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The Quest for an HIV-1 Vaccine — Moving Forward

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Vaccines have historically been the most effective biomedical interventions for controlling global infectious diseases. The development of a safe and effective vaccine against human immunodeficiency virus type 1 (HIV-1) is therefore a critical research priority. Although other HIV-1 prevention efforts based on behavioral risk reduction, male circumcision, topical microbicides, preexposure prophylaxis, and treatment as prevention have had substantial effects on HIV-1 transmission rates, it is likely that a vaccine will be required to end the global HIV-1 epidemic.

The challenges in the development of a prophylactic HIV-1 vaccine, however, are unprecedented in the history of vaccinology. First, HIV-1 exhibits tremendous global genetic diversity as well as mutational capacity that can evade both humoral and cellular immune responses. The generation of vaccine antigens that will elicit immunologically relevant and broadly cross-reactive immune responses thus represents a major challenge. Second, HIV-1 rapidly integrates into the host genome and establishes a latent reservoir that cannot be eliminated by conventional antiretroviral drugs or virus-specific immune responses. A vaccine will therefore most likely need to induce potent and functional virus-specific antibodies that block establishment of initial infection, in addition to high levels of T lymphocytes for virologic control. Third, there are no known examples of spontaneous immune-mediated clearance of HIV-1 infection indicative of natural immunity, and thus the precise types of immune responses that need to be induced by a vaccine are not well understood. Fourth, although a series of broad and potent neutralizing monoclonal antibodies have recently been discovered, such antibodies are induced only in a subgroup of HIV-1-infected persons after several years of infection and typically exhibit extensive somatic hypermutation. No method currently exists to induce such antibodies by vaccination.

Over the past 30 years, only four HIV-1 vaccine concepts have been evaluated in clinical efficacy trials. The relative paucity of such trials speaks to the tremendous scientific and logistical challenges associated with HIV-1 vaccine development. The vaccine platforms that have been evaluated in efficacy studies have included purified Env proteins, recombinant adenovirus and poxvirus vectors, and plasmid DNA vaccines. The first concept that was tested was the AIDSVAX Env gp120 protein vaccines, which were tested in two

phase 3 efficacy studies in the United States and Thailand and were reported in 2003 to have no efficacy in the populations studied.^{1,2}

The second concept that was evaluated was an adenovirus serotype 5 (Ad5) vector expressing the internal proteins Gag, Pol, and Nef. This vaccine was shown in a phase 2b efficacy study in North and South America in 2007 to have no efficacy and in fact potentially increased the risk of HIV-1 acquisition in certain subgroups.³ A parallel study involving the same vaccine in South Africa was terminated shortly after initiation, and unblinded follow-up also showed increased rates of HIV-1 infections in vaccinees.

The third concept that was evaluated was a prime–boost vaccine regimen that involved the canarypox ALVAC vector followed by the AIDSVAX Env gp120 proteins. This was a phase 3 study (RV144) conducted in a low-risk population in Thailand and demonstrated in 2009 a 31% reduction in the rate of HIV-1 acquisition.⁴ Vaccine-elicited antibodies against the first and second variable loops (V1–V2) of Env correlated with a reduced risk of HIV-1 infection,⁵ although the applicability of these findings to other vaccine platforms remains unclear.

The fourth HIV-1 vaccine concept for which clinical efficacy testing has been completed is reported in this issue of the *Journal* (see pages xxx-xx). This vaccine was produced by the National Institutes of Health (NIH) Vaccine Research Center and included priming with DNA vaccines and boosting with Ad5 vectors expressing Env, Gag, and Pol. The trial was a phase 2b efficacy study (HVTN 505) conducted in the United States in men who have sex with men. Vaccinations were halted at the interim analysis in April 2013 because of lack of efficacy. Although the vaccine induced both humoral and cellular immune responses in the majority of recipients, the levels of neutralizing antibodies, nonneutralizing antibodies, and V2-specific antibodies were low. There was, however, no evidence of increased rates of HIV-1 acquisition among vaccinees, although unblinded follow-up of participants is still ongoing.

Despite the lack of efficacy, this study represents an important contribution to the HIV-1 vaccine field. It was a well-designed study that reached a clear conclusion upon which future research can build. Future HIV-1 vaccine candidates will need to elicit immune responses that are either qualitatively different or quantitatively superior to those induced by the DNA–Ad5 vaccine. It also appears that preclinical evaluation of future vaccine candidates should involve stringent challenge models, since the DNA–Ad5 vaccine afforded substantial protection against challenges with the easy-to-neutralize simian immunodeficiency virus (SIV) strain E660 (SIVsmE660) in rhesus monkeys but failed to protect against the more difficult-to-neutralize virus SIVmac251. In addition, despite the need to offer the best available HIV-1 prevention methods to all participants, potentially including preexposure prophylaxis with antiretroviral drugs, it is still operationally feasible to conduct rigorous HIV-1 vaccine clinical efficacy trials.

There are clear reasons for optimism in the quest to develop an HIV-1 vaccine. The modest protection achieved in the RV144 study provides the proof of concept that an HIV-1 vaccine is in fact possible. There have also been major advances in our basic understanding of

HIV-1 immunology and virology that inform vaccine design. The discovery of many new broad and potent neutralizing antibodies (see diagram) has raised the possibility that vaccination strategies could be developed to induce such antibodies. Emerging data on the structure of the HIV-1 Env glycoprotein and the ontogeny of Env-specific B-cell responses have led to the design of novel immunogens. The impressive virologic control achieved by virus-specific T lymphocytes in certain settings has also suggested important new strategies for improving cellular immune responses. Moreover, preclinical studies involving stringent challenge models have shown that several novel vaccine candidates exhibit substantially better protective efficacy than previously tested vaccine regimens.

The HIV-1 vaccine pipeline currently encompasses several concepts that are moving towards clinical efficacy trials. Vaccine candidates for which efficacy studies are planned include ALVAC-gp120 vaccines specifically designed for South Africa and Thailand, which build directly on the results of the RV144 study, as well as novel vaccine regimens that include poxvirus vectors with greater potency than ALVAC vectors, alternative serotype adenovirus vectors that are biologically different from and superior to Ad5 vectors, mosaic antigens that provide improved immunologic coverage of global HIV-1 diversity, improved Env protein immunogens, and adjuvants with increased potency. Additional concepts that have shown considerable promise in preclinical studies include replicating vaccine vectors, such as cytomegalovirus vectors, and novel strategies for generating broadly neutralizing antibodies, including stabilized Env trimers that mimic the native viral spike, scaffolds that display specific antibody epitopes, and immunogens designed to stimulate particular B-cell lineages.

Yet HIV-1 vaccine development remains slow and challenging. It is therefore critical now to capitalize on the wealth of basic scientific advances and the current pipeline of vaccine candidates to accelerate the development of an HIV-1 vaccine. One important lesson from the efficacy studies conducted to date is that the results of these studies are often surprising. Regardless, both positive and negative outcomes of clinical efficacy trials provide critically important feedback that affects preclinical and early-phase clinical studies and informs the development of the next generation of HIV-1 vaccine candidates.

Testing four HIV-1 vaccine concepts for clinical efficacy over the past three decades is insufficient given the scope of the global HIV-1 epidemic. We clearly need more “shots on goal.” We should therefore accelerate the advancement of a diverse series of novel and promising HIV-1 vaccine candidates into clinical efficacy trials over the next several years.

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