

Lessons from the failure of the adenovector HIV vaccine

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Abstract

The much-publicised halting of the joint Merck/HIV Vaccine Trials Network phase IIB candidate HIV-1 vaccine trial in 2007 has led to an unprecedented degree of discussion and introspection amongst the HIV research community. In this commentary, we will summarise the lessons learned from the trial and examine the current state of HIV vaccine research.

Introduction and context

The Merck/HIV Vaccine Trials Network (HVTN) 502 study, called STEP, started in late 2004 and was terminated in September 2007. The phase IIB test-of-concept, double-blinded, placebo-controlled trial was conducted in North and South America, the Caribbean, and Australia (areas where the predominant HIV-1 subtype is clade B). The aim of the STEP trial was to generate a potent HIV-specific T-cell response, with the hope of either conferring protection against infection or decreasing 'set-point' plasma viraemia in subjects who subsequently became infected with HIV-1, thus reducing disease progression and potential viral transmission. Almost 3,000 healthy uninfected young adult volunteers considered to be at high risk of HIV-1 infection were involved. Vaccinated subjects received three immunisations of three replication-defective adenoviral vectors (rAd5), each carrying a gene encoding an HIV clade B protein (Gag, Pol and Nef). At the time the trial was started, this vaccine was the leading T-cell candidate and had elicited the highest levels of T cell responses in phase I studies [1]. As specified in the protocol, the trial data were reviewed by the Data and Safety Monitoring Board after 30 subjects had become infected. The trial was then terminated because there was no apparent vaccine efficacy, and - worryingly - a trend was noted for an increased risk of infection in vaccinated subjects with high titres of pre-existing neutralising antibodies (nAbs) against adenovirus serotype 5 (Ad5), from which the vector was derived [2,3]. Inevitably, halting the trial at

this stage meant that subsequent analysis was limited by small numbers, a total of 49 infections in the vaccinated group and 33 in the placebo group.

Overall, the STEP vaccine was as immunogenic as had been predicted from earlier human studies, eliciting significant interferon-gamma (IFN- γ) secretion in response to two or three of the HIV proteins in most subjects, detected by enzyme-linked immunosorbent spot (ELISpot) assay, in 77% of vaccinees [3]. Moreover, high frequencies of polyfunctional HIV-specific CD4⁺ and CD8⁺ T cells were observed following vaccination, however, these were primarily IFN- γ ⁺ and IFN- γ ⁺/tumour necrosis factor-alpha-positive (TNF- α ⁺) cells as opposed to interleukin-2-positive (IL-2⁺), IFN- γ ⁺, TNF- α ⁺ T cells, which are regarded as being fully polyfunctional. In terms of magnitude, breadth and functionality, the vaccine-induced responses in those who became infected were not significantly different from the responses in those who remained uninfected [3]. However, despite the encouraging early data in humans, the response to the Ad5 vector had been - with hindsight - less encouraging in studies conducted in non-human primates [4]. Although there had been evidence of a reduction in viral load of 1 to 3 logs in vaccinated macaques following challenge with SHIV [a chimaeric virus expressing HIV internal genes and simian immunodeficiency virus (SIV) envelope] [5], a more stringent challenge with the more virulent SIV strain, SIVmac239, led to just a modest (1 log) decrease of viral load, which was seen only in

monkeys carrying the protective major histocompatibility complex class I allele Mamu-A*01 [6]. It has been argued that more attention needs to be paid to the outcome of appropriate macaque challenge models in selecting the vaccine candidates that go through to large clinical trials in humans [7].

Although the numbers of new HIV-1 infections in the STEP trial were too small to demonstrate unequivocally that pre-existing Ad5 immunity actually increased susceptibility to infection, there was a trend toward a higher infection rate in subjects with high titres of Ad5-specific nAbs, particularly in uncircumcised men, however, the data could also be interpreted - somewhat paradoxically - as showing a lower rate of infection in placebo recipients with high Ad5 antibody titres [8]. If pre-existing Ad5 immunity really does increase HIV-1 susceptibility, one possible mechanism would be a vaccine-mediated increase in immune activation leading to a larger pool of activated HIV-susceptible T cells. In order to address this question, cellular immune activation and expression of HIV-1 co-receptors were studied in infected and uninfected vaccine recipients with different levels of Ad5 antibodies. Activation levels were in fact higher in those with higher antibody titres, but only in placebo recipients and in vaccine recipients who did not become infected, suggesting that cellular activation did not play a major part in increasing susceptibility in those with prior Ad5 immunity. Nevertheless, *in vitro* studies have shown that Ad5-antibody immune complexes can promote HIV-1 infection by inducing dendritic cell maturation and enhancing HIV-1 transmission to T cells [9]. Moreover, prior adenoviral immunity impinged on vaccine immunogenicity: frequencies of HIV-specific CD8⁺ T cells were significantly lower in subjects with pre-existing Ad5 nAbs compared with naïve subjects [3]. However, examination of further data from the STEP trial, looking at participants who, despite extensive counselling, became infected after the trial was terminated, shows that the effect of pre-existing adenovirus immunity no longer has an impact on the likelihood of infection in vaccines (Julie McElrath, presentation at the Keystone meeting on HIV prevention, March 2009).

Major recent advances

Does the setback of the STEP study imply that the general concept of T cell-based vaccine is flawed or is this simply a failure of a particular product? Could other T cell vaccination regimens using different vectors fare better? Recently, Liu and colleagues [10] succeeded in eliciting a protective T-cell response against SIV using an immunisation strategy similar to that of the STEP study, but using two different adenovirus vectors. Significant

protection of rhesus monkeys from challenge with SIVmac251 was afforded following immunisation with an rAd26-Gag prime/rAd5-Gag boost regimen. This heterologous prime-boost strategy elicited a Gag-specific T-cell response of higher magnitude, breadth and poly-functionality than the rAd5-Gag prime/rAd5-Gag strategy used in the STEP study, and this correlated with control of set-point viral loads. HIV-specific T cells were primarily IL-2⁺ (as opposed to IFN- γ ⁺ generated with the rAd5-Gag prime/rAd5-Gag regimen and the STEP study), and gastrointestinal CD4⁺ T cells and peripheral CCR5⁺ central memory CD4⁺ T cells were preserved. These results strongly suggest that the use of vectors other than the Ad5 vector used during the STEP trial should be considered and provide encouragement that a setback of the STEP trial does not imply a failure of the overall T cell-based vaccine concept. Following a period of considerable introspection after the STEP trial, HIV vaccine researchers have identified some critical considerations to be addressed before embarking upon further large-scale clinical vaccine studies.

Achieving a better fundamental understanding of the pathogenesis and immune response to HIV-1 infection

The critical features of protective immunity against HIV-1 infection remain poorly understood because, in contrast to most infections for which we have effective preventative vaccine, there are no records of any individuals having completely eliminated the virus. Continued studies of people with a good outcome of their encounter with HIV-1 infection (HEPS [highly exposed persistently seronegative] subjects and those with long-term viral control, not only with HIV-1 but also with HIV-2 infection [11]), as well as new and improved animal models, are needed to determine the correlates of protective immunity.

Improving the definition of the correlates of T cell-mediated protection during HIV infection and following vaccination

It has been well established that neither the magnitude nor the breadth of the HIV-specific IFN- γ response measured by ELISpot assays correlates with any clinical parameter in infected patients [12], strongly implying that there are better functional correlates of an effective antiviral T-cell response. Migueles and colleagues [13] recently developed an assay that detects the delivery of functional Granzyme B into HIV-infected cells. Lytic granule loading of effectors and delivery to target cells are critical determinants of cytotoxicity and immunologic control. Assuming that diminished killing capacity of HIV-specific cytotoxic CD8⁺ T cells is due to deficient loading of lytic granules into targets, such an assay should be considered in the testing of new vaccines.

Moreover, since the presence of polyfunctional T cells (IL-2⁺, IFN- γ ⁺, TNF- α ⁺) correlates with delayed disease progression [14], the concept of polyfunctionality should be more clearly defined: could other even more critical soluble factors or effector functions be identified? Furthermore, the field needs to develop assays to measure renewal and persistence of the memory T-cell response. Hansen and colleagues [15] have shown that SIV-infected rhesus macaques vaccinated with a RhCMV (rhesus cytomegalovirus) vector expressing SIV Gag, Rev-Tat-Nef and Env developed robust and sustainable CD4⁺ and CD8⁺ T-cell responses that were sufficient to mediate protection against infection with the highly pathogenic strain, SIVmac239, after repeated mucosal challenges. Protection was associated with effector memory T (T_{EM}) cells producing TNF- α , IFN- γ and MIP-1 β (macrophage inflammatory protein-1-beta) in the absence of nAbs [15]. This implies that T_{EM} cells may have the ability to prevent sexual transmission of HIV, hence correlates of functional memory need to be easily identifiable. Progressive impairment of T cell fitness during chronic infection is also an important parameter. T cell exhaustion and senescence correlate with an increase in viral load [16], whilst preservation of proliferative capacity is associated with viral control [17,18]. The ability of T cells to suppress virus *in vitro* may be a better indication of their antiviral potency and does not always correlate with other assays of T cell function [19]; it would be valuable to develop similar suppression assays that could be scaled up in vaccine studies. Lastly, although blood remains the most accessible tissue, recent appreciation that crucial immunopathological events occur in mucosal compartments early after infection [20,21] suggests that sampling these sites may provide more relevant data about pathogenesis and protective immunity. Studies of non-human primates infected with SIV would be useful in determining whether this approach is feasible.

A better characterisation of the innate response to HIV-1 would influence the quality and magnitude of the adaptive immune response

The strong relationship between KIR (killer immunoglobulin-like receptor) genotypes and HIV-1 disease outcome [22,23] strongly suggests that natural killer (NK) cell responses are likely to play an important role at early stages of infection and thus be decisive for the outcome of disease, but correlates of an effective innate immune response are still ill defined and it is not yet clear how this may be influenced by vaccine strategies [24].

Selecting alternative vaccine vectors

Other vectors, such as other adenoviral vectors that rarely cause infection in humans (for example, simian and

ovine adenoviruses), and poxviruses, merit further study. The impact of pre-existing immunity as well as the immune response to these vectors should be characterised in detail. Poxvectors are a particularly promising option since most individuals born after 1974 have not been in contact with the virus, thus preventing the scenario that appeared to be an issue during the STEP study. It is also important to consider that similar vectors are being developed for other novel vaccines, such as for tuberculosis and malaria, so consideration should be given to how these vaccines can be effectively used together.

Determining whether a broadly neutralising antibody response against HIV-1 infection is achievable

Given that most of the successful licensed vaccines rely on the generation of virus-specific nAbs and that administration of high doses of broadly neutralising monoclonal antibodies provides sterilising immunity to HIV [25], it has become imperative to determine how this could be achieved in the context of HIV infection. Masking of epitopes by glycosylation and the high mutation rate of the viral envelope are two main reasons why nAbs against HIV are difficult to induce [26]. However, other antibody-mediated antiviral activities such as antibody-dependent cell-mediated cytotoxicity (ADCC) may be equally valuable. The phase III trial of the Aventis Pasteur ALVAC-HIV (vCP1521)/VaxGen gp120 B/E (AIDSVAX B/E) prime-boost vaccine in Thailand is promising in this regard. This study started in October 2003, involved more than 16,000 healthy uninfected volunteers and will be completed by June 2009. The vaccination strategy was as follows: (a) at weeks 0, 4, 12 and 24, subjects were primed with ALVAC-HIV (vCP1521), a recombinant canarypox vector expressing subtype E HIV-1 gp120 linked to a transmembrane anchoring portion of gp41, and HIV-1 Gag and protease, and (b) at weeks 12 and 24, subjects were given a bivalent AIDSVAX B/E gp120 boost [27]. Preliminary results showed that the vaccine induced a potent ADCC significantly different from that of placebo recipients. In previous phase I/II testing, this regimen induced higher binding and nAb titres and a lymphoproliferative response in vaccine recipients compared with the placebo group. Whether this prime-boost vaccine combination can afford protection against HIV is not yet known, but the presence of gp120 ADCC antibodies following vaccination is encouraging.

Learning from other successful anti-viral vaccines

Inspiration for the HIV vaccine endeavour has been sought from other vaccines that have been successful at eliciting protective immunity [28,29]. Recently, microarray transcriptional profiling and multiplex cytokine

analysis revealed that activation of master-switch genes following yellow fever vaccination induces several pathways of innate and adaptive immune response, including complement, Th1/Th2 polarisation and B cells [30]. This approach permitted the identification of a distinct signature of gene activation and accurately predicted CD8⁺ T-cell and B-cell responses. Thus, new technologies and system biology approaches should be included in future studies in order to decipher the intricacy of HIV and to assist the design of future effective vaccines.

Future directions

In summary, the next generation of HIV vaccines will probably need to elicit broader and more polyfunctional, potent, and persistent T-cell responses than those achieved in the STEP study and then may provide partial protection against HIV-1 infection. T cell immunity could be enhanced by mobilising innate immunity (NK cells in particular), whilst the generation of a broadly nAb response remains elusive. Huge challenges nevertheless will remain to generate vaccines that can effectively protect against the multiplicity of HIV-1 variants that have emerged worldwide in the past few decades and to combat the ability of this virus to create latent lifelong reservoirs.

Abbreviations

Ad5, adenovirus serotype 5; ADCC, antibody-dependent cell-mediated cytotoxicity; ELISpot, enzyme-linked immunosorbent spot; HEPs, highly exposed persistently seronegative; HVTN, HIV Vaccine Trials Network; IFN- γ , interferon-gamma; IL-2, interleukin-2; KIR, killer immunoglobulin-like receptor; MIP-1 β , macrophage inflammatory protein-1-beta; nAb, neutralising antibody; NK, natural killer; rAd5, replication-defective adenovirus serotype 5; RhCMV, rhesus cytomegalovirus; SIV, simian immunodeficiency virus; T_{EM}, effector memory T; TNF- α , tumour necrosis factor-alpha.

Competing interests

The authors declare that they have no competing interests.

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