Published in final edited form as:
Cell. 2014 November 20; 159(5): 969–972. doi:10.1016/j.cell.2014.10.046.

Accelerating HIV-1 Vaccine Efficacy Trials

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Abstract

Despite major advances in HIV-1 therapeutics and prevention strategies, the development of a safe and effective prophylactic HIV-1 vaccine will likely be critical for ending the global HIV-1 epidemic. Yet only four HIV-1 vaccine concepts have been tested for clinical efficacy over the past 30 years. In this Commentary, we describe key hurdles facing the HIV-1 vaccine development field and outline strategies to accelerate efficacy evaluation of novel HIV-1 vaccine candidates.

Current State of the HIV-1 Vaccine Field

Despite the urgent need for a globally effective prophylactic HIV-1 vaccine, only four HIV-1 vaccine concepts have been tested in six clinical efficacy trials to date (Table 1). These concepts have included (i) Env gp120 proteins, (ii) recombinant adenovirus serotype 5 (rAd5) vectors, (iii) canarypox (ALVAC) vectors with gp120 boosts, and (iv) DNA vaccines with a rAd5 boost. The first efficacy studies evaluated monomeric HIV-1 envelope (Env) gp120 protein vaccines with alum adjuvant and were tested in two phase III vaccine trials. These vaccines failed to prevent HIV-1 acquisition in men who have sex with men (MSM) and high-risk women in the United States and Europe (Vax004) (Flynn et al., 2005) as well as in injection drug users in Thailand (Vax003) (Pitisuttithum et al., 2006).

A rAd5 vector-based vaccine expressing the HIV-1 internal proteins *gag/pol/nef* was then tested in the Step (HVTN 502) and Phambili (HVTN 503) phase IIb trials. The Step trial, which was conducted in MSM and high-risk women in the Americas, Caribbean, and Australia, was stopped for futility to block HIV-1 acquisition (Buchbinder et al., 2008). Subsequent analyses suggested an increase in HIV-1 acquisition in vaccinees, particularly in the subgroup of uncircumcised men who were seropositive at baseline for Ad5. This finding cast a pall over the HIV-1 vaccine development field and led to increased research emphasis on the potential importance of vector-specific immune responses. The Phambili study tested the same vaccine in high-risk heterosexuals in South Africa and was stopped during its

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The authors declare no competing financial interests.

enrollment phase shortly after the Step results were announced (Gray et al., 2011). Unblinded follow-up of Phambili participants suggested a very late effect of excess HIV-1 infections in heterosexual male vaccinees without a clear mechanism of action (Gray et al., 2014). Concordant with the lack of efficacy observed in these clinical trials, preclinical studies similarly demonstrated that analogous rAd5 vectors expressing *gag/pol/nef* from the related simian immunodeficiency virus (SIV) afforded no protection against acquisition of infection following mucosal SIV challenges in rhesus monkeys (Reynolds et al., 2012).

The third vaccine concept involved priming with a canarypox vector (ALVAC) expressing the HIV-1 antigens *gag/pol/env* and boosting with the same gp120 protein subunits that were used in the Vax003 study. The RV144 study was conducted in a low-incidence, mostly heterosexual population in Thailand and demonstrated vaccine efficacy of 31% at 42 months (Rerks-Ngarm et al., 2009). Efficacy was 60% at 12 months, indicative of an early protective effect that waned over time. Subsequent analyses demonstrated that the risk of HIV-1 infection correlated inversely with antibodies directed against the first and second HIV-1 Env variable regions (V1V2) and correlated directly with Env-specific IgA antibodies (Haynes et al., 2012). Additional analyses suggested that HIV-1 infection risk also inversely correlated most clearly with V2-specific antibodies of the IgG3 isotype and non-neutralizing functional activity. Furthermore, a molecular sieve analysis showed immune selection pressure on specific V2 amino acids in vaccinees (Rolland et al., 2012). Consistent with the clinical results, modest protective efficacy was also observed with analogous ALVAC/gp120 vaccines against mucosal SIV challenges in rhesus monkeys.

The fourth vaccine concept that was tested involved priming with DNA vaccines expressing *gag/pol/nef/env* and boosting with rAd5 vectors expressing *gag/pol/env* in the HVTN 505 study, which was a phase IIb study conducted in MSM in the Americas. Importantly, preclinical data showed that this vaccine afforded partial protection against low stringency SIV challenges (strain SIVsmE660) in rhesus monkeys but failed to protect against high stringency SIV challenges (strain SIVmac251) (Letvin et al., 2011). HVTN 505 was halted at its first interim efficacy analysis for futility to protect against HIV-1 acquistion or lower HIV-1 viral RNA in breakthrough infections (Hammer et al., 2013). These data strongly suggest that preclinical studies of HIV-1 vaccines should be evaluated exclusively in stringent preclinical challenge models.

Future HIV-1 Vaccine Efficacy Studies

Several HIV-1 vaccine candidates are expected to be evaluated in clinical efficacy studies in the next few years. The Poxvirus-Protein Public Private Partnership (“P5”) is a collaborative group that has been formed to build on the results of the RV144 trial and to test the identified V2 correlate of risk in a new series of HIV-1 vaccine efficacy trials in sub-Saharan Africa and Thailand. For studies in Africa, new ALVAC and gp120 vaccine products with HIV-1 clade C antigens are currently being manufactured. ALVAC vectors expressing clade C antigens and MF59-adjuvanted gp120 subunits are planned for a phase III licensure study in sub-Saharan Africa. Other strategies, including NYVAC and DNA-NYVAC priming prior to gp120 boosting, are planned for evaluation in non-licensure track

phase IIb efficacy studies. High-risk MSM cohorts are also being explored in Thailand for further efficacy testing.

Additional HIV-1 vaccine candidates are also being developed for efficacy testing. A recombinant adenovirus serotype 26 (rAd26) prime expressing *gag/pol/env* with a modified vaccinia Ankara (MVA) boost expressing the same antigens has shown substantial protection against both SIVmac251 and SHIV-SF162P3 challenges in rhesus monkeys (Barouch et al., 2012; Barouch et al., 2013). Boosting with an Env gp140 trimer appears to improve this observed protective efficacy in monkeys (Barouch, unpublished observations). A prototype rAd26 vector expressing *env* was also recently shown to be safe and immunogenic in humans with no evidence for activation of total or vector-specific CD4+ T cells in colorectal mucosa (Baden et al., 2014). A multivalent Ad26/MVA vaccine expressing HIV-1 “mosaic” *gag/pol/env* immunogens designed for optimal coverage of global virus diversity, together with a stable Env gp140 trimer, are expected to enter clinical trials later this year. These Ad26/MVA and Ad26/gp140 vaccines are currently under consideration for advancement into efficacy testing.

Other promising vaccine candidates that have entered early phase clinical trials include priming with DNA vaccines and boosting with MVA vectors. In addition, early phase clinical trials are planned with cytomegalovirus (CMV) vectors, which showed substantial virologic control and possible clearance of SIVmac251 in approximately half of vaccinated monkeys following challenge (Hansen et al., 2013).

Why So Few HIV-1 Vaccine Efficacy Studies?

Why so have so few HIV-1 vaccine efficacy trials been conducted to date for a problem of such global importance? Factors include the enormous scientific challenges in designing a vaccine for a highly variable virus that integrates in the host genome, rapidly establishes latency, and effectively evades both humoral and cellular immune responses. Although certain correlates of risk were identified in the RV144 study, it is currently not clear whether these are true mechanistic correlates of protection or whether they will prove generalizable beyond the RV144 study. In addition, although nonhuman primate challenge models have proven informative, they do not yet represent validated animal models that are necessarily predictive of clinical efficacy trials. As a result, large, complex, iterative clinical efficacy studies are required to show the efficacy of candidate HIV-1 vaccines in humans. Moreover, the primary endpoint of such studies has to be incident new HIV-1 infections in large populations of high risk individuals. Such studies are expensive and logistically challenging, and thus they pose substantial risk to the pharmaceutical industry that traditionally drives advanced clinical development of vaccines.

Accelerating Clinical Efficacy Trials

Accelerating efficacy testing of novel and promising HIV-1 vaccine candidates will be vital for the field. In the absence of a validated and generalizable immune correlate of protection, only carefully designed clinical efficacy trials can determine if a HIV-1 vaccine works in humans. The results of such trials, regardless of their outcomes, will have major impacts on the HIV-1 vaccine field, and they will lead to immediate prioritization and deprioritization

of vaccine candidates and strategies. Studies that show partial protective efficacy will also refine our understanding of immune correlates of protection. The efficacy trials conducted to date have had surprising outcomes that have been discordant with the expectations of experts in the field, and thus the current state of knowledge is inadequate to predict the results of any such efficacy trials with certainty. To accelerate efficacy testing of next generation HIV-1 vaccine candidates, increased industry involvement, mobilization of resources, expansion of the current vaccine pipeline, and robust preclinical challenge studies will likely prove critical.

Increased industry involvement would be highly desirable for the HIV-1 vaccine field, particularly for advanced clinical development. Industry provides unique expertise in terms of manufacturing, regulatory affairs, and product development as well as downstream licensure capacity to produce and to deliver a vaccine in the event that efficacy trials are successful. Currently, industry involvement has been relatively modest for the reasons described previously. Both the NIH and the Bill & Melinda Gates Foundation have programs that actively support academic-industry partnerships, and these programs should be continued and expanded. Engaging and encouraging industry involvement at the earliest stages in vaccine development may interest a potential industry partner in a particular vaccine platform and may lead to increased involvement for advanced clinical development should the scientific rationale prove compelling. Early involvement of industry may also be critical as companies may need the use of particular raw materials, cell lines, vectors, or manufacturing technologies to be consistent with their internal platforms or processes.

The size, cost, and logistic complexity of HIV-1 vaccine efficacy trials are substantial. Thus, in addition to the major current investments from the NIH, Gates Foundation, and multiple other organizations, mobilization of new resources would greatly accelerate HIV-1 vaccine efficacy studies. Three potential sources for new funding include industry, governments, and additional philanthropy. Pharmaceutical companies may provide direct support for development activities, including clinical efficacy trials, if they are sufficiently interested in a particular vaccine product. Additional investment of governments worldwide would be highly enabling for the field. Finally, new philanthropic funding will also accelerate the development of an HIV-1 vaccine, as exemplified by the Ragon Institute of MGH, MIT, and Harvard.

Accelerating clinical efficacy trials of HIV-1 vaccine candidates also requires multiple distinct and scientifically promising vaccine candidates in preclinical and early phase clinical studies to be ready for efficacy testing. It is therefore essential to maintain and expand a diverse portfolio of vaccine concepts. For example, novel Env immunogens are being developed by multiple groups to elicit broadly neutralizing antibodies as well as to optimize functional non-neutralizing antibodies, a series of new vectors have been explored that expand the breadth and efficacy of virus-specific T cell responses, and potential global antigens have been developed that begin to address the challenge of global virus diversity. A robust pipeline of new concepts and fresh perspectives will also require the engagement and encouragement of young and early career investigators, particularly those from the developing world.

Expanding preclinical efficacy studies will also help support the rationale for clinical efficacy trials. Although the ability of nonhuman primate challenge studies to predict the outcomes of clinical efficacy trials still remains uncertain, stringent SIV and SHIV challenges in rhesus monkeys represent the most robust model for assessing vaccine candidates prior to clinical efficacy trials. Such preclinical challenge studies should therefore be expanded, particularly for vaccine candidates under consideration for efficacy trials. When clinical efficacy data with these vaccines become available, the clinical results can then be used to refine and to improve the preclinical models.

Perspectives

HIV-1 vaccine development will likely be an iterative process. Robust basic research must continue but needs to be matched with clinical efficacy testing of promising new vaccine candidates. Information learned from each rigorous efficacy trial will be pivotal and will provide clear directions for the field. A more detailed understanding of immune correlates of protection will also be obtained from these clinical efficacy trials and may, ultimately, reduce the need to conduct large studies for each new vaccine concept. However, at the present time, there is no other way of determining whether a vaccine will prevent HIV-1 infection in humans other than clinical efficacy studies in which incident new HIV-1 infections are the primary endpoint.

There are numerous reasons for optimism in the HIV-1 vaccine field. The RV144 study showed that an HIV-1 vaccine is possible, and several novel vaccine candidates have demonstrated unprecedented efficacy in stringent nonhuman primate challenge studies. Our basic understanding of HIV-1-specific humoral and cellular immunity has expanded considerably, and preclinical and clinical immune correlates of protection have been identified in certain contexts. Increasing the momentum to accelerate the conduct of efficacy trials will substantially accelerate the development of a safe and effective HIV-1 vaccine, which will presumably be required to control the global HIV-1 pandemic.

Acknowledgments

The authors thank Bill Snow for insights and comments. The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.

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Table 1

Clinical HIV-1 vaccine efficacy trials. MSM, men who have sex with men. Ad5, adenovirus serotype 5.

Study	Vaccines	Phase	Risk Group	HIV incidence per 100 person-years	Location	Result
Vax003	AIDSVAX B/E gp120 in alum	III	Injecting drug users	3.40%	Thailand	No vaccine efficacy
Vax004	AIDSVAX B/B gp120 in alum	III	High risk women and MSM	2.60%	United States, Europe	No vaccine efficacy
HVTN 502 Step	MRKAd5 HIV-1 gag/pol/nef B	IIb	High risk women and MSM	3.00%	United States	Halted at interim analysis for futility; early transient increased infection in vaccinees
HVTN 503 Phambili	MRKAd5 HIV-1 gag/pol/nef B	IIb	High risk heterosexual men and women	3.70%	South Africa	No vaccine efficacy; late increased HIV infection in unblinded male vaccinees
RV144	ALVAC-HIV vCP1521, AIDSVAX B/E rgp120 in alum	III	Community risk heterosexual men and women	0.28%	Thailand	31.2% efficacy at 42 months as primary endpoint; 60% efficacy at 12 months
HVTN 505	DNA, rAd5 (A, B, C)	IIb	Circumcised MSM without preexisting Ad5 antibodies	1.80%	United States	Halted at interim analysis for futility