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Human versus HIV: round 2 defeat in AIDS vaccine development

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"It is in the interest of world health that we win the next round in the battle against HIV and develop a safe and effective HIV vaccine, which will set a key milestone for vaccinology in the 21st Century."

On 21st September 2007, the worldwide HIV research community received a press statement via email from the US National Institute of Allergy and Infectous Disease (NIAID) announcing that immunizations of volunteers in a large, international HIV vaccine Phase IIb clinical trial, known as the STEP study, had been discontinued [101]. The clinical trial, which began enrolling volunteers in December 2004, is cosponsored by the NIAID and the pharmaceutical company, Merck, and took place at sites in North America, South America, the Caribbean and Australia [102].

Merck developed and supplied the candidate vaccine, MRKAd5 HIV-1 gag/pol/nef trivalent vaccine, which is based on a weakened serotype 5 adenovirus (Ad5) that causes common upper-respiratory infections in humans. For the purposes of the vaccine, the Ad5 vector has been genetically altered in order to render it unable to replicate. The MRKAd5 HIV vaccine is a mixture of three weakened adenoviruses that act as vectors to deliver three HIV antigens, Gag, Pol and Nef, into the host with the goal of inducing an immune response against HIV, the virus causing AIDS [1]. Since none of the three antigens were expected to elicit protective antibodies, the MRKAd5 HIV vaccine was developed to test its ability to induce only cell-mediated immunity (CMI) as the mechanism of protection.

Given the concern that pre-existing immunity against adenoviral vector components may reduce the efficacy of adenoviral vector-based vaccines, the STEP study was organized in two stages. The first 1500 volunteers had a low level of pre-existing antibodies against the Ad5 vector and the second phase opened to another 1500 volunteers with high-titer antibodies toward the Ad5 vector.

On 18th September, 3 days prior to the NIAID press release, the Data and Safety Monitoring Board for the STEP study reviewed the interim data obtained from the first 1500 volunteers and concluded that the vaccine cannot be shown to prevent HIV infection and, thus, immunization of all volunteers should cease. As a result of this decision, another similar trial, named Phambili (the Xhosa word meaning 'moving forward'), designed to test the same Merck vaccine in South Africa with 801 volunteers already enrolled and 55 of them fully immunized since its inception in January of 2007, was also permanently suspended [102].

"The STEP trial has taught us that great advancements must be made before we can rely fully on our existing knowledge of immunology to develop an effective human vaccine."

However, a little over 1 month following the discontinuation of the trials, the second shoe dropped with a truly shocking finding announced by NIAID. A trend toward a higher rate of HIV infection was found among volunteers immunized with the MRKAd5 vaccine compared with those in the placebo group, particularly among those volunteers with

EXPERT REVIEWS

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high-level antibodies against the Ad5 vector [103]. In a subsequent meeting organized by HIV Vaccine Trial Network (HVTN), the organization that manages the STEP trial, researchers from both HVTN and Merck presented data from studies, which were organized in remarkable speed, in an attempt to understand what may have caused these results. While Merck's vaccine formulation appeared to be immunogenic, as expected from results obtained during its preclinical and earlier clinical trials [2], it was ineffective in preventing infection with HIV in human volunteers. The trend toward an increased frequency of HIV infection in the vaccinated group is completely unexpected and has been difficult to explain [3,4]. Therefore, in the fight to develop a vaccine against HIV, human was again defeated by this cunning virus, after failures from previous Phase III efficacy trials organized by VaxGen using a recombinant gp120-based HIV vaccine showed no protection efficacy.

Indeed, it is unprecedented for a vaccine to increase the rate of infection with the pathogen against which it was supposed to protect, as shown by STEP trial. While there have been mishaps in the history of vaccinology, for example, the poorly inactivated polio vaccine that caused polio infections [5] and the inactivated respiratory syncytial virus (RSV) vaccine that may have worsened the pathogenesis for the vaccinated population upon re-exposure to RSV [6], it is highly unusual for a human vaccine to actually increase the rate of infection shortly after immunization.

The immediate impact of the STEP trial results on HIV vaccine development is not difficult to imagine. Over the last several years, a great majority of candidate HIV vaccines that progressed into Phase I or II clinical trials or remained active in the research and development pipeline incorporated many of the same elements as Merck's Ad5 HIV vaccine into their design [7]. In fact, Merck is the pioneer in bringing the concept of the adenoviral vector to HIV vaccine development. With this unexpected setback, the developers of other HIV vaccine formulations that are based on the adenoviral vector approach will have to differentiate their products from Merck's in order to move their formulations forward.

At the moment, there are two major alternative adenoviral vector-based approaches. First, a DNA-prime plus Ad5-vector-boost approach, which has been in line to start the next major Phase IIb trial through HVTN [104]. Developers of this vaccine formulation will need to justify how the addition of the DNA vaccine component will not lead to increased rates of infection, despite the fact that this combination immunization approach may induce higher anti-HIV cell-mediated immune responses compared with an adenoviral vector alone. Second, adenoviral vectors from other human serotypes, such as Ad26 and Ad35, or adenovirus vector of a chimpanzee origin, have been proposed due to [8,9]:

- Low pre-existing immunity against these serotypes in targeted human population to avoid the issue directly related to the Ad5 vector
- The fact that many of these adenoviruses do not share the same receptor as Ad5

However, since the molecular and/or virological mechanisms that are involved in the increased infection rate in the high-Ad5 immunity group are unclear at this point, it will be difficult to completely rule out that the same phenomenon will not occur with other serotype adenoviral vectors. The more challenging issue is vaccine efficacy. Since there was no protective efficacy with Merck's Ad5-based vaccine, even in the group with low Ad5 immunity despite no increase in HIV infection, it is unclear why we are to expect that vaccine formulations using other adenoviral vectors will elicit better protection against HIV.

The impact of the STEP trial also extends to other viral vector-based HIV vaccine approaches. Although the exact mechanism for the failure of the Ad5-based vaccine is unknown, there is concern over whether the finding of an increased rate of HIV infection with adenoviral vector-based vaccines can also be applied to other viral vector-based vaccines, such as pox viral vectors, the second most popular viral vector strategy in HIV vaccine development [10,11]. More critically, the STEP study raised a fundamental question about the potential roles of CMI in vaccine-induced protection. It is anticipated that more effort will be applied to developing HIV vaccines that can elicit neutralizing antibodies, despite this having been difficult to achieve for the last two decades. Alternatively, a more balanced vaccination approach that is able to elicit both CMI and antibody responses will be adopted [12].

The setback from the STEP trial may further support the skeptic's view among some HIV researchers that it is basic research, rather than a rushed vaccine development effort, that should receive more attention and a greater amount of resources. Even for scientists working in the broad field of HIV vaccine research and development, some would like to see a shift of resources to focus more on animal models or correlates of protection against HIV. The pharmaceutical and biotech industries will be even less interested in maintaining their involvement in HIV vaccine development, despite the fact that US NIH has already underwritten many of the industry's HIV vaccine programs over the last 10 years. Merck should be applauded for putting its own resources into developing the prototypic adenoviral vector-based HIV vaccines. However, it appears as though the future of HIV vaccine programs at the major pharmaceutical companies is in jeopardy.

Despite the well-publicized failure of the STEP trial, it is critical to continue well-designed and fully justified efficacy trials with other vaccination approaches. One key contribution from the STEP trial is the quick answer that the Ad5 vector-based, CMI antigen-only vaccine approach was not protective. Human trials are the only definitive way of knowing the efficacy of a vaccine formulation. It is true that human trials are expensive, but the continuous expansion of preclinical studies without well-established animal models is not without cost. Vaccine research is still, by and large, an empirical science. The STEP trial has taught us that great advancements must be made

before we can rely fully on our existing knowledge of immunology to develop an effective human vaccine. Scientific policy makers and program managers should be wise enough to continue, or even expand, the scope of clinical testing on more worthwhile ideas while avoiding concentrating a high percentage of resources on many similar HIV vaccine formulations that fall under one or two approaches, which have yet to be proven efficacious in clinical trials.

There is much to be learned from the STEP trial for the entire field of vaccinology, even beyond HIV vaccine development. Knowledge gained from this study can be used for the future development of vaccines against other viral and nonviral pathogens. More importantly, we cannot underestimate the negative impact this trial will have on our society. There are already many misconceptions regarding vaccines among people living in either developed or developing countries. Efforts are needed to coordinate the education of the general public on the facts of the STEP trial and the lessons learned. The public should be ensured that there is a well-established system to safeguard the process of developing and testing human vaccines. It is in the interest of world health that we win the next round in the battle against HIV and develop a safe and effective HIV vaccine, which will set a key milestone for vaccinology in the 21st Century.

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