Another HIV vaccine failure: where to next?

The recent high-profile failure of an HIV vaccine trial (HVTN 505) raises some key questions for researchers in this field[1]. The authors tested a vaccine regimen consisting of a DNA vector encoding HIV-1 Gag, Pol, Nef and Env proteins followed by a recombinant adenovirus type 5 (rAd5) boost in an at-risk population in the US, with ~1,250 individuals given the vaccine and a similar number given a placebo. The vaccine did not reduce the rate of HIV-1 acquisition or the viral-load set point in the population studied. We asked four experts for their opinions on this trial and how they think the HIV field should move on from this disappointing result.

Andrew McMichael

The HVTN 505 trial result[1] is disappointing at first sight, but it has several important messages. Aside from the failure of this vaccine to prevent infection, its failure to reduce virus load in HIV-infected people does not mean that such a T cell–stimulating HIV vaccine cannot work. For example, a recent study convincingly showed that stimulating $CD8^+$ T cell responses with a cytomegalovirus vector can clear virus from monkeys infected with pathogenic SIVmac239 (ref. 10).

So why do such T cell–stimulating approaches work, whereas human Ad5 HIV vaccines fail[1,11]? Most likely, the outcome of vaccination depends on a combination of the strength of the induced T cell response and its breadth, state of activation and duration. Furthermore, in the SIV experiments in monkeys the vaccine and challenge viruses were closely matched[10]; in humans this is not the case. Furthermore, the HVTN 505 trial vaccine biased the $CD8^+$ T cell response toward Env[1]. Previous studies have shown that such T cells are not effective in control of HIV-1 infection[12], probably because of sequence variability across Env in different HIV strains. Future studies should separate the induction of Env-specific helper T and B cells for making antibodies from the induction of $CD8^+$ T cells specific for conserved virus targets such as Gag p24, optimizing both the antibody and $CD8^+$ T cell responses and avoiding interference.

A second issue concerns the potential for Ad5 enhancement of HIV-1 infection rates. Known risk factors for this phenomenon—preexisting Ad5 seropositivity and uncircumcised status—were excluded in HVTN 505. Although there was a slightly higher HIV-1 acquisition rate in vaccinated individuals compared to controls[1], this was not significant and seems to be disappearing with time as the trial continues. This is good news, as it suggests that adenovirus vectors, which are so good at stimulating $CD8^+$ T cells and antibodies, are not doomed, and it opens up opportunities to use rarer serotypes of adenovirus as vectors. The HVTN 505 trial tells us far more than a simple "yes, it works" or "no, it doesn't."

Professor of Molecular Medicine, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK.

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Louis J Picker

In HIV/AIDS vaccine development, concepts rapidly evolve, but facts, such as those obtained from randomized, double-blind, placebo-controlled clinical efficacy trials, come extremely slowly. Although the outcome of one such trial, HVTN 505, was disappointing, it establishes an all-too-infrequent factual benchmark by which evolving vaccine concepts can be judged[1].

HVTN 505 tested the efficacy of a vaccine combining a DNA vector prime and rAd5 vector boost that in the mid to late 2000s was among the most promising of HIV/AIDS vaccine platforms. This highly immunogenic vaccine could elicit the multifunctional HIV-specific $CD4^+$ and $CD8^+$ T cell responses and multiclade anti–HIV envelope responses that were thought necessary for clinical efficacy. Although the failure of the rAd5 vector–only vaccine (which targets the HIV-specific T cell response) in the earlier STEP trial[5,6] was a cause for concern, the HVTN 505 prime-boost regimen was more potent than the STEP trial vaccine in nonhuman primate (NHP) models in lowering viral-load set points[6]. In addition, the modest success of the poxvirus vector prime and Env boost vaccine in preventing HIV acquisition in the Rv144 trial[7] spurred interest in determining whether the HIV Env–expressing DNA rAd5 vaccine would also have this effect.

HVTN 505 was powered to assess whether the DNA/rAd5 vaccine could prevent HIV acquisition or exert post-acquisition viral control,

John P Moore

The HVTN 505 HIV-1 vaccine trial reached a definitive conclusion: the vaccine had no protective efficacy against acquisition of infection or subsequent viral load[1]. This failure mirrors the outcome of two earlier efficacy trials (STEP and Phambili) of another rAd5 vector vaccine expressing Gag, Pol and Nef[2]. There is consensus, then—the rAd5 vectors tested to date have been ineffective. But there are indications of deeper problems: a presentation at the recent Barcelona AIDS Vaccine meeting described how the rAd5 vector was directly responsible for a higher HIV-1 infection rate compared to placebo in the South African Phambili trial—and by an unknown mechanism (G. Gray, University of the Witwatersrand, personal communication). This disturbing conclusion may have serious implications for rAd5-based vaccines.

The HVTN 505 report emphasizes that no vaccine-mediated enhancement of HIV-1 infection occurred[1]. A late upwards separation of the vaccine and placebo infection-rate curves is not significant (although the number of 'infection events' in the vaccine group at that time seems greater than when the infection rate for the placebo group darted upwards in the RV144 trial, thereby creating modest efficacy[3]). There was also a greater HIV-1 infection rate in the STEP vaccine arm compared to placebo, but various confounding variables preclude conclusions about vaccine-mediated enhancement[2]. A key question is whether it can be proven that any adenoviral vector vaccines for HIV-1 and other pathogens, including ones based on alternative serotypes, are safe enough for large-scale testing in HIV-endemic areas. If the Phambili enhancement mechanism is unknown, how can we be sure that the problem is absent from similar vectors? Several microbicide or passive antibody trials in Africa have also enhanced HIV-1 infection[4]. How will ethics and regulatory committees now react to the Phambili trial? Is it time to be prudent and switch to more potent next-generation vectors? If so, more attention should be given to what HIV proteins the vectors actually express. Preventing HIV

and it did neither[1]. This outcome was not entirely surprising as studies in the stringent rhesus macaque simian immunodeficiency virus (SIVmac)-NHP model had failed to show prevention of SIV acquisition with this vaccine and did show that post-acquisition SIV control was typically modest and short-lived[8,9]. HVTN 505 thus confirms emerging data that the goal of an HIV/AIDS vaccine should not be a balanced, multifunctional cellular and humoral immune response and instead emphasizes the need for an HIV/AIDS vaccine to elicit responses that precisely target specific immunologic vulnerabilities of HIV, including broadly neutralizing and/or non-neutralizing (but potentially HIV acquisition–preventing) V1 and V2 loop–specific antibodies and high-frequency effector memory T cells[7–9]. HVTN 505 also made another valuable contribution to an HIV/AIDS vaccine field hypersensitized to the possibility that any incompletely effective vaccine might increase the rate of HIV acquisition[2]. No such effect was observed in HVTN 505 (ref. 1), which may provide some comfort as the search for an effective HIV/AIDS vaccine continues.

Associate Director and Senior Scientist, Vaccine and Gene Therapy Institute, Oregon Health & Science University, Beaverton, Oregon, USA.

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infection consistently may require the additional induction of virus-neutralizing antibodies, something the tested rAd5 vectors were never designed to do. Does that omission account for their failure or, worse, the enhancement seen with the Phambili vaccine?

Professor of Microbiology and Immunology, Weill Cornell Medical College, New York, New York, USA.

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Dennis R Burton

Another well-conducted HIV vaccine trial has failed to show efficacy[1], which is five failures and one possible partial success in the last decade. What have we learned? Views differ.

I believe an important outcome from these trials is that we are beginning to get a better understanding of what monkey models may be telling us about human protection. The HVTN 505 protocol failed in humans. A similar protocol failed to protect monkeys against a robust SIV challenge (SIVmac251), although it did show some protection against a virus challenge with SIVsmE660 (ref. 13), which has been shown to have some substantial limitations[14]. Similarly, the earlier STEP protocol failed to protect monkeys against a stringent viral challenge[6]. By contrast, cytomegalovirus (CMV) vectors expressing SIV proteins have shown the ability to induce immune responses that tightly control and even clear highly pathogenic SIV infections in primate models[10]. Recent preliminary evidence has shown that another persistent herpes virus, rhadinovirus, expressing SIV proteins can tightly control SIV replication, and alternative viral vectors, with or without a protein boost, have shown some moderate protective effects against SIV in monkeys[8]. Just as importantly, passively administered neutralizing antibodies have been shown to provide sterilizing immunity against high-dose pathogenic SHIV (simian-human immunodeficiency virus) challenge in macaques[15].

"I believe an important outcome from these trials is that we are beginning to get a better understanding of what monkey models may be telling us about human protection."

Therefore, we now need to build on these successes in primate models. Inducing broadly neutralizing antibodies is a huge task, but recent advances in antibody isolation and characterization and understanding of the development of broad responses in natural infection, as well as the determination of the HIV envelope spike structure and the design of a new generation of HIV immunogens, may encourage measured optimism. Unraveling the mechanisms of action of the herpes viral vectors could be invaluable in harnessing T cell immunity for HIV vaccine protection. Meanwhile, small-scale studies in humans of existing HIV immunogens can provide useful information to help shape the design of future immunogens and immunization strategies.

Professor, Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, California, USA.

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