Behaviors, Circumcision Status, and Preexisting Immunity to Adenovirus Type 5 Among Men Who Have Sex With Men Participating in a Randomized HIV-1 Vaccine Efficacy Trial: Step Study. J Acquir Immune Defic Syndr. 2012; 60:405–413. [PubMed: 22421748]
114. Curlin ME, Cassis-Ghavami F, Magaret AS, et al. Serological immunity to adenovirus serotype 5 is not associated with risk of HIV infection: a case-control study. AIDS. 2011; 25:153–158. [PubMed: 21150554]
115. Cheng C, Wang L, Gall JG, et al. Decreased pre-existing Ad5 capsid and Ad35 neutralizing antibodies increase HIV-1 infection risk in the Step trial independent of vaccination. PLoS One. 2012; 7:e33969. [PubMed: 22496775]
116. 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; 11:507–515. [PubMed: 21570355]
117. Cohen J. More Woes for Struggling HIV Vaccine Field. Science. 2013; 340:667. [PubMed: 23661729]

118. 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; 194:1661–1671. [PubMed: 17109337]
119. Gilbert P, Wang M, Wrin T, et al. Magnitude and breadth of a nonprotective neutralizing antibody response in an efficacy trial of a candidate HIV-1 gp120 vaccine. J Infect Dis. 2010; 202:595–605. [PubMed: 20608874]
120. Forthal DN, Gilbert PB, Landucci G, et al. 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. 2007; 178:6596–6603. [PubMed: 17475891]
121. Forthal DN, Gabriel EE, Wang A, et al. Association of Fcγ receptor IIIa genotype with the rate of HIV infection after gp120 vaccination. Blood. 2012; 120:2836–2842. [PubMed: 22915639]
122. Flynn NM, Forthal DN, Harro CD, et al. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. J Infect Dis. 2005; 191:654–665. [PubMed: 15688278]
123. Gilbert PB, Ackers ML, Berman PW, et al. HIV-1 virologic and immunologic progression and initiation of antiretroviral therapy among HIV-1-infected subjects in a trial of the efficacy of recombinant glycoprotein 120 vaccine. J Infect Dis. 2005; 192:974–983. [PubMed: 16107949]
124. 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; 191:666–677. [PubMed: 15688279]
125. Schneider JA, Alam SA, Ackers M, et al. Mucosal HIV-binding antibody and neutralizing activity in high-risk HIV-uninfected female participants in a trial of HIV-vaccine efficacy. J Infect Dis. 2007; 196:1637–1644. [PubMed: 18008247]
126. 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; 38:176–186. [PubMed: 23313589]
127. Liu P, Yates L, Shen X, et al. Infectious Virion Capture by HIV-1 gp120 Specific IgG from RV144 Vaccinees. J Virol. 2013 in press.
128*. Plotkin SA, Gilbert PB. Nomenclature for immune correlates of protection after vaccination. Clin Infect Dis. 2012; 54:1615–1617. Comprehensive review of the definition of immune correlates of protection. [PubMed: 22437237]
129. Ferrari G, Pollara J, Kozink D, et al. An HIV-1 gp120 envelope human monoclonal antibody that recognizes a C1 conformational epitope mediates potent antibody-dependent cellular cytotoxicity (ADCC) activity and defines a common ADCC epitope in human HIV-1 serum. J Virol. 2011; 85:7029–7036. [PubMed: 21543485]
130. Bonsignori M, Pollara J, Moody MA, et al. Antibody-Dependent Cellular Cytotoxicity-Mediating Antibodies from an HIV-1 Vaccine Efficacy Trial Target Multiple Epitopes and Preferentially Use the VH1 Gene Family. J Virol. 2012; 86:11521–11532. [PubMed: 22896626]
131. Moody MA, Yates NL, Amos JD, et al. HIV-1 gp120 vaccine induces affinity maturation in both new and persistent antibody clonal lineages. J Virol. 2012; 86:7496–7507. [PubMed: 22553329]
132. Tomaras GD, Ferrari G, Shen, et al. Vaccine induced plasma IgA specific for the C1-region of the HIV-1 envelope blocks binding and effector function of IgG. Proc Natl Acad Sci USA. 2013 in press.
133. Nakamura GR, Fonseca DP, O'Rourke SM, et al. Monoclonal antibodies to the V2 domain of MN-rgp120: fine mapping of epitopes and inhibition of α4β7 binding. PLoS One. 2012; 7:e39045. [PubMed: 22720026]
134. Gorse GJ, Patel GB, Mandava M, et al. MN and IIIB recombinant glycoprotein 120 vaccine-induced binding antibodies to native envelope glycoprotein of human immunodeficiency virus type 1 primary isolates. National Institute of Allergy and Infectious Disease Aids Vaccine Evaluation Group. AIDS Res Hum Retroviruses. 1999; 15:921–930. [PubMed: 10408729]
135. Banerjee K, Klasse PJ, Sanders RW, et al. IgG subclass profiles in infected HIV type 1 controllers and chronic progressors and in uninfected recipients of Env vaccines. AIDS Res Hum Retroviruses. 2010; 26:445–458. [PubMed: 20377426]

136. Roussilhon C, Oeuvray C, Müller-Graf C, et al. Long-term clinical protection from falciparum malaria is strongly associated with IgG3 antibodies to merozoite surface protein 3. PLoS Med. 2007; 4:e320. [PubMed: 18001147]

137. Kam YW, Simarmata D, Chow A, et al. Early appearance of neutralizing immunoglobulin G3 antibodies is associated with chikungunya virus clearance and long-term clinical protection. J Infect Dis. 2012; 205:1147–1154. [PubMed: 22389226]

138. Fitzgerald DW, Janes H, Robertson M, et al. An Ad5-vectored HIV-1 vaccine elicits cell-mediated immunity but does not affect disease progression in HIV-1-infected male subjects: results from a randomized placebo-controlled trial (the Step study). J Infect Dis. 2011; 203:765–772. [PubMed: 21343146]

139. Li F, Finnefrock AC, Dubey SA, et al. Mapping HIV-1 vaccine induced T-cell responses: bias towards less-conserved regions and potential impact on vaccine efficacy in the Step study. PLoS One. 2011; 6:e20479. [PubMed: 21695251]

140. Koff WC. HIV vaccine development: challenges and opportunities towards solving the HIV vaccine-neutralizing antibody problem. Vaccine. 2012; 30:4310–4315. [PubMed: 22100891]

141. Burton DR, Ahmed R, Barouch DH, et al. A Blueprint for HIV Vaccine Discovery. Cell Host Microbe. 2012; 12:396–407. [PubMed: 23084910]

142. Haynes BF, Kelsoe G, Harrison SC, Kepler TB, et al. B-cell lineage immunogen design in vaccine development with HIV-1 as a case study. Nat Biotechnol. 2012; 30:423–433. [PubMed: 22565972]

143. Benjelloun F, Lawrence P, Verrier B, Genin C, Paul S. Role of human immunodeficiency virus type 1 envelope structure in the induction of broadly neutralizing antibodies. J Virol. 2012; 86:13152–13163. [PubMed: 23015715]

144*. Alam SM, Liao HX, Tomaras GD, et al. Antigenicity and immunogenicity of RV144 vaccine AIDSVAX clade E envelope immunogen is enhanced by a gp120 N-terminal deletion. J Virol. 2013; 87:1554–1568. Study showing how to improve Env immunogen design based on the RV144 analysis of correlates of risk. [PubMed: 23175357]

145. Liao HX, Tsao CY, Alam SM, et al. Antigenicity and Immunogenicity of Transmitted/Founder, Consensus and Chronic Envelope Glycoproteins of Human Immunodeficiency Virus Type 1. J Virol. 2013 Jan 30.

146. Yates NL, Stacey AR, Nolen TL, et al. HIV-1 gp41 envelope IgA is frequently elicited after transmission but has an initial short response half-life. Mucosal Immunol. 2013 Jan 9.

147. Duerr A. Update on mucosal HIV vaccine vectors. Curr Opin HIV AIDS. 2010; 5:397–403. [PubMed: 20978380]

148. Bomsel M, Tudor D, Drillet AS, et al. Immunization with HIV-1 gp41 subunit virosomes induces mucosal antibodies protecting nonhuman primates against vaginal SHIV challenges. Immunity. 2011; 34:269–280. [PubMed: 21315623]

149. Barouch DH, O'Brien KL, Simmons NL, et al. Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys. Nat Med. 2010; 16:319–323. [PubMed: 20173752]

150. Letourneau S, Im EJ, Mashishi T, et al. Design and Pre-Clinical Evaluation of a Universal HIV-1 Vaccine. PLoS One. 2007; 2:e984. [PubMed: 17912361]

151. Frahm N, DeCamp AC, Friedrich DP, et al. Human adenovirus-specific T cells modulate HIV-specific T cell responses to an Ad5-vectored HIV-1 vaccine. J Clin Invest. 2012; 122:359–367. [PubMed: 22201684]

152. Penaloza-MacMaster P, Provine NM, Ra J, et al. Alternative serotype adenovirus vaccine vectors elicit memory T cells with enhanced anamnestic capacity compared to Ad5 vectors. J Virol. 2013; 87:1373–1384. [PubMed: 23152535]

153. Sheehy SH, Duncan CJ, Elias SC, et al. ChAd63-MVA-vectored blood-stage malaria vaccines targeting MSP1 and AMA1: assessment of efficacy against mosquito bite challenge in humans. Mol Ther. 2012; 20:2355–2368. [PubMed: 23089736]

154. Dicks MD, Spencer AJ, Edwards NJ, et al. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. PLoS One. 2012; 7:e40385. [PubMed: 22808149]

155. Excler JL, Parks CL, Ackland J, et al. Replicating viral vectors as HIV vaccines: summary report from the IAVI-sponsored satellite symposium at the AIDS vaccine 2009 conference. Biologicals. 2010; 38:511–521. [PubMed: 20537552]

156. Ruzagira E, Wandiembe S, Abaasa A, et al. Prevalence and incidence of HIV in a rural community-based HIV vaccine preparedness cohort in Masaka, Uganda. PLoS One. 2011; 6:e20684. [PubMed: 21677779]

157. Shaffer DN, Ngetich IK, Bautista CT, et al. HIV-1 incidence rates and risk factors in agricultural workers and dependents in rural Kenya: 36-month follow-up of the Kericho HIV cohort study. J Acquir Immune Defic Syndr. 2010; 53:514–521. [PubMed: 19855286]

158. Price MA, Rida W, Mwangome M, et al. Identifying at-risk populations in Kenya and South Africa: HIV incidence in cohorts of men who report sex with men, sex workers, and youth. J Acquir Immune Defic Syndr. 2012; 59:185–193. [PubMed: 22227488]

159. Mishra S, Steen R, Gerbase A, Lo YR, Boily MC. Impact of High-Risk Sex and Focused Interventions in Heterosexual HIV Epidemics: A Systematic Review of Mathematical Models. PLoS One. 2012; 7:e50691. [PubMed: 23226357]

160. Smith AD, Tapsoba P, Peshu N, Sanders EJ, Jaffe HW. Men who have sex with men and HIV/AIDS in sub-Saharan Africa. Lancet. 2009; 374:416–422. [PubMed: 19616840]

161. Sanders EJ, Okuku HS, Smith AD, et al. High HIV-1 incidence, correlates of HIV-1 acquisition, and high viral loads following seroconversion among MSM. AIDS. 2013; 27:437–446. [PubMed: 23079811]

162. Beyrer C, Baral SD, van Griensven F, Goodreau SM, Chariyalertsak S, Wirtz AL, Brookmeyer R. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012; 380:367–377. [PubMed: 22819660]

163. van Griensven F, de Lind van Wijngaarden JW. A review of the epidemiology of HIV infection and prevention responses among MSM in Asia. AIDS. 2010; 24 (Suppl 3):S30–S40. [PubMed: 20926926]

164. van Griensven F, Thienkrua W, McNicholl J, et al. Evidence of an explosive epidemic of HIV infection in a cohort of men who have sex with men in Bangkok, Thailand. AIDS. 2012 Nov 19.

165. Dutta A, Wirtz AL, Baral S, Beyrer C, Cleghorn FR. Key harm reduction interventions and their impact on the reduction of risky behavior and HIV incidence among people who inject drugs in low-income and middle-income countries. Curr Opin HIV AIDS. 2012; 7:362–368. [PubMed: 22647588]

166. Nitayaphan S, Ngauy V, O'Connell R, Excler JL. HIV epidemic in Asia: optimizing and expanding vaccine development. Expert Rev Vaccines. 2012; 11:805–819. [PubMed: 22913258]

167. Corey L, Nabel GJ, Dieffenbach C, et al. HIV-1 vaccines and adaptive trial designs. Sci Transl Med. 2011; 3:79ps13.

168. Padian NS, McCoy SI, Manian S, Wilson D, Schwartländer B, Bertozzi SM. Evaluation of large-scale combination HIV prevention programs: essential issues. J Acquir Immune Defic Syndr. 2011; 58:e23–28. [PubMed: 21694607]

169. Cremin I, Alsallaq R, Dybul M, Piot P, Garnett G, Hallett TB. The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis. AIDS. 2013; 27:447–458. [PubMed: 23296196]

Key Points

- Vaccine-induced protection against HIV acquisition has been demonstrated
- Correlates of risk for HIV acquisition have been identified
- Immunogens inducing broadly neutralizing antibodies are being designed
- Heterosexual populations in Africa and men who have sex with men in Asia are potential target for future efficacy trials
- Strong international collaborations along with sustained political and funding commitments are necessary to develop and bring to licensure a safe and efficacious HIV vaccine

Table 1

Generic HIV-1 vaccine candidates including mode and route of administration, recently tested in Phase I/II trials

Vaccine Products	HIV-1 Subtype	Adjuvant, Formulation	Mode and Route of Administration	References
Subunits				
Lipopeptides	B		IM	[10,11]
Oligomeric gp160	B	DC-Chol	Nasal, Vaginal	ANRS VAC14
Trimeric gp140	B'/C	Carbopol, GLA, Chitosan	Vaginal, IM, IN, Oral	[12]
Trimeric gp140	B, C	PCPP, MF59	IM	[13]
Tat protein	C	Alum	SC, ID	[14,15]
Fusion protein Env-Nef-Tat	B	AS02A, AS02V, AS01B	IM	[16,17]
gp41 P1 peptide		Virosomes	IM, IN	[18]
Pox vectors				
ALVAC (vCP1521)	CRF01_AE		IM	[19]
Replicating vaccinia (VV Tiantan)	B'/C		Scarification	[20]
Modified Vaccinia Ankara (MVA)	A, B, C		IM	[21–23]
NYVAC	C		IM	[24]
DNA				
	A, B, C		IM, EP	[25–28]
Conserved epitopes	Multiclades		IM	[29–31]
PENNVAX	B	IL-12, IL-15	IM, EP	[32]
Replication-defective Adenovirus Vectors				
Ad5	B		IM	[33,34]
Ad35	B, A		IM	[35]
Ad26	A		IM	[36,37]
Adeno-associated Virus Vector type 2	C		IM	[38–40]
Alphavirus Replicon VEE	C		IM	[41]
Replication-competent Measles Vector	B		IM	Ongoing
Vesicular Stomatitis Virus Vector	B		IM	Ongoing, [42]
Prime-Boost Combinations				
DNA + Trimeric V2-deleted gp140	B	PLG, MF59	IM	[43]
DNA + Env subunit	A, B, C, CRF01-AE	QS-21	ID, IM	[44,45]
DNA + MVA	A, B, C, CRF01_AE, B epitopes	GMCSF	IM, ID, Biojector*	[46–56]
DNA + Fowlpox	B		IM	[57,58]
DNA + VV Tiantan	B'/C		Scarification	[20]
DNA + NYVAC	C		IM	[59–61]
Ad5 + NYVAC	A, B, C and B		IM	[62]
DNA + Ad5 or Ad35	A, B, C		Biojector*, IM, ID, SC	[63–68]
DNA IL-12 EP + Ad35-GRIN/ENV	B, A		EP, IM	Ongoing, [69]
DNA + MVA + ChAdV63	Conserved sequences		IM	Ongoing, [70]

Vaccine Products	HIV-1 Subtype	Adjuvant, Formulation	Mode and Route of Administration	References
DNA + VSV	B	IL-12	EP, IM	Ongoing
MVA + Fowlpox	B		IM	[71,72]
Ad35 *env* + Ad26 *env*	A		IM	Ongoing
ALVAC (vCP1521) + AIDSVAX B/E gp120	B, CRF01_AE	Alum	IM	Ongoing
Ad26 *env* A + MVA (natural vs. mosaic)	A, CRF01_AE, mosaic		IM	Ongoing
Ad35-GRIN + adjuvanted fusion protein (non-Env)	A, B		IM	Ongoing
Ad35-GRIN + replicating Sendai	A		IM, IN (Sendai)	Ongoing

Pox: Recombinant Poxvirus-vectored vaccine; ALVAC: recombinant canarypox vector

Ad5: Replication-defective recombinant Adenovirus subtype 5; ChAdV63: Replication-defective recombinant Chimpanzee adenovirus subtype 63

MVA: Modified Vaccinia Ankara; VEE: Venezuelan equine encephalitis; VV Tiantan: Attenuated replicating vaccinia Tiantan developed in China

EP: Electroporation; GLA: Glucopyranosyl Lipid Adjuvant

GRIN: *gag, reverse transcriptase, integrase*, and *nef* genes from HIV-1 subtype A

GRIN/ENV: Ad35-GRIN + Ad35 expressing *env* gp140 from HIV-1 subtype A

PCPP: Polyphosphazene; IFA: Incomplete Freund's Adjuvant

Sendai: replication-competent murine parainfluenza type 1 paramyxovirus

* For DNA only

Table 2

Main immunogenicity findings of Phase I/II trials

No broadly neutralizing antibodies are induced by current vaccines.
Binding antibodies and neutralizing antibodies against Tier-1 and limited Tier-2 HIV-1 isolates were induced by Env subunit proteins formulated with potent adjuvants.
Polyfunctional CD4+ and CD8+ T-cell responses measured by ICS and INF-γ ELISpot assays generally of low to moderate magnitude immune responses have been detected in a majority of vaccinees immunized by vectors alone and to some extent by DNA alone. These responses are generally significantly augmented after priming.
CD8-mediated inhibition of *in vitro* viral replication can be detected after vector-based vaccination.
Cell-mediated responses to DNA administered by electroporation are significantly augmented compared to intramuscular needle injection
Systems biology can identify specific gene activation immune signatures predictive of the immune responses
Pre-existing immunity to pox vectors does not or minimally impact on the pox vector vaccine-induced immune responses, in particular after DNA prime
Pre-existing immunity to Ad5 (high prevalence) decreases the Ad5 vaccine-induced immune responses, which led to the development of low prevalence rare serotype adenovirus vectors.
Env subunit protein boosts induce higher levels of serum antibodies that rapidly wane.

Table 3

Completed and ongoing Phase IIb and III human HIV-1 vaccine trials

Study Protocol	Candidate Vaccine	Phase	Sample Size	Population enrolled	Location	Result	References
HVTN 505	DNA (VRC-HIVDNA016-00-VP) and rAd5 (VRC-HIVADV014-00-VP) (A, B, and C)	IIb	2,494 in MITT analysis	Circumcised MSM and TG Ad5 Ab negative	USA	Stopped for futility. No efficacy on HIV acquisition and on plasma viral load	www.niaid.nih.gov/news/QA/Pages/HVTN505qa2013.aspx
RV144	ALVAC-HIV vCP1521 and AIDSVAX B/E (MN and CRF01_AE CM244) rgp120 in alum	III	16,403	Community	Thailand	31.2% efficacy against HIV-1 acquisition. No effect on plasma viral load	[19,97**,98,99*,100**,101–103**,104,105*,106,107]
HVTN 502 Step trial	MRKAd5 HIV-1 gag/pol/nef B	IIb	3,000	MSM, high-risk heterosexual men and women	North and South America, Australia, Caribbean	No efficacy; transiently increased infection risk Stopped	[87,108**–115]
HVTN 503 Phambili trial	MRKAd5 HIV-1 gag/pol/nef B	IIb	3,000 801 enrolled	Heterosexual men and women	South Africa	No efficacy – Stopped Follow-up analysis suggests increase rate of HIV infection in vaccine recipients	[116,117]
Vax003	AIDSVAX B/E gp120 (MN and CRF01_AE CM244) gp120 in alum	III	2,500	Injecting Drug Users	Thailand	No efficacy	[118]
Vax004	AIDSVAX B/B gp120 (MN and GNE8) gp120 in alum	III	5,400	MSM, high risk women	USA	No efficacy	[119–125]

MITT: modified intent-to-treat analysis

ALVAC-HIV (vCP1521): recombinant canarypox vector expressing Gag and Protease subtype B (LAI) and *env* gp120 CRF01_AE (TH023) linked to the transmembrane-anchoring portion of subtype B gp41 (LAI) genes.

Ad5: Replication-defective recombinant Adenovirus 5-vectored vaccine; Ad5 Ab: Ad5-specific neutralizing antibody

VRC-HIVDNA-016-00-VP: DNA plasmids expressing Gag, Pol, and Nef subtype B (strains HXB2, NL4-3, NY5/BRU, respectively) and HIV-1-1 Env subtype A (strain 92rw020), B (strains HXB2/BaL), and C (strain 97ZA012)

VRC-HIVADV014-00-VP: mixture of four rAd5 vectors encoding the HIV-1 Gag-Pol polyprotein subtype B (strains HXB2-NL4-3) and Env A, B and C matching the DNA Env components

MSM: men who have sex with men; TG: male-to-female transgender persons who have sex with men

Table 4

Planned and foreseen clinical trials within the next 5 years

Vaccine regimens	Phase	Country	Concepts tested based on lessons learned
RV305: ALVAC-HIV (vCP1521) + AIDSVAX B/E	I	Thailand	Comparison of late boosts in RV144 vaccinees; memory of antibody response (V2); immune responses in peripheral and mucosal compartments
RV306: ALVAC-HIV (vCP1521) + AIDSVAX B/E	I	Thailand	RV144 regimen + one-year boost: augment and sustain Env antibody response, in particular V2, ADCC, IgG subclasses, IgA in peripheral and mucosal compartments; CMI in gut tissues; innate immunity
RV328: AIDSVAX B/E	I	Thailand	Env antibodies and CMI responses in peripheral and mucosal compartments
RV307: Ad26 *env* A + MVA natural vs. mosaic	I	Thailand, Kenya, Uganda	Heterologous vector prime-boost; breadth, depth and memory of CMI responses induced by mosaic vs. natural genes; Env antibodies
Ad26 mosaic + MVA mosaic ± adjuvanted Env subunit protein	I–IIB	Thailand, Kenya, Uganda, Mozambique	Heterologous vector prime-boost; breadth, depth and memory of CMI responses induced by mosaic genes; induction of Env antibodies
ALVAC + adjuvanted Env subunit protein	I–III	Thailand, RSA	Improved Env design to induce V2 antibodies; Efficacy and mode of transmission: heterosexual population at high risk in RSA and in MSM
DNA + NYVAC ± adjuvanted Env subunit protein	I–IIB	RSA, Southern Africa	DNA + pox vector for potent CMI responses; Env boost for antibodies; Efficacy in heterosexual population at high risk; adaptive trial designs
DNA + Vaccinia ± adjuvanted Env subunit protein	IIB	China	DNA + pox vector for potent CMI responses; Env boost for antibodies; Efficacy in MSM
New trimeric Env subunit proteins and adjuvants	I	US, UK, Africa	Induction of broadly neutralizing antibodies in peripheral and mucosal compartments; systemic and mucosal administration
Vaccine and PrEP or microbicides	I–IIB	To be determined	Synergistic effect of prevention technologies

CMI: cell-mediated immunity; MSM: men who have sex with men; ADCC: antibody-dependent cell-mediated cytotoxicity; RSA: Republic of South Africa