

Lessons Drawn From Recent HIV Vaccine Efficacy Trials

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Abstract: A safe and effective HIV vaccine is needed to curtail the US and global epidemics. However, the search for one has been elusive despite more than 25 years of focused research. Results from the RV144 Thai efficacy trial have renewed hope that a vaccine may protect against HIV acquisition. We can draw several scientific and operational lessons from RV144 and other recent tests-of-concept efficacy trials. Here we describe how trial results, some unexpected, highlight the fundamental role these clinical studies play in HIV vaccine discovery. These trials also teach us that transparency in data analysis and results dissemination can yield substantial rewards and that efforts to engage communities, particularly those most heavily affected by the epidemic, are needed to augment research literacy and trial recruitment. Future efficacy trial designs may incorporate novel, partially effective prevention strategies. Although greater in size and complexity, these trials may offer unique opportunities to explore synergies with vaccines under study.

Key Words: clinical trials, combination prevention, efficacy trials, HIV vaccines

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INTRODUCTION

Approximately 56,000 people in the United States become infected with HIV each year—one new HIV infection every 9½ minutes—reinforcing the urgent need to expand access to proven prevention strategies and identify new ones.¹ Historically, vaccines have been the most effective method to combat a wide range of infectious pathogens and in the United States are responsible for eradicating the threat from smallpox and poliomyelitis. It is widely believed that a vaccine must be a component of the HIV prevention armamentarium, yet more than 25 years of vaccine research

has not delivered one. A recently completed vaccine efficacy trial has inspired new hope that an HIV vaccine is achievable. Here we describe how the results from these large clinical studies, some unexpected, are driving vaccine discovery. We also outline important lessons about data analysis, dissemination, and recruitment of communities at risk.

HIV VACCINE EFFICACY TRIALS TO DATE

Since the first gp160 vaccine entered clinical testing in 1987, more than 150 trials of different vaccine candidates have been conducted.² These trials reflect 3 distinct waves of vaccine development, including approaches designed to elicit broadly neutralizing antibodies and cell-mediated immune (CMI) responses, and the latest wave, focused on generating combined humoral and CMI responses.³ However, only 6 trials testing 4 distinct strategies have advanced to efficacy trials (Table 1). We have previously outlined several lessons gleaned from the VAX 004 study, conducted largely among US men who have sex with men (MSM).⁹ Here we will focus attention on more recent efficacy trials.

LESSONS LEARNED

Good Science Often Leads to Surprising Results

The pair of test-of-concept efficacy trials evaluating a replication incompetent adenovirus serotype 5 (MRKAd5) trivalent HIV vaccine has advanced our understanding of vaccines designed to induce CMI responses. In September 2007, the first interim analysis of the Step trial in men and women from North and South America, the Caribbean, and Australia demonstrated that the MRKAd5 HIV vaccine failed to prevent infection or reduce early viral load.⁶ Unexpectedly, post hoc analysis revealed that male participants who were uncircumcised and Ad5 seropositive at baseline were at higher risk for HIV acquisition if they received the vaccine than if they received placebo. Investigators have suggested mechanisms by which the vaccine could increase susceptibility to infection among participants with preexisting Ad5 antibody,^{10,11} although none have been demonstrated in actual trial volunteers.^{12,13} On the other hand, several analyses suggest that the vaccine may have caused transient modest reductions in early viral load,^{14,15} giving leads about potentially effective vaccine-induced immune responses to build upon. In the Phambili trial, a companion trial to the Step trial among heterosexuals in South Africa, vaccinations were halted after only 801 of 3000 participants were enrolled. No

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TABLE 1. HIV Vaccine Efficacy Trials

Vaccine Strategy	Vaccine Manufacturer(s) and Regimen*	Trial (Dates Conducted)	Populations and Locations Tested	Seroincidence (No. per 100 Person-Years)†	Results Summary
Completed trials					
Recombinant, monomeric gp120 subunit (B/B; B/E)	VaxGen, Inc IM injections at 0, 1, 6, 12, 18, 24, and 30 months	VAX 004 (1997–2002)	VAX 004: 5417 MSM and heterosexual women in the United States, Canada, Netherlands	Men: 2.7 Women 0.8	Neither VAX 004 or VAX 003 demonstrated efficacy to prevent infection or alter viral load/CD4 count in infected vaccinees ^{4,5}
		VAX 003 (1999–2003)	VAX 003: 2546 male and female Thai IDU	Overall: 3.4	
Recombinant Ad 5 (clade B gag/pol/ nef)	Merck Research Laboratories IM injections at 0, 1, and 6 months	Step (2004–2009)	3000 MSM, heterosexual men and women in the United States, Canada, Caribbean, South America, Australia	Men V: 3.8; P: 2.8 Women V: 0.52; P: 0.51	No effect on HIV acquisition or early VL set point in Step or Phambili; possible increased HIV infection rate among subgroup of Ad5 Seropositive, uncircumcised men in Step ⁶
		Phambili (2006–2009)	801 South African heterosexual men and women	Men V:4.2; P: 3.7; Women V:6.8; P: 5.9	
Recombinant Canarypox virus (ALVAC vcp 1521) prime + monomeric gp120 (B/E) boost	Sanofi Aventis (ALVAC) and VaxGen, Inc IM injections of ALVAC at 0, 1, 3, and 6 months; gp120 boost at 3 and 6 months	RV144 (2003–2009)	16,402 Thai men and women, largely at heterosexual risk; mostly at low or medium risk of infection	Men V: 0.20; P: 0.27 Women V: 0.19; P: 0.31	Modest efficacy to prevent infection in primary MITT 31% (confidence interval: 1.1 to 51%, $P = 0.04$). No effect on postinfection early VL set point or CD4 count ⁸
Ongoing trials					
Multiclade DNA prime + multiclade Ad5 boost	NIH Vaccine Research Center IM injections of DNA via Biojector at 0, 1, and 2 months; Ad5 boost at 6 months	HVTN 505 (2009–)	1350 US MSM	Currently enrolling	Currently enrolling

*All intramuscular injections delivered via needle and syringe unless otherwise stated.

†For VAX004, overall seroincidence rates are provided for men and women as they were identical in vaccinees and placebo recipients; the pooled and not sex-specific seroincidence estimates for VAX003 were reported by Pitisuttithum, et al. Overall, 201 infections were detected in men (100 in vaccinees, 101 in placebo recipients); 10 infections were detected in women (6 in vaccinees, 4 in placebo recipients).

Ad5, adenovirus serotype 5; HVTN, HIV Vaccine Trials Network; IM, intramuscular; MITT, modified intent to treat; VL, viral load; NS, non significant; V, vaccine; P, placebo.

overall efficacy was seen, although analyses among female vaccinees vs. placebo recipients found a nonsignificant trend toward lower early viral load (12,000 vs. 35,000, $P = 0.14$) and a significant reduction in progression to CD4 <350 cells per cubic millimeter (hazard ratio: 0.33, 95% confidence interval: 0.12 to 0.91).⁷

Taken together, findings from Step and Phambili offer a number of key lessons. First, the field is looking beyond the gamma interferon ELISpot assay as the central measure of CMI; responses were detected in a majority of vaccinees

but were not found to correlate with either protective or harmful effects in these trials.¹⁶ Although developers are using a number of strategies such as DNA priming of vector-based regimens^{17,18} and novel HIV inserts¹⁹ to produce immune responses of greater magnitude, breadth, or quality, laboratory correlates of protection must be determined in clinical trials.

Second, the Step trial reinforced limitations of non-human primate (NHP) challenge models to predict efficacy in humans. We learned that a challenge model using a chimeric

simian immunodeficiency virus (SHIV 89.6P) failed to predict the results of human trials.²⁰ In addition, NHP studies were not designed to evaluate the potential for increased susceptibility to infection nor the impact of vector-based preexisting immunity or the role of foreskin on vaccine effects. NHP models can be used to study events that cannot be adequately monitored in human trials, such as events shortly after simian immunodeficiency virus exposure. Clinical trials must inform how best to use NHP models and to ultimately validate the utility of these models to predict responses in humans.

Another lesson from these trials is the potential for heterogeneity of vaccine effects in different populations. The Phambili trial, although limited in size and power, suggested potential for gender-based differences in vaccine effects, as has been seen in studies of a herpes simplex vaccine.²¹ Although more than one third of enrolled participants in the Step trial were women—many of whom reported high levels of unprotected sex with numerous partners—HIV incidence was quite low in this group. Despite a substantial HIV epidemic in subpopulations of US women,¹ identifying high seroincidence cohorts of US women has been challenging.^{22,23} Two feasibility studies testing novel approaches to recruit at-risk women in the United States are currently underway in the NIAID-sponsored HIV Vaccine and Prevention Trials Networks.

The RV144 study, conducted by the US Military HIV Research Program in collaboration with several Thai institutions, met with early skepticism among members of the scientific community²⁴ due to the vaccine regimen's relatively poor immunogenicity by standard cytotoxic T lymphocyte assays.²⁵ As a welcome surprise to many, the trial demonstrated a 31% reduction in HIV incidence, a marginal but statistically significant result.⁸ More than 30 investigators working in teams are actively attempting to identify potential correlate(s) of immune protection in this study,²⁶ with a particular focus on antibody-mediated mechanisms, including binding antibodies and antibody-dependent cell-mediated cytotoxicity.²⁷ Also surprising was the suggestion of increased efficacy among participants with lower reported baseline risk behavior, raising the possibility that vaccines with modest efficacy may have a threshold effect, with limited efficacy for participants who are heavily exposed to HIV.

Transparency Yields Many Rewards

The standards of Good Participatory Practices outlined by AVAC and the Joint United Nations Program on HIV/AIDS²⁸ state that research teams must engage with relevant stakeholders at all stages of the trial life cycle. In the Step and Phambili trials, study sites released results to participants and the public beginning within 72 hours of the Data and Safety Monitoring Board review of interim Step efficacy results. In addition, when the suggestion of increased susceptibility in the Step study came to light, the protocol team worked closely with trial sites, community advisory boards, and advocates to develop a clear communication plan to disseminate these complex results and make decisions about study unblinding. The RV144 study team developed a communication plan that chose to share results with participating communities before presenting data to scientific audiences at the AIDS Vaccine 2009 conference and in print. These studies

have opened up data and specimens to the broad scientific community, which has established an important standard in advancing HIV vaccine science and increasing transparency during the discovery process.

It Takes a Village (Several, Actually)

The success of large-scale efficacy trials depends heavily on the mobilization and participation of communities at risk for infection. Sustained community engagement efforts are needed to address the lack of urgency about HIV/AIDS and limited knowledge of HIV vaccine research, particularly among African Americans, Latinos, and MSM.²⁹ Recruitment into large-scale efficacy trials, an activity distinct from but inextricably linked to community education, has become increasingly challenging yet pressing because the rate of new HIV diagnoses in MSM is 44 times that of other men in the United States.³⁰ In HVTN 505, an ongoing trial of the Vaccine Research Center's DNA prime Ad5 boost regimen, the early phase of enrollment has been slower than anticipated. This may be due, in part, to the need to identify men and transgender women who are fully circumcised and Ad5 seronegative (inclusion criteria based on data from Step that this group was not at elevated risk for HIV after Ad5 vaccination). But several other complex social forces may be at play including prevention fatigue,³¹ saturation of HIV messages in public media, and competition for MSM participants across different HIV prevention studies, among other reasons.

Operationally, the Step trial highlighted the importance of centrally coordinated recruitment strategies and sharing of materials and techniques across participating trial sites. The most effective campaigns may be those that feature the altruistic motivations that encourage MSM to come forward to join trials in the first place.^{32,33} In addition, both Step and HVTN 505 have made significant use of new Internet-based recruitment strategies, including online social media sites, to attract MSM who often use the Web to find sexual partners.³⁴ The effectiveness of these online recruitment approaches requires further evaluation and should be optimized to accelerate recruitment efficiency.

There is No Silver Bullet for HIV Prevention

A first-generation HIV vaccine will likely be partially protective³⁵—a fact evidenced by the RV144 findings. Ultimately, it is hoped that such a vaccine can be combined with other partially protective biomedical and behavioral strategies to achieve synergistic effects. For example, Hallett et al have modeled HIV incidence in Southern Africa and have found that a circumcision intervention applied with behavioral risk reduction interventions will lead to a much greater impact than would be expected on the basis of either alone.³⁶ A partially effective antiretroviral-based microbicide was identified in July 2010,³⁷ and several clinical trials of preexposure prophylaxis regimens will report results over the next 3 years. To detect vaccine-induced effects, future trial designs that incorporate any of these new strategies with ongoing risk reduction counseling may be greater in size and complexity. But they may also provide new opportunities to explore potential synergies with vaccines under study. Ultimately, there is no silver bullet for HIV prevention. Incremental

successes in vaccine and drug discovery are the norm and will continue to be driven by our large-scale efficacy trials enrolling engaged and willing participants from communities at risk.

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