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Perspective

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HIV Vaccine Development — Improving on Natural Immunity

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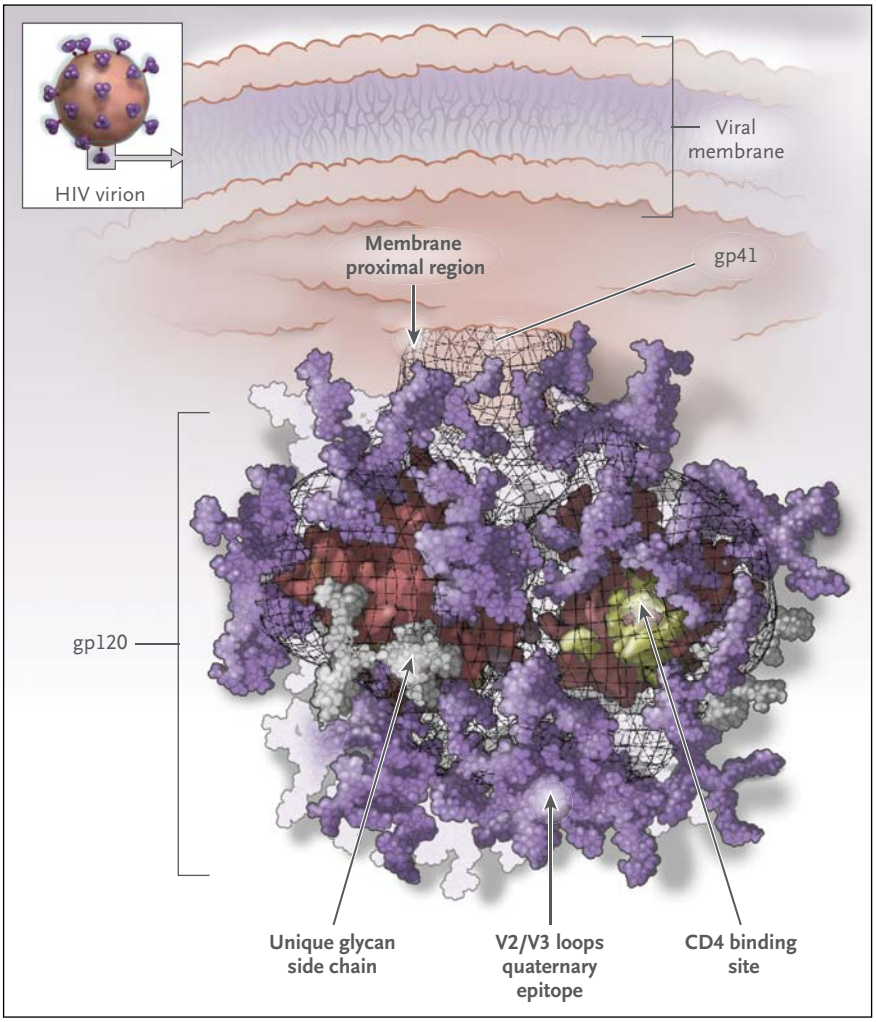
Although a number of methods of preventing infection with the human immunodeficiency virus (HIV) have proven effective to varying degrees, it is generally agreed that a safe and effective vaccine against HIV infection would be a critical component of a highly effective prevention toolkit for controlling and ultimately ending the global AIDS pandemic. For nearly all important pathogens for which effective vaccines have been developed, such as smallpox, measles, and poliovirus, there exists a natural model of protection: the immune response to the pathogen ultimately clears the microbe from the body and confers durable protection against reinfection. Under these circumstances, the human immune system has already provided us with proof of the concept that it can generate a protective response. This fact has led to a fundamental tenet of vaccinology: the best way to develop an effective vaccine is to design a candidate that mimics infection and induces responses akin to natural immunity.

Unfortunately, this lesson does not apply to HIV infection. We have known since the mid-1980s that the body's natural immune response to HIV infection is completely inadequate. A "natural" immune response that might adequately control HIV infection does not occur at all, occurs too rarely, is too weak, or is too slow to begin. Thus, a key goal for an effective HIV vaccine is to induce in the recipient a response that differs qualitatively, quantitatively, or both from that induced by natural infection — a response that has been referred to as "unnatural immunity."[1]

Although an HIV-vaccine candidate was recently shown to be modestly protective, it induced neither broadly neutralizing antiserum nor broadly reactive cytotoxic T-cell responses against HIV. This finding raises the possibility that a modest degree of protection against HIV acquisition could be mediated by non-neutralizing mechanisms — for example, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cell-mediated viral inhibition, or other responses not classically associated with vaccine efficacy.[2] Nonetheless, with most viral infections,



HIV-1 Epitopes Targeted by Broadly Neutralizing Human Monoclonal Antibodies.

Shown at the top is an HIV virion with trimeric HIV envelope proteins (purple), which consists of a gp41 transmembrane portion and a gp120 protein spike. Below the virion is an enlarged depiction of the viral membrane and the HIV envelope protein. The arrows indicate four areas, or epitopes, of the envelope that are the targets of human monoclonal antibodies that, in laboratory assays, have proved capable of neutralizing a wide array of virus strains. Vaccines that present these epitopes to the immune system in a conformationally precise manner may induce the body to produce such antibodies and provide a high level of protection from HIV infection. Adapted from a figure provided by William Schief, University of Washington.

the appearance of antibodies, particularly neutralizing antibodies, correlates closely with clearance of the virus and subsequent protection from reinfection. Thus, induction of neutralizing antibodies has served as the gold standard for vaccine-induced protection against infection — and is an appropriate goal for HIV infection as well, given that passive infusion of several broadly neutralizing antibodies completely prevented virus acquisition in nonhuman primate models of AIDS.[3] Although non-neutralizing antibody functions appeared to contribute somewhat to protection in this model, and although conserved regions of internal proteins could serve as important vaccine targets, an HIV vaccine that results in the production of broadly neutralizing antibodies before or very soon after exposure to HIV is likely to be highly effective. Since HIV infection does not naturally induce broadly neutralizing antibodies, a key challenge is inducing such antibodies.

Neutralizing antibodies generated during HIV infection are mostly directed toward exposed, highly variable portions of the HIV envelope protein on the viral particle. Antibodies found early in the course of HIV infection are directed at the infecting viral strain, which rapidly evolves to escape recognition. In contrast, antibodies that neutralize a broad array of HIV strains — broadly neutralizing antibodies — are directed against highly conserved regions of the envelope that are essential for viral entry into the host cell. Unfortunately, these conserved sites are recessed, hidden by glycans, partially embedded in the viral membrane, or otherwise relatively inaccessible to recognition by the immune system. For these reasons, broadly neutralizing antibodies are rarely found in the serum of acutely infected persons. When they do appear, they are detected at least 1 to 2 years after initial infection and do not seem to be clinically relevant.[4]

An important challenge for HIV vaccinologists is to design vaccines that induce these unnatural immune responses. The application of new research tools to the study of broadly neutralizing antibodies is helping to guide

the design of vaccines that might induce such antibodies. Until recently, the body was thought to be incapable of producing these antibodies; only a few monoclonal antibodies that were broadly neutralizing had been found, and rarely were they derived from the B cells of HIV-infected patients. However, with the utilization of extremely-high-throughput screening of B-cell clones derived from HIV-infected persons, the rapid cloning of their immunoglobulin genes, and characterization of the resulting monoclonal antibodies, it became clear that many patients can indeed make broadly neutralizing antibodies.[3] Unfortunately, they do so only after the establishment of persistent infection. In this regard, the ability to screen tens of millions of B-cell clones for HIV-envelope specificity has allowed researchers to isolate additional broadly neutralizing monoclonal antibodies and precisely identify their target epitopes on the HIV envelope (see figure).

A recent research focus has been on "structure-based vaccine design" — that is, applying knowledge of the crystallographic structure and conformation of the HIV-envelope epitope in the context of the binding site of a broadly neutralizing monoclonal antibody to design a vaccine that effectively presents that epitope in its relevant conformation to the immune system. Crystallographic studies have revealed that broadly neutralizing and non-neutralizing antibodies can bind to the same conserved region of the envelope in similar but subtly different ways.[5] Thus, determining how to replicate the precise three-dimensional conformation of the HIV-envelope epitope as it resides in the antibody binding site will prove challenging. One approach being actively pursued is scaffolding the desired epitope onto an exposed portion of a soluble or membrane-associated protein.

The body is indeed capable of producing potent, broadly neutralizing antibodies.

However, producing an antibody with high avidity to the highly conserved regions of the HIV envelope may prove to be more complex than simply presenting the desired envelope epitope to the immune system. All potent broadly neutralizing antibodies that have been described to date have one or more unusual structural features that may result only from years of chronic viral infection and exposure to viral antigen. These structural features appear to arise through a complex evolutionary process, referred to as "somatic hypermutation," which over time generates B cells that produce antibodies of increasingly higher avidity. Whether a B cell must undergo a long evolutionary process to produce a broadly neutralizing antibody against HIV remains uncertain. If such a process were required, that would pose a sobering challenge to HIV vaccinologists. Researchers are now dissecting the steps in this evolutionary process to understand how B cells evolve for the production of broadly neutralizing HIV antibodies and to design novel vaccines that might accelerate that process.

Thus, we have learned that the body is indeed capable of producing potent, broadly neutralizing antibodies; however, it does not do so readily or efficiently. We are optimistic that the tools of modern science will enable us to develop HIV vaccines that induce effective immune responses that do better than natural immunity and prevent HIV infection.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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