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Nonreplicating vectors in HIV vaccines

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Abstract

Purpose of review—We review the broad spectrum of nonreplicating viral vectors which have been studied extensively, from preclinical studies through clinical efficacy trials, and include some of our most promising HIV vaccine candidates.

Recent findings—The success of the RV144 trial, with an ALVAC (canarypox)-based regimen, contrasts with the failures of the Adenovirus 5-based regimens in the Step study, the Phambili study (HVTN 503), and the HVTN 505 study which was recently modified to halt vaccinations due to clinical futility.

Summary—The safety profile, immunogenicity, and variety of available candidates make the nonreplicating viral vectors attractive in HIV vaccine development. Building from the success of the RV144 study, further studies of Orthopoxvirus-based vaccines, including Vaccinia-based vaccines, are ongoing and planned for the future. Despite the failures of the Ad5-based vaccines in clinical efficacy trials, other adenovirus serotypes remain promising candidates, especially in prime-boost combination with other products, and with the potential use of mosaic inserts. Other nonreplicating viral vectors such as the rhabdoviruses, alphaviruses and the non-human adenoviruses, provide additional avenues for exploration.

Keywords

HIV vaccine; nonreplicating vector; Orthopoxvirus; canarypox; Vaccinia; adenovirus

Introduction

A successful vaccine to prevent HIV infection will likely require both the elicitation of antibody and cell-mediated responses. Virus specific CD8+ cytotoxic T lymphocytes (CTL)

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Conflicts of Interest

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are critically important to the control of viral replication and disease progression for HIV-1. Viral vector-based HIV vaccines have been traditionally considered in the light of eliciting cell-mediated responses but recent work suggests that certain vectors may elicit significant antibody responses as well. The nonreplicating viral vectors are attractive due to their inherent immunogenicity and safety profile. Some of the viral vectored vaccines approaches have reached advanced testing – with two vaccine strategies reaching clinical efficacy trials – ALVAC and Adenovirus serotype 5. The best studied nonreplicating viral vector approaches for HIV vaccines include the poxviruses, adenoviruses, adeno-associated virus, rhabdoviruses and alphaviruses [Table 1]. Considerations in evaluating novel nonreplicating vectors include: pre-existing vector specific immunity, replication incompetence, nature of illness associated with the wild type virus, tissue tropism, quality of the immune response elicited, manufacturability, and of course all available human clinical trial data.

Poxvirus vectors

The poxvirus vectors are double-stranded DNA virus vectors which have been extensively studied in preclinical and clinical studies over the past two decades with recent promising results. The large genomes of these vectors allow for larger inserts while maintaining high levels of gene expression allowing for induction of HIV specific immune responses. The four poxvirus vectors which have been most extensively studied as HIV vaccine vectors and have undergone clinical trials include: canarypox (ALVAC), two vaccinia vectors – Modified vaccinia Ankara (MVA) and NYVAC, and fowlpox.

Canarypox (ALVAC)

ALVAC is derived from a canarypox virus which had been passaged repeatedly in chick embryo fibroblasts. Canarypox is host range restricted and does not replicate in mammalian cells; this property fundamentally decreases the potential pathogenicity of this vector in humans. In the domain of veterinary medicine, multiple ALVAC-vector based vaccines are currently licensed for clinical use for cats and horses, including vaccines for rabies, influenza, and West Nile virus. In humans, some concerns have been raised that canarypox (and fowlpox) vectors may be less immunogenic than other human virus vectors, but a theoretical advantage to these particular vectors is the absence of pre-existing vector immunity in humans. ALVAC has been shown to be generally safe in early clinical trials, advancing to phase II and III clinical trials in adults and also to early clinical trials in infants. HPTN 027 was a phase 1 trial of 60 HIV-exposed infants in Uganda who were randomized to receive ALVAC-HIV vCP1521 or placebo. The vaccine was safe with tolerable reactogenicity [21]. In a US study, infants born to HIV-infected mothers were randomized to receive ALVAC vCP1452 with and without boost from r-GP120 subunit proteins or placebo. Both vaccine strategies were safe and the prime-boost regimen induced lymphoproliferative responses and neutralizing activity to HIV-1 in ~ 50% of the infants [22].

In adults, ALVAC-based vaccines were modestly effective at inducing HIV antibodies, but the cellular immune responses in early trials were considered sub-optimal by standard assays in use at the time. In HVTN 203, ALVAC vCP1452 boosted with recombinant gp120 (MN-GNE8 rgp120) yielded IFN- γ ELISpot reactions in 16% of the vaccinated participants [23].

This prime-boost regimen failed to produce pre-determined significant CD8+ CTL responses in the phase II study, leading some in the field to argue to reconsider any further development of this vaccine approach against HIV. However, a prime-boost regimen with ALVAC and recombinant gp120 boost was advanced to a phase III efficacy trial (RV144) and did show a significant but modest protective effect, illustrating that our understanding of the laboratory markers of clinically relevant immunologic protection against HIV acquisition remain limited and highlighting the critical importance of human field trials.

The RV-144 trial was a phase III study of a prime-boost regimen of two initial injections of ALVAC-HIV (vCP 1521) followed by two more injections of ALVAC-HIV which were given concurrent with booster injections of protein-based AIDSVAX B/E (recombinant gp120 subunit vaccine) [24]. The study enrolled over 16,000 participants in Thailand at “community risk” for HIV acquisition. Within this group, the studied prime-boost regimen yielded a 31.2% reduction in HIV-1 acquisition, as per the modified intention to treat analysis at 3.5 years after vaccination. The vaccine induced Env- and Gag- specific IFN- γ ELISPOT responses and Env-specific intracellular cytokine staining, and lymphoproliferative responses and binding antibodies to Env in most vaccine recipients [1]. In those participants who acquired HIV despite vaccination, the vaccine did not appear to alter the course of HIV infection [25]. There have been multiple subsequent analyses of the available data and there are ongoing investigations of the potential correlates of immune protection and viral sieve analysis from RV144 with findings to date suggesting an IgG response against the V2 loop may be protective [26] [27]. Since the protective response seen with the vaccine strategy in RV144 appeared to wane after 6 months post-vaccination, strategies to boost this response are being investigated. One such investigation is an ongoing study of additional late boost regimens of AIDSVAX B/E, ALVAC-HIV or the combination in HIV-uninfected participants from RV 144 which is scheduled to be completed in October 2013 [28]. The Pox-Protein Public-Private Partnership, otherwise known as P5, was established in 2010 to build on the results of RV144. Through this effort, further studies are planned in Thailand and Southern Africa to improve the regimen used in RV144 and test new vaccine candidates.

Vaccinia

In contrast to canarypox, vaccinia vectors are highly immunogenic in humans, but pre-existing population immunity due to prior smallpox vaccination may be problematic in some demographics. The NYVAC vector is derived from the Copenhagen strain of attenuated vaccinia (VACV) and is rendered attenuated by deletions in 18 genes encoding proteins involved in host range and virulence. In a phase I study (EV01) of NYVAC-C (vP2010) alone the vaccine was well-tolerated and elicited ELISpot responses in half of the vaccine recipients, generating interest in further studies with NYVAC in prime-boost regimens [2]. Early clinical trials of DNA prime with NYVAC boost, including EV02, have shown that this strategy is generally safe and elicits greater immune response than NYVAC alone, with predominantly CD4+ T cell responses [3] [29]. There are additional ongoing and planned studies of NYVAC in prime-boost combinations with DNA and protein-based immunogens (AIDSVAX B/E) [4] [5]. Chronically HIV-infected patients have received a NYVAC-based vaccine with expression of gag, pol, nef and env from HIV clade B in Theravac-01, and this

increased HIV-specific T-cell responses in all vaccine recipients and expanded pre-existing T cell responses [30].

The modified vaccinia virus Ankara (MVA) was prepared by serial passaging in chick embryo fibroblasts resulting in loss of more than 10% of its genome which renders it unable to replicate in nearly all mammalian cells. Approximately 120,000 persons were vaccinated with MVA, primarily in West Germany and Turkey, as a part of smallpox eradication efforts and no significant safety concerns were identified in this context [31]. MVA has also been used as a vector for therapeutic cancer vaccine, advancing to phase III clinical trials in prostate cancer patients, and has been given to hematopoietic stem cell transplant (HSCT) recipients, with no significant safety concerns in either population [32] [33]. Interestingly, the route of administration of MVA has been shown to have a significant effect on immunogenicity, with similar responses to an intramuscular injection as to a 10-fold lower dose of intradermally administered MVA [34]. Pre-clinical studies of MVA-based HIV vaccines have shown greater antigen expression, particularly in human dendritic cells, and increased T-cell stimulation as compared with ALVAC [35]. Many early clinical studies with MVA-based HIV vaccines have been completed, often with promising results, but no MVA-based vaccines have yet advanced to efficacy trials. A phase I study of MVA with fowlpox (HVTN 055) demonstrated that this heterologous prime-boost regimen generated increased CD8+ T-cell responses than MVA alone [7]. Further work has shown that repeated doses of an MVA vaccine (up to 5 doses) does not increase the immune response to MVA beyond two doses and that elicitation of vaccine induced vector (MVA) immunity does not appear to abrogate insert (anti-HIV) responses [36].

Prime-boost regimens with DNA prime and MVA boost have also been shown to elicit greater T-cell responses than administration of MVA alone. HVTN 065 was a phase 1 study of prime-boost series with Geovax HIV-1 DNA vaccine (pGA2/JS7 DNA) and MVA62 (encoding gag, PR, RT, Env), both producing virus-like particles (VLPs), compared with the MVA vaccine alone. In this study, one of the prime-boost strategies was most immunogenic, with persistent CD4+ and CD8+ T cell responses, and the MVA62 generated greater T cell responses than the canarypox vaccine used in RV144 [8]. Building on these early data, a follow-up phase 2a clinical trial [6] of Geovax DNA prime with MVA/HIV62 boost has been completed and results from this study are anticipated soon. Another follow-up study of Geovax DNA prime co-expressing GM-CSF along with the HIV-1-derived insert and an MVA62 boost is currently underway [9]. Multigenic MVA vaccine candidates have been studied in early clinical trials and future studies with multigenic MVA vaccines alone and in prime-boost strategies are planned [10].

Fowlpox

Fowlpox vaccines have been widely studied in cancer therapeutics, most frequently for breast and prostate cancer. Fowlpox-based HIV vaccines have been studied in early clinical trials with evidence of safety and some immunogenicity. As discussed above, a prime-boost regimen of recombinant MVA with fowlpox with matched HIV-1 inserts yielded a modest CD8+ CTL response in HVTN 055 [7]. However, no fowlpox-based HIV vaccines have

advanced to clinical efficacy trials, and future HIV vaccine studies with this delivery system are uncertain.

Adenoviruses

Adenoviruses, which have a three decade history of development for gene therapy, are now widely studied as vectors for HIV vaccines, as well as other disease targets, including malaria, hepatitis C, and tumor therapies. There are many attractive features of adenoviruses as vaccine candidates including manufacturability, safety profile, and ability to elicit broad immune responses. These double-stranded DNA viruses can target mucosal sites, infect both dividing and non-dividing cells, including dendritic cells, and elicit high levels of antigen expression as well as cytokine and chemokine responses, resulting in potent immune responses. This is achieved without integration into the host genome. One challenge with adenovirus vectors, especially Adenovirus serotype 5 (Ad5), is the prevalence of high level anti-vector immunity in large segments of the population especially in Sub-Saharan Africa. This theoretical concern is being formally examined in ongoing studies, and this obstacle may be minimized by use of rare serotypes and engineered chimeric vectors.

Adenovirus serotype 5

Ad5 has been particularly well-studied, with pre-clinical and clinical evidence of immunogenicity and safety. The Step study (HVTN 502/Merck 023) was a multicenter phase IIb study of the Merck Ad5 HIV-1 clade B gag/pol/nef vaccine compared with placebo. The multiple enrollment sites for the three thousand participants included North America, South America, the Caribbean and Australia, where clade B HIV-1 is the predominant clade, and the study population included mostly men who have sex with men (MSM) and heterosexual women at high risk for HIV acquisition. The study was halted in October of 2007 due to lack of efficacy. The vaccine did elicit IFN- γ ELISPOT responses and polyfunctional T cells, but there was no effect on HIV acquisition or viral load setpoint. Post-hoc analysis showed more HIV infections in the subgroup of vaccine recipients consisting of uncircumcised men who were Ad5 seropositive prior to enrollment [11]. This generated widespread concern that the vaccine may lead to a window of increased susceptibility to HIV infection shortly after vaccination, though the available data and analysis are limited on this point [37]. Additional studies of the Step population have shown that the vaccine did not affect the course of HIV infection among vaccine recipients who became HIV infected, despite the CD8⁺ T cell responses elicited by the vaccine [12]. A similar study (Phambili/HVTN 503) of the same MRCK Ad5 vaccine in heterosexual men and women in South Africa also showed no effect on HIV acquisition or viral setpoint in those who became HIV-infected. Vaccinations in this study were also stopped early, after 801 of the planned 3000 subjects had been enrolled, in light of the Step data which had emerged during the early part of this trial. Few subjects received the full vaccination series and the study was unblinded very early, thus it is difficult to make firm conclusions from these data [13].

Despite the lack of efficacy with the Merck Ad5 vaccine in the Step study, another Ad5-based vaccine regimen advanced to an efficacy trial. HVTN 505 was designed to assess the efficacy of the Vaccine Research Center (VRC) multiclade HIV-1 DNA plasmid (EnvA,

EnvB, EnvC, gagB, polB, nefB) boosted with rAd5 (EnvA, EnvB, EnvC, gag/polB) at moderating the course of HIV infection among those who became infected despite vaccination. The study opened in 2009, enrolling MSM who are circumcised and Ad5 seronegative at enrollment. During enrollment the scope of the study was expanded to detect efficacy in preventing HIV-1 acquisition during the 18 months following completion of the vaccination regimen. The study completed enrollment in March 2013 with 2,504 participants [14]. In April 2013 a pre-scheduled Data Safety Monitoring Board (DSMB) review indicated that the study had reached statistical futility thresholds – there was no possibility of demonstrating efficacy at HIV prevention or efficacy at achieving lower viral load setpoint for those who became infected after vaccination. So, vaccinations were halted early in this study due to futility. At the time of the DSMB analysis there were 71 incident HIV infections (41 in vaccine and 30 in placebo recipients) of which 48 HIV infections occurred after 28 weeks or 4 weeks after completing the vaccination regimen. Of these 48 incident HIV infections, 27 occurred among the vaccine recipients and 21 among the placebo recipients. The difference in number of HIV infections between the vaccine and placebo groups was not statistically significant [15]. There were 14 HIV infections among participants who had only received DNA priming and had not reached the Ad5 boosting portion of the study, compared with 9 infections among placebo recipients who had reached the same stage in the study. Further follow-up of the study participants, now unblinded and without further vaccinations, is ongoing; hopefully additional data and analysis from this study will enhance our understanding of these early findings of futility with this Ad5-based vaccine regimen.

Other Adenovirus serotypes

Despite the recent failure of the DNA-Ad5 combination in the HVTN 505 efficacy trial, other adenovirus serotypes remain promising vector candidates due to their lower seroprevalence and other advantageous biological differences. Both adenovirus serotype 26 (Ad26) and adenovirus 35 (Ad35) are rare serotypes in the US and southeast Asia, both generally have lower seroprevalence than Ad5 in Africa, and even when seropositive Ad26 neutralizing antibody titers are generally substantially lower than with Ad5 [38] [39] [40] [41]. It has also become clear that different Ad serotypes are substantially biologically different [42]. Ad26 utilizes different cellular receptors [43] and exhibits different in vivo tropism [44], interaction with dendritic cells [45] [46], innate immune profiles [47], adaptive immune phenotypes [48], and improved preclinical protective efficacy [49] [50] as compared with Ad5. Emerging data also suggests that Ad26 triggers substantially less systemic and mucosal inflammation than does Ad5.

In a phase 1 dose-escalation study an Ad26-based EnvA-insert HIV vaccine elicited Ad26 vector-specific and EnvA insert-specific responses that persisted for at least one year after vaccination, and the vaccine was generally well-tolerated up to a dose of 10^{11} [16]. Significant humoral and cellular responses were elicited, with a dose-dependent expansion of epitope diversity of the Env-specific binding antibody responses and antibody-dependent cell-mediated phagocytosis and virus inhibition [17]. Additional studies of Ad26-based HIV vaccines have shown the elicitation of anti-HIV mucosal responses and significant responses even in subjects with prior Ad26 vector immunity [51]. A prime-boost regimen with Ad26-

ENVA and an Ad35-based vaccine (Ad35-ENV) is under investigation in another phase I multicenter study which has completed enrollment but not yet reported results [19]. Pre-clinical trials with Ad26-MVA prime-boost regimens have yielded promising results, such that phase I clinical trials of the Ad26/MVA regimen with mosaic antigen are planned to initiate enrollment in 2013.

Adenovirus 35 (Ad35) offers similar advantages to Ad26. Pre-clinical studies with heterologous and homologous vectors and gene inserts using rAd35 and rMVA constructs yielded robust cellular immune responses with the heterologous prime-boost regimens [52]. In a phase I dose escalation study of Ad35-GRIM (HIV-1 subtype A gag, RT, integrase, nef) and Ad35-ENVA both were generally safe and immunogenic, with elicitation of IFN- γ ELISPOT responses in > 90% of participants [18]. In addition to the ongoing Ad26-Ad35 prime-boost phase I study, another phase I study with intranasal Sendai virus vectored HIV vaccine prime and Ad35-GRIN boost is planned [53].

Non-human adenovirus vectors are also under investigation for possible use in HIV vaccines. Chimpanzee adenovirus vectors have been shown to elicit T-cell immune responses in animal models, though these have not been used in humans yet [54] [55] [56]. Simian adenovirus vectors, such as ChAd63, are also in ongoing development [57] [58]. The clinical utility of these nonhuman viral vectors remains to be seen.

Rhabdoviruses

Attenuated recombinant rabies virus has been used as a vector for HIV vaccines in animal studies, where they have been shown to be generally safe and immunogenic. The low prevalence of immunity to rhabdovirus in humans is an attractive feature of these viruses as vectors for HIV vaccines. In order to eliminate the risk of vector-associated disease in humans a recombinant rabies virus with a glycoprotein G mutation to remove the neurotropic quality was constructed. Nonhuman primate studies of this highly-attenuated vaccine demonstrated elicitation of immune responses including control of subsequent SIV challenge, without notable toxicities [59]. Rhabdovirus vector HIV vaccines have also been evaluated in a preclinical prime-boost study with VSV (vesicular stomatitis virus), again with evidence of humoral and cellular immune responses [60]. There are 2 main VSV serotypes which occur in the US, Indiana and New Jersey, and are typically livestock associated. Consequences of wild-type infection with VSV in humans include a febrile illness in some infected individuals [61]. However the potential for significant neurologic disease especially with another VSV serotype, Chandipura, which occurs in India exists [62]. Thus significant effort has occurred to attenuate a recombinant VSV vector which is being developed as a candidate HIV vaccine with multiple genetic manipulations to substantially decrease the risk of human neurovirulence [63]. A phase I study (HVTN 090) of the VSV serotype Indiana (VSVIN) HIV vaccine is ongoing [20].

Alphaviruses

Within the alphavirus family, Venezuelan equine encephalitis (VEE) virus has been used in an attenuated replicon form as an HIV vaccine vector. The AVX101 alphavirus-based HIV vaccine was studied in two consecutive early clinical trials (HVTN 040 and 059), both of

which were stopped early due to vaccine stability and manufacturing issues. AVX101 was found to be safe in both studies, but the cellular and humoral immune responses were limited [64].

Conclusions and future directions

The array of non-replicating vectors for HIV vaccines is varied, but against this background of numerous vectors and prime-boost strategies there are points of light, such as RV144, which offer hints to a path forward toward an effective vaccine. In addition to the ongoing and planned studies discussed with candidate vaccine delivery systems, significant work is ongoing to improve the inserts to elicit a broad anti-HIV response given the global HIV diversity. One such strategy is the development of mosaic inserts to hopefully improve clinically-relevant immune response by HIV vaccines. The nonreplicating viral vectors, including Ad26, MVA and NYVAC, will be the vectors of choice in the upcoming clinical trials of these novel mosaic insert strategies. Assessment of these candidate delivery systems in combination with other strategies such as DNA and protein are areas of active investigation. The spectrum of nonreplicating viral vectors forms a broad platform for ongoing research toward an effective HIV vaccine.

References

1. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med*. 2009; 361:2209–2220. [PubMed: 19843557]
2. Bart P, 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]
3. McCormack S, Stohr 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]
4. National Institute of Allergy and Infectious Diseases (NIAID). ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Evaluating the safety and immune response to three HIV vaccine schedules in healthy, HIV-uninfected adults. [cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01783977?term=01783977&rank=1> NLM Identifier: NCT01783977
5. HIV Vaccine Trials Network. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Evaluating the safety and priming response of an HIV vaccine regimen in healthy, HIV-uninfected adults. cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01799954?term=01799954&rank=1> NLM Identifier: NCT01799954
6. National Institute of Allergy and Infectious Diseases (NIAID). ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Safety of and immune response to a prime-boost vaccine regimen in HIV-uninfected vaccine-naïve adults. [cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT00820846?term=00820846&rank=1> NLM Identifier: NCT00820846
7. 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(10):1948–1958. [PubMed: 21216311]
8. Goepfert PA, Elizaga ML, Sato A, et al. Phase I safety and immunogenicity testing of DNA and recombinant modified vaccinia Ankara vaccines expressing HIV-1 virus-like particles. *J Inf Dis*. 2011; 203:610–619. [PubMed: 21282192]

9. National Institute of Allergy and Infectious Diseases (NIAID). ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Evaluating the safety and immune response of a prime-boost HIV vaccine regimen in healthy, HIV-uninfected, vaccinia-naïve adults. [cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01571960?term=01571960&rank=1> NLM Identifier: NCT01571960
10. Currier JR, Ngauy V, de Souza MS, Ratto-Kim S, Cox JH, 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(11):e13983. [PubMed: 21085591]
11. Buchbinder SP, Mehrotra DV, Duerr A, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomized, placebo-controlled, test-of-concept trial. Lancet. 2008; 372:1881–1893. [PubMed: 19012954]
12. Fitzgerald DW, Janes H, Robertson M, Coombs R, Frank I, Gilbert P, Loufty M, Mehrotra D, Duerr A. Step Study Protocol Team. 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(6):765–772. [PubMed: 21343146]
13. 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, randomized, placebo-controlled test-of-concept phase 2b study. Lancet Inf Dis. 2011; 11:507–515.
14. National Institute of Allergy and Infectious Diseases (NIAID). ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Safety and effectiveness of HIV-1 DNA plasmid vaccine and HIV-1 recombinant adenoviral vector vaccine in HIV-uninfected, circumcised men and male-to-female (MTF) transgender persons who have sex with men. [cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT00865566?term=NCT00865566&rank=1> NLM Identifier: NCT00865566
15. National Institute of Allergy and Infectious Diseases (NIAID). NIAID.NIH.gov [Internet]. Bethesda (MD): 2013 Apr 25. STATEMENT: NIH discontinues immunizations in HIV vaccine study. Available from: <http://www.niaid.nih.gov/news/newsreleases/2013/Pages/HVTN505April2013.aspx>
16. 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(2):240–247. [PubMed: 23125444] • This first-in-human evaluation of a novel Ad26 vector based vaccine demonstrated dose-related reactogenicity and no significant toxicities, providing an alternative to Ad5 among the adenovirus vector candidates for HIV vaccines.
17. 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(2):248–256. [PubMed: 23125443] • Broad immune responses, including humoral and CD4+ and CD8+ T-cell responses, were observed in the same first-in-human study of this Ad26 vector-based vaccine.
18. 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(8):e41936. [PubMed: 22870265] • This was a first-in-human dose-escalation study of combination vaccine mixture of Ad35-GRIN and Ad35-ENV which demonstrated dose-related reactogenicity, no significant toxicities, and immune responses including humoral and T-cell responses.
19. International AIDS Vaccine Initiative; HIV Vaccine Trials Network; National Institute of Allergy and Infectious Diseases (NIAID); Beth Israel Deaconess Medical Center; Ragon Institute of MGH, MIT and Harvard. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Safety and immunogenicity study of Ad26-ENVA and Ad35-ENV HIV vaccines in healthy HIV-uninfected adults. [cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01215149?term=NCT01215149&rank=1> NLM Identifier: NCT01215149.
20. National Institute of Allergy and Infectious Diseases (NIAID). ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Evaluating the safety of and immune

response to the VSV-Indiana HIV vaccine in healthy, HIV-uninfected adults. [cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01438606?term=NCT01438606&rank=1> NLM Identifier: NCT01438606.

21. 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. *JAIDS*. 2013; 63(1):1–8. [PubMed: 23221981]
22. McFarland EJ, Johnson DC, Muresan P, et al. HIV-1 vaccine induced immune responses in newborns of HIV-1 infected mothers. *AIDS*. 2006; 20(11):1481–1489. [PubMed: 16847402]
23. Russell ND, Graham BS, Keefer MC, McElrath MJ, Self SG, Weinhold KJ, Montefiori DS, Ferrari G, Horton H, Tomaras GD, et al. Phase 2 study of an HIV-1 canarypox vaccine (vCP1452) alone and in combination with rgp120. Negative results fail to trigger a phase 3 correlates trial. *JAIDS*. 2007; 44:203–212. [PubMed: 17106277]
24. US Army Medical Research and Materiel Command; United States Army Medical Materiel Development Activity Armed Forces Research Institute of Medical Sciences, Thailand; Walter Reed Army Institute of Research (WRAIR); Sanofi Pasteur MSD; VaxGen; The EMMES Corporation; Ministry of Health, Thailand; Mahidol University; Royal Thai Army Medical Department; Tripler Army Medical Center; Henry M Jackson Foundation. *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. HIV Vaccine Trial in Thai Adults. [cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT00223080?term=NCT00223080&rank=1> NLM Identifier NCT00223080.
25. Rerks-Ngarm S, Paris RM, Chunsuttiwat, et al. Extended evaluation of the virologic, immunologic, and clinical course of volunteers who acquired HIV- infection in a phase III vaccine trial of ALVAC-HIV and AIDSVAX B/E. *J Inf Dis*. 2013; 207(8):1195–1205. [PubMed: 22837492] • Vaccinations during RV 144 did not alter the clinical course of HIV infection for those who became infected after vaccination.
26. Haynes BF, Gilbert PB, McElrath J, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. *NEJM*. 2012; 366(14):1275–1286. [PubMed: 22475592] • An IgG antibody response versus the V2 loop may have been responsible for protective efficacy of the vaccine regimen in RV 144.
27. Rolland M, Edlefsen PT, Larsen BB, et al. Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2. *Nature*. 2012; 490(7420):417–420. [PubMed: 22960785]
28. US Army Medical Research and Materiel Command. *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Study of late boost strategies for HIV-uninfected participants from protocol RV 144. [cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01435135?term=01435135&rank=1> NLM Identifier: NCT01435135
29. Harari A, Bart PA, Stohr E, 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]
30. Harari A, Rozot V, Cavassini M, et al. NYVAC immunization induces polyfunctional HIV-specific T cell responses in chronically-infected ART-treated HIV patients. *Eur J Immunol*. 2012; 42(11): 3038–3048. [PubMed: 22930439]
31. Walsh SR, Dolin R. Vaccinia viruses: vaccines against smallpox and vectors against infectious diseases and tumors. *Expert Rev Vaccines*. 2011; 10(8):1221–1240. [PubMed: 21854314]
32. Amato RJ, Stephankiw M. Evaluation of MVA-5T4 as a novel immunotherapeutic vaccine in colorectal, renal and prostate cancer. *Future Oncol*. 2012; 8(3):231–237. [PubMed: 22409460]
33. Walsh SR, Wilck MB, Dominguez DJ, et al. Safety and immunogenicity of Modified vaccinia Ankara in hematopoietic stem cell transplant recipients: a randomized, controlled trial. *J Infect Dis*. 2013; 207(12):1888–1897. [PubMed: 23482644]
34. Wilck MB, Seaman MS, Baden LR, et al. Safety and immunogenicity of modified vaccinia Ankara (ACAM3000): effect of dose and route of administration. *J Infect Dis*. 2010; 201(9):1361–1370. [PubMed: 20350191]
35. Zhang X, Cassis-Ghavami F, Eller M, Currier J, Slike BM, Chen X, Tartaglia J, Marovich M, Spearman P. Direct comparison of antigen production and induction of apoptosis by canarypox virus- and modified vaccinia virus Ankara-human immunodeficiency virus vaccine vectors. *J Virol*. 2007; 81:7022–7033. [PubMed: 17409140]

36. 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 response. *Vaccine*. 2012; 31(1):114–119. [PubMed: 23142302] • Vector seropositivity does not affect immunogenicity for MVA-based vaccine.
37. 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). *JID*. 2012; 206(2):258–266. [PubMed: 22561365] • Increased risk of HIV acquisition after AD5-based vaccine in Step study was documented within the first 18 months after vaccination, but waned after that time period.
38. Chen H, Xiang ZQ, Li Y, Kurupati RK, Jia B, Bian A, Zhou DM, Hutnick N, Yuan S, Gray C, Serwanga J, Auma B, Kaleebu P, Zhou X, Betts MR, Ertl HCJ. Adenovirus-based vaccines: comparison of vectors from three species of Adenoviridae. *J Virol*. 2010; 84(20):10522–10532. [PubMed: 20686035]
39. Abbink P, Lemchert AA, Ewald BA, Lynch DM, Denholtz M, Smits S, Holterman L, Damen I, Vogels R, Thorner AR, O'Brien KL, Carville A, Mansfield KG, Goudsmit J, Havenga MJ, Barouch DH. Comparative seroprevalence and immunogenicity of six rare serotype recombinant adenovirus vaccine vectors from subgroups B and D. *J Virol*. 2007; 81:4654–4663. [PubMed: 17329340]
40. Mast TC, Kierstead L, Gupta SB, Nikas AA, Kallas EG, Novitsky V, Mbewe B, Pitisuttithum P, Schechter M, Vardas E, Wolfe ND, Aste-Amezaga M, Casimiro DR, Coplan P, Straus WL, Shiver JW. International epidemiology of human pre-existing adenovirus (Ad) type-5, type-6, type-26 and type-36 neutralizing antibodies: correlates of high Ad5 titers and implications for potential HIV vaccine trials. *Vaccine*. 2010; 28:950–957. [PubMed: 19925902]
41. Barouch DH, Kik SV, Weverling GJ, et al. International seroepidemiology of adenovirus serotypes 5, 26, 35 and 48 in pediatric and adult populations. *Vaccine*. 2011; 29:5203–5209. [PubMed: 21619905]
42. Barouch DH. Novel adenovirus vector-based vaccines for HIV-1. *Curr Opin HIV/AIDS*. 2010; 5:386–390.
43. Li H, et al. Adenovirus serotype 26 utilizes CD46 as a primary cellular receptor and only transiently activates T lymphocytes following vaccination of rhesus monkeys. *J Virol*. 2012; 86:10862–10865. [PubMed: 22811531]
44. Waddington SN, McVey JH, et al. Adenovirus serotype 5 hexon mediates liver gene transfer. *Cell*. 2008; 132(3):397–409. [PubMed: 18267072]
45. Lore K, Adams WC, et al. Myeloid and plasmacytoid dendritic cells are susceptible to recombinant adenovirus vectors and stimulate polyfunctional memory T cell responses. *J Immunol*. 2007; 179(3):1721–1729. [PubMed: 17641038]
46. Perreau M, Welles HC, et al. The number of Toll-like receptor 9-agonist motifs in the adenovirus genome correlates with induction of dendritic cell maturation by adenovirus immune complexes. *J Virol*. 2012; 86(11):6279–6285. [PubMed: 22491454]
47. Teigler JE, Iampietro MJ, Barouch DH. Vaccination with adenovirus serotypes 35, 26, and 48 elicits higher levels of innate cytokine responses than adenovirus serotype 5 in rhesus monkeys. *J Virol*. 2012; 86:9590–9598. [PubMed: 22787208]
48. Penaloza-Macmaster P, 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] • As compared with Ad5, the alternative serotype Ad vectors (Ad26, Ad35 and Ad48) exhibited longer-lasting functional memory T cell responses which may translate into immunologic advantages of these vectors for HIV vaccines.
49. Letvin NL, Rao SS, et al. Immune and genetic correlates of vaccine protection against mucosal infection by SIV in monkeys. *Sci Transl Med*. 2011; 3(81) 81ra36.
50. Barouch DH, Liu J, et al. Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys. *Nature*. 2012; 482(7383):89–93. [PubMed: 22217938] • Prime-boost vaccine regimens (Ad26/MVA or Ad26/Ad26) were effective in preventing acquisition of SIV in rhesus monkeys despite pathogenic heterologous neutralization-resistant SIV challenges. The inclusion of Env in the vaccine was critical to the protective effect.

51. National Institute of Allergy and Infectious Diseases (NIAID). ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Evaluating the safety and immune response of an adenovirus-based HIV vaccine in HIV-uninfected adults. [cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01103687?term=NCT01103687&rank=1> NLM Identifier: NCT01103687.
52. Ratto-Kim S, Currier JR, Cox JH, et al. Heterologous prime-boost regimens using rAd35 and rMVA vectors elicit stronger cellular immune responses to HIV proteins than homologous regimens. PLOS ONE. 2012; 7(9):e45840. [PubMed: 23049876] • When compared with homologous prime-boost (MVA-MVA or Ad35GE-Ad35GE), a heterologous prime boost approach (Ad35-GE prime, MVA boost) generated superior immune responses.
53. International AIDS Vaccine Initiative. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Safety and immunogenicity study of SeV-G(NP) HIV vaccine administered intranasally and Ad35-GRIN HIV vaccine given intramuscularly in prime-boost regimens in HIV-uninfected volunteers. [cited 2013 May 17]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01705990?term=NCT01705990&rank=1> NLM Identifier: NCT01705990.
54. 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(7):e40385. [PubMed: 22808149] • Preclinical data on a non-human adenovirus vector which may be an option for use in HIV vaccine development in the future.
55. Santra S, Sun Y, Koriath-Schmitz B, et al. Heterologous prime/boost immunizations of rhesus monkeys using chimpanzee adenovirus vectors. Vaccine. 2009; 27(42):5837–5845. [PubMed: 19660588]
56. Roshorn Y, Cottingham MG, Potash MJ, et al. T cells induced by recombinant chimpanzee adenovirus alone and in prime-boost regimens decrease chimeric EcoHIV/NDK challenge virus load. Eur J Immunol. 2012; 42(12):3243–3255. [PubMed: 22930183]
57. O'Hara GA, Duncan CJ, Ewer KJ, et al. Clinical assessment of a recombinant simian adenovirus ChAd63: a potent new vaccine vector. J Infect Dis. 2012; 205(5):772–781. [PubMed: 22275401] • This was the first in-human study of this non-human adenovirus vector for human vaccine. This was studied for malaria vaccine, found to be safe and immunogenic, may translate as a valuable vector option for HIV vaccine development in the future.
58. Colloca S, Barnes E, Folgori A, et al. Vaccine vectors derived from a large collection of simian adenoviruses induce potent cellular immunity across multiple species. Sci Transl Med. 2012; 4(115) 115ra2.
59. McKenna PM, Koser ML, Carlson KR, et al. Highly Attenuated Rabies virus-based vaccine vectors expressing Simian-Human Immunodeficiency Virus Env and Simian Immunodeficiency Virus Gag are safe in Rhesus Macaques and protect from an AIDS-like disease. J Infect Dis. 2007; 195:980–988. [PubMed: 17330788]
60. Tan GS, McKenna PM, Koser ML, et al. Strong cellular and humoral anti-HIV Env immune responses induced by a heterologous rhabdoviral prime-boost approach. Virology. 2005; 331(1): 82–93. [PubMed: 15582655]
61. Johnson KM, Vogel JE, Peralta PH. Clinical and serological response to laboratory-acquired human infection by Indiana type vesicular stomatitis virus (VSV). Am J Trop Med Hyg. 1966; 15(2):244–246. [PubMed: 4286381]
62. Rao BL, Basu A, Wairagkar NS, et al. A large outbreak of acute encephalitis with high fatality rate in children in Andhra Pradesh, India, in 2003, associated with Chandipura virus. Lancet. 2004; 364(9437):869–874. [PubMed: 15351194]
63. Cooper D, Wright KJ, Calderon PC, et al. Attenuation of recombinant vesicular stomatitis virus/human immunodeficiency virus type 1 vaccine vectors by gene translocations and g gene truncation reduces neurovirulence and enhances immunogenicity in mice. J Virol. 2008; 82(1): 207–219. [PubMed: 17942549]
64. 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(10):1651–1660. [PubMed: 22914365] • This was the first in-human

study of alphavirus-based HIV vaccine; the vaccine was safe, but only modest immunogenicity observed

Key Points

- Within HIV vaccine development the relevant nonreplicating viral vectors, which are generally safe and immunogenic, include: canarypox (ALVAC), Vaccinia vectors (NYVAC and MVA), fowlpox, adenoviruses (Ad5, Ad26, Ad35, and nonhuman adenoviruses), rhabdoviruses and alphaviruses.
- The RV-144 study was a phase III trial of a ALVAC prime and DNA boost regimen which demonstrated 31.2% prevention efficacy in the study population in Thailand; post-trial investigations of the immune correlates of protection in RV-144 are ongoing.
- Ad5 vaccines given in the Step study (HVTN 502) and Phambili study (HVTN 503) efficacy trials did not protect against acquisition of HIV, and within the subgroup of Ad5-seropositive uncircumcised men in the Step study there were more HIV infections among vaccine recipients than placebo recipients.
- Another Ad5-based vaccine regimen (DNA prime, Ad5 boost) was given in the HVTN 505 clinical efficacy trial, but vaccinations were halted in April of 2013 due to lack of efficacy with 41 HIV infections among vaccine recipients and 30 HIV infections among placebo recipients.
- Future research may include advanced clinical trials of HIV vaccine regimens that employ other adenovirus serotypes (Ad26 and Ad35, which are biologically distinct from Ad5), use of novel mosaic inserts, and early clinical trials of non-human viral vectors, such as chimpanzee adenoviruses.

Table 1

Characteristics and advanced clinical trials of nonreplicating vectors as HIV-1 vaccines.

Vector	Pros	Cons	Most advanced clinical trial
ALVAC (canarypox)	<ul style="list-style-type: none"> - Induces T-cell response - Immunogenic in prime-boost combinations - No pre-existing population vector immunity - Evidence for clinical efficacy on HIV acquisition 	<ul style="list-style-type: none"> - Weakly immunogenic by standard laboratory assays - Unknown correlate(s) of immune protection that lead to observed efficacy in RV144 	<p>Many earlier clinical trials, and most advanced evaluation: Phase III: RV144 [1]</p> <ul style="list-style-type: none"> - Thailand - NCT00223080 - Prime: subtype B and A/E ALVAC-HIV-<i>gag-pr-gp41-gp120</i> - Boost: subtypes B and E AIDSVAX B/E (gp120 subunit proteins) <p>Modest prevention efficacy:</p> <ul style="list-style-type: none"> - 31.2% in general population - 3.7% in high-risk
NYVAC (vaccinia)	<ul style="list-style-type: none"> - Immunogenic in preclinical and early studies - Can accommodate larger inserts 	<ul style="list-style-type: none"> - Theoretical safety concerns with vaccinia, though generally seen as safe with attenuation 	<p>Phase I completed: EV01 [2] – NYVAC alone Phase I completed: EV02 [3] – DNA prime + NYVAC boost Phase I ongoing: HVTN 092 [4] – DNA prime + NYVAC boost Phase I ongoing: HVTN 096 [5] – NYVAC, DNA and protein (AIDSVAX B/E) combinations</p>
MVA (vaccinia)	<ul style="list-style-type: none"> - Induces T-cell responses - Immunogenic in prime-boost combinations - Minimal pre-existing population vector seropositivity (groups that received smallpox vaccine) - Can accommodate larger inserts 	<ul style="list-style-type: none"> - Significant attenuation needed to prevent human disease - Modest immunogenicity after attenuation - Safety concerns, even with attenuation, though widely used for smallpox vaccination 	<p>Phase IIa completed: HVTN 205 [6] – DNA prime + MVA62 Phase I completed: HVTN 055 [7] – MVA + fowlpox Phase I completed: HVTN 065 [8] – DNA prime + MVA62 boost Phase I ongoing: HVTN 094 [9] – DNA prime (with GM-CSF) + MVA62 Early studies of multigenic MVA [10] Phase I planned: Ad26 + MVA</p>
Fowlpox	<ul style="list-style-type: none"> - Shown to be safe in cancer therapeutics (breast and prostate cancer) 	<ul style="list-style-type: none"> - Limited clinical data 	<p>Phase I completed: HVTN 055 [7] – MVA + fowlpox</p>
Ad5 (adenovirus)	<ul style="list-style-type: none"> - Induces T-cell responses - Immunogenic in prime-boost combinations 	<ul style="list-style-type: none"> - High pre-existing population vector seropositivity (Ad5 seropositive subjects excluded from HVTN 505) 	<p>Many early clinical studies, and most advanced evaluations: Phase IIb: Step (HVTN 502) [11] [12]</p> <ul style="list-style-type: none"> - Americas

Vector	Pros	Cons	Most advanced clinical trial
		<ul style="list-style-type: none"> No efficacy in two phase IIb trials 	<ul style="list-style-type: none"> NCT00095576 Subtype B, MRKAd5-<i>gag/pol/nef</i> No efficacy (possible increased infections) <p>Phambili/HVTN 503 [13]: similar results, no efficacy</p> <p>Phase IIb: HVTN 505 [14][15]</p> <ul style="list-style-type: none"> North America NCT00865566 Vaccinations halted for lack of efficacy, follow-up and data analysis ongoing <p>- Prime: subtypes A, B & C DNA plasmid with <i>envA</i>, <i>envB</i>, <i>envC</i>, <i>gagB</i>, <i>polB</i>, <i>nefB</i></p> <p>- Boost: subtypes A, B & C</p> <ul style="list-style-type: none"> rAd5-<i>envA-envB-envC-gagB-polB</i>
Ad26, Ad35 (adenoviruses)	<ul style="list-style-type: none"> Low population seroprevalence Immunogenic alone, and in prime-boost combinations 	<ul style="list-style-type: none"> Can accommodate relatively only smaller inserts 	<p>Phase I completed: IPCAVD 001 [16][17] – Ad26 dose escalation</p> <p>Phase I completed: Ad35 dose escalation studies [18]</p> <p>Phase I completed: IAVI 003 [19] – Ad26/Ad35 prime-boost</p> <p>Phase I planned: Ad26/MVA prime-boost</p>
Rhabdoviruses (VSV, Rabies)	<ul style="list-style-type: none"> Absence of vector immunity in humans 	<ul style="list-style-type: none"> Safety concerns – risk of vector-induced disease in humans 	<p>Preclinical studies</p> <p>Phase I ongoing: HVTN 090 [20] – VSVIN</p>