

# An HIV Vaccine — Challenges and Prospects

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Now well into the third decade of the pandemic of human immunodeficiency virus (HIV) and AIDS, we have seen dramatic successes in the treatment of HIV-infected persons in the United States and many other countries. Yet the pandemic still rages, with 2.7 million new infections in 2007. Indeed, for every infected person who began receiving antiretroviral therapy in 2007, 2.5 people were newly infected with HIV. Historically, vaccines have been among the most effective public health interventions, preventing the spread of viral infections. But an HIV vaccine has thus far been elusive and the quest disappointing and frustrating, prompting some to wonder whether an effective vaccine will ever be added to the HIV-prevention toolbox.

Although many viral infections cause severe illness and even death over a period of days to weeks, such infections typically induce immune responses involving both neutralizing antibodies that prevent further viral replication and cytotoxic T lymphocytes that recognize and eliminate infected cells that produce progeny virus. Such responses ultimately control and eliminate the virus effectively. Immunologic memory is established, and the person is left with protective immunity against subsequent infection with the same virus; this immunity is usually complete and long lasting.

Typically, vaccine development is based on this successful experiment of nature. An iterative approach of fundamental research coupled with empirical testing of immunogens leads to the identification of a product that, when

given in an appropriate formulation and dose before exposure, induces immune responses that mimic the response to natural infection and protect recipients from the development of clinically apparent disease when they are exposed to the virus. Historically, the development of vaccines has relied heavily and successfully on empirical testing.

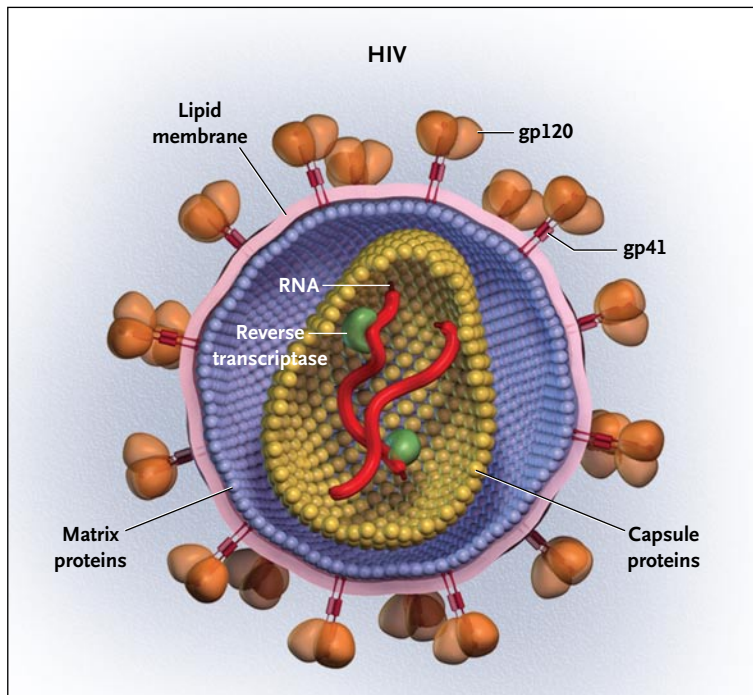
The situation is strikingly different with HIV infection. For the most part, the natural immune response against HIV is completely inadequate and, once primary infection is established, fails to eradicate the virus. With uncommon exceptions, HIV disease is relentlessly progressive, and virtually no one has a spontaneous recovery. Unlike other viruses for which we have successful human vaccines, HIV quickly integrates itself into the DNA of the host cell, where, in some cells, it remains latent and essentially invisible to the immune system. Because latency is established very early — within days to weeks after infection — the window of opportunity wherein HIV remains vulnerable to eradication through the immune response is very short.<sup>1</sup> Once latency is established, it has not yet been possible to eradicate the virus, even in patients receiving highly active antiretroviral therapy for extended periods.

The extraordinary mutability and resulting genetic diversity of HIV, which is substantially more complex than that of other human viruses, also present a formidable obstacle to immune control. By the time the body produces antibodies directed at the outer

HIV envelope protein, which is the key target for neutralizing antibodies, the protein has mutated in such a way that the circulating antibodies cannot neutralize it. New antibodies are induced, but new mutations repeatedly enable the virus to evade the immune system. Furthermore, although broadly neutralizing antibodies could persist in the host and potentially neutralize the virus even as it mutates, these are rarely found in vivo and are apparently difficult to induce, since their epitopes tend to be conformationally masked and not readily accessible for immune recognition and response.<sup>2</sup>

The initial empirical approach of immunizing with VaxGen's AIDSVax, a recombinant form of the outer glycoprotein-120 (gp120) portion of the HIV envelope, which was based on a strategy that was successful with hepatitis B, failed to protect volunteers from infection, apparently because the vaccine did not induce broadly neutralizing antibodies.<sup>3</sup> A combination vaccine composed of priming doses of Sanofi Pasteur's vCP1521, a recombinant canarypox viral vector, followed by a boosting dose of both the vector and VaxGen's AIDSVax, induces both T cells and antibodies and is now being tested in a large-scale clinical trial in Thailand; results are expected at the end of 2009.

A successful vaccine will probably need to induce both broadly neutralizing antibodies and cytotoxic T lymphocytes. Since the former have remained elusive, however, empirical approaches have focused on vaccine candidates that primarily induce cytotoxic T lymphocytes. Such vaccines would



**Structure of HIV.**

An interactive graphic is available at [www.nejm.org](http://www.nejm.org).

not be expected to prevent infection but could control virus levels, reduce the early destruction of CD4<sup>+</sup> T cells in gut-associated lymphoid tissue, and delay disease progression, as has been seen in certain nonhuman-primate models.<sup>3</sup> Furthermore, if persons immunized before being exposed to HIV were rendered less infectious because of decreased virus levels, the risk of secondary transmission might also be reduced. But several caveats need to be emphasized.

First, the concept that a “T-cell vaccine” can affect HIV disease in humans remains unproved. Only one T-cell vaccine, Merck’s MRKAd5 HIV-1 gag/pol/nef trivalent vaccine, has been tested, in two efficacy trials. The first was referred to as the STEP trial (ClinicalTrials.gov number, NCT00095576) and was conducted in North America, South America, the Caribbean, and Australia; the second, called Phambili (ClinicalTrials.gov num-

ber, NCT00413725), was conducted in South Africa. Both trials were terminated ahead of schedule when data from the STEP trial showed that the vaccine failed to prevent HIV infection and failed to lower virus levels in vaccinated volunteers who became infected. Unexpectedly, post hoc analyses of the STEP trial also found a trend toward a greater number of new infections among vaccine recipients than among placebo recipients. The highest relative risk of HIV infection among vaccinees appeared to be among men who, at enrollment, were both uncircumcised and had naturally acquired neutralizing antibodies against the vaccine vector, adenovirus type 5 — whereas no apparent increased risk of HIV acquisition was observed among circumcised men with no neutralizing antibodies against the adenovirus at enrollment.

The effectiveness of the im-

mune response to a T-cell vaccine may vary from person to person, just as the immune response to HIV infection does, and this variation may be strongly related to HLA haplotype.<sup>4</sup> Thus, a T-cell vaccine may augment the body’s genetically determined natural ability to respond to HIV, resulting in varying levels of control that depend on the person’s HLA haplotype. In other words, such vaccines may only be effective in people with favorable HLA haplotypes.

Classic viral vaccines, such as those for polio, smallpox, and measles, enable the vaccinee to avoid the development of clinical disease, to clear the infection completely, and to remain protected against subsequent exposure to that virus. The vaccination of a substantial proportion of the population reduces the number of infected people and the likelihood that a nonvaccinated person will come into contact with an infectious person. This “herd effect” can result in a dramatic decrease in the spread of infection even when only a portion of susceptible persons are vaccinated. If an HIV vaccine does not prevent infection but instead slows disease progression by lowering virus levels, the probability of secondary transmission may be reduced but not eliminated. Some level of viral replication will probably remain. HIV will inevitably mutate and probably eventually escape from immune control, increasing the risk of secondary transmission. Thus, any herd effect of a T-cell vaccine may be transient.

The failure of the first T-cell vaccine to affect the risk of infection or viral levels has led to a reexamination of the direction of the HIV-vaccine field and, in particular, of the balance between

### Selected Obstacles to HIV-Vaccine Development and Their Implications.

#### Obstacles

The window of opportunity for the immune system to clear the initial infection is narrow, since HIV integrates and establishes latent infection within days or weeks.

Destruction of CD4+ T cells begins early after infection.

Enormous genetic diversity and mutations that occur with replication enable HIV to avoid immune surveillance.

Conserved antibody targets on the outer envelope protein are “hidden” from immune recognition.

#### Implications

Rational, empirical approaches to vaccine development have not been successful to date.

Fundamental questions regarding HIV disease and the host response to the virus need to be answered.

Fresh new ideas beyond the scope of classic vaccinology are urgently needed.

fundamental-discovery research and more empirical development efforts. Since an empirical approach is less compelling for HIV than for other human viruses, from which it differs so fundamentally, this reexamination has pointed to a need to emphasize fundamental questions of HIV-vaccine discovery and discovery-related research.<sup>5</sup>

Understanding why the body does not readily develop broadly neutralizing antibodies during natural infection might suggest vaccine designs that induce such antibodies. In essence, we must do better than natural infection in inducing effective immune responses. The existence of rare monoclonal antibodies that possess broad neutralizing capability indicates that, although we have thus far failed to achieve it, induction of such antibodies should be possible. For example, x-ray crystallography has revealed how HIV uses the CD4 receptor to enter cells and how the broadly neutralizing b12 antibody binds to part of the CD4-binding site to neu-

tralize HIV effectively. Determining the structure of the trimeric form of the envelope protein is currently a research priority and is expected to yield additional insights. Efforts to design novel envelope immunogens include the use of a “scaffold” protein unrelated to the HIV envelope to which conformation-dependent conserved regions of the envelope are added, ensuring their exposure to and recognition by the immune system.

Vaccine candidates that induce broadly reactive cytotoxic T lymphocytes and neutralizing antibodies will not be effective unless the responses they elicit can contain the virus during the narrow window of opportunity before viral latency is established. Better understanding of the earliest steps of HIV infection could elucidate the role of innate and mucosal immune responses in the control of HIV infection and suggest how those responses might be manipulated — to widen the window of opportunity for viral eradication, to prevent HIV from advancing to

the gut-associated lymphoid tissue, or both.

We may not be able to develop an HIV vaccine that is highly effective in the classic sense of successful viral vaccines. If we do, it will be in the face of enormous scientific challenges. To tackle these challenges we must turn to fundamental research to a degree that has not been required in the development of vaccines for other viral diseases. We remain cautiously optimistic that a substantial increase in our understanding of HIV infection and disease will lead to creative ideas about how to design an effective HIV vaccine.

No potential conflict of interest relevant to this article was reported.



An interview with Anthony Fauci is available at [www.nejm.org](http://www.nejm.org).

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