REVIEW ARTICLE

CURRENT CONCEPTS

# An HIV Vaccine — Evolving Concepts

Margaret I. Johnston, Ph.D., and Anthony S. Fauci, M.D.

Classic preventive vaccines are designed to mimic the effects of natural exposure to microbes. They provide a high level of long-lasting protection against infection in the vast majority of recipients and serve as free-standing preventive measures. Although a classic preventive vaccine remains the ultimate goal of efforts to develop a vaccine for protection against the human immunodeficiency virus (HIV), the enormous genetic diversity and other unique features of the HIV envelope protein have thus far thwarted attempts to identify an effective candidate. However, we have learned from studies of HIV pathogenesis in humans and from animal models that a vaccine that induces strong T-cell–mediated immune responses in the absence of broadly neutralizing antibodies may prove beneficial even if infection is not completely prevented. Vaccine-induced T-cell responses may blunt initial viremia and prevent the early and massive destruction of memory CD4+ T cells that help control infection and prolong disease-free survival. Furthermore, secondary transmission may also be reduced if the vaccine helps to control viral replication; efficiency of transmission is directly related to plasma virus levels. T-cell vaccines represent uncharted territory, and their use may have outcomes that challenge researchers and regulators alike. If proven successful, a disease-modifying HIV vaccine would also present new challenges for the entire public health community, since it would not be a stand-alone preventive measure, as are most classic preventive vaccines. Instead, it would need to be delivered in the context of a comprehensive HIV-prevention program.

From the Division of AIDS (M.I.J.) and the Office of the Director (A.S.F.), National Institute of Allergy and Infectious Diseases, Bethesda, MD. Address reprint requests to Dr. Fauci at the National Institute of Allergy and Infectious Diseases, 31 Center Dr., MSC 2520, Bldg. 31, Rm. 7A03, Bethesda, MD 20892, or at afauci@niaid.nih.gov.

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## OBSTACLES TO VACCINE DEVELOPMENT

The development of more than two dozen antiretroviral therapies to combat HIV infection has resulted in a dramatic decrease in morbidity and mortality associated with the acquired immunodeficiency syndrome (AIDS) in developed countries and, increasingly, in low- and middle-income countries as these therapies become more widely available. Despite ongoing prevention efforts, however, HIV continues to spread unabated in many parts of the world, with an estimated 14,000 new infections occurring daily. A safe and effective HIV vaccine would be an enormously valuable tool in the campaign to stop the spread of HIV.

Most viruses against which successful vaccines have been developed undergo some level of initial replication and dispersal from the portal of entry before the virus reaches its target organ and triggers pathogenic sequelae. During this period, the virus remains vulnerable to eradication by the immune system. When prior immunization or exposure to a virus has elicited virus-specific immunologic memory, the increased speed and intensity of the immune response can prevent or mitigate disease.

The nature of the interaction between HIV and the immune system is complex, and the relevance of different immune responses to the control of infection is only partially understood (Fig. 1). The primary stage of HIV infection begins with a burst

of viremia that is detected by about day 7 and that peaks about 3 weeks after exposure (Fig. 2A). Although there is considerable variability in viral load and immune responses among infected persons, the first indications of HIV-specific immune responses are increases in the levels of HIV-specific CD8+ and CD4+ T cells (Fig. 3). Virus levels then decline by a factor of 10 to 100 on average and reach a set point, or point of equilibration, 2 to 6 months after infection. The CD8+ T-cell responses are believed to be responsible for this reduction in viremia.[2] Although binding antibodies appear 6 to 12 weeks after infection, neutralizing antibodies do not emerge until after plasma viremia has declined substantially from its peak. The effectiveness of the antibody response is subsequently thwarted by rapid genetic changes in the envelope protein that allow the virus to escape recognition by antibodies in circulation at that time.[3] Once a viral set point is reached, CD8+ T cells continue to suppress the virus, but with a specificity that evolves over time, most likely in response to changes in the sequence of the envelope protein.

The set point has predicted the course of disease in cohorts of untreated persons.[4,5] A unique feature of HIV is that a pool of latently infected, resting CD4+ T cells is established very early during primary infection.[6] HIV infection is established indefinitely in essentially all patients and as a rule is relentlessly progressive, even though only a small fraction of susceptible cells are infected at any point in time.[7] Virtually no person clears HIV infection. Furthermore, the HIV reservoir is not eradicated even after extended antiretroviral therapy that reduces viremia to undetectable levels (<50 RNA copies per milliliter).[8,9] This persistence of the HIV reservoir is evidence of continual replenishment of the pool of HIV-infected cells, which counteracts any gradual decay that might otherwise occur.

Thus, the window of opportunity to clear HIV and prevent long-term, established infection may close permanently once a pool of latently infected cells is in place. This aspect of HIV infection puts it in sharp contrast with almost all other viral infections, in which the initial rounds of viral replication do not establish a permanent reservoir of infection. For this reason, HIV poses a greater challenge to the classic vaccination paradigm in which prevention of clinically relevant infection ultimately leads to the eradication of the microbe, even though initial rounds of viral replication may occur.

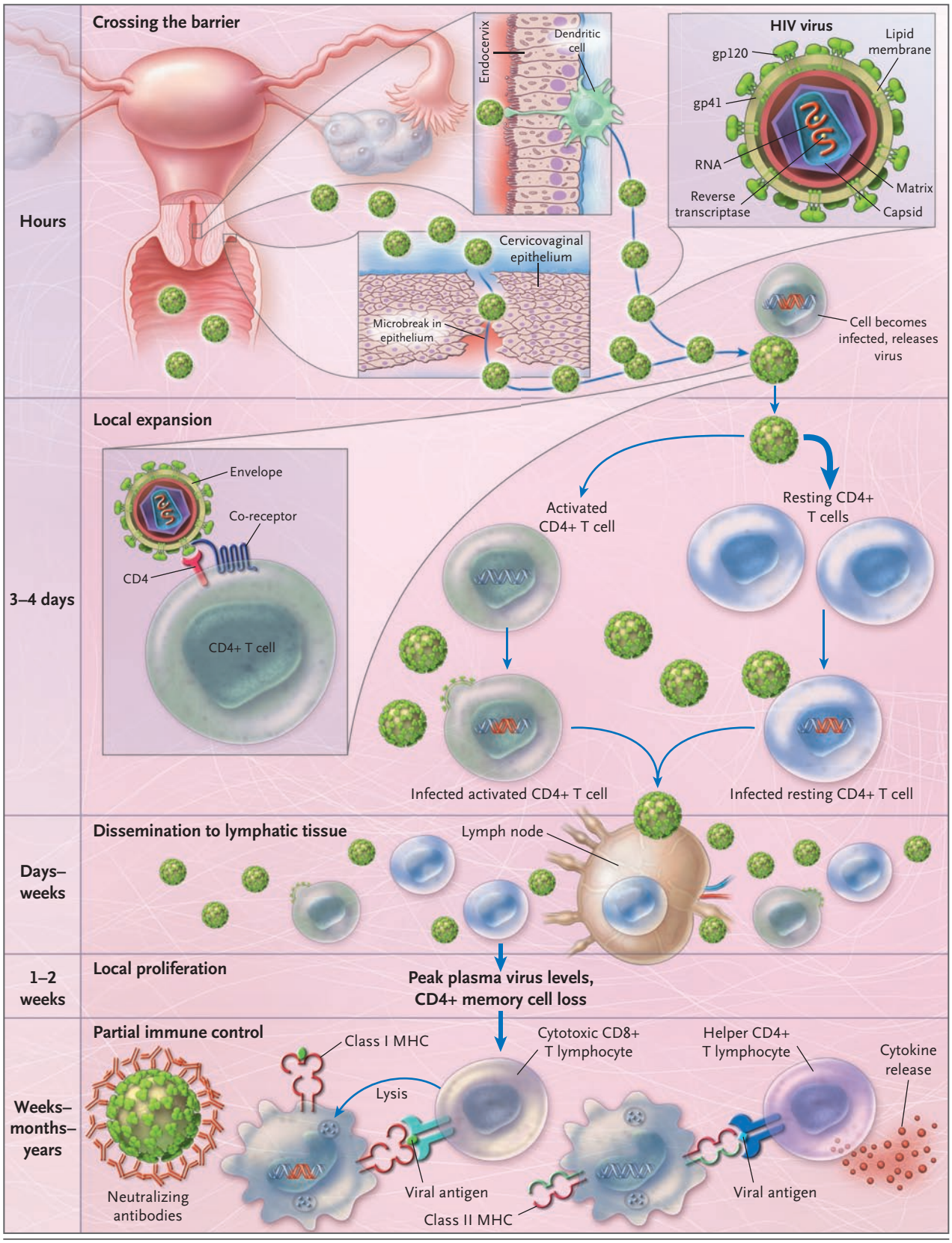
**Figure 1 (facing page). Early Events in the Vaginal Transmission of HIV, Modeled after Studies of Simian Immunodeficiency Virus Infection in Nonhuman Primates.**

The binding of the HIV gp120 envelope protein to CD4 on resting or activated T cells results in conformation change in the envelope, interaction with the coreceptor, and fusion of the viral and cell membranes, and it gives the HIV genome access to the interior of the cell. HIV particles and infected cells produced during the initial local infection are carried first to draining lymph nodes and then spread systemically. HIV-specific immune responses, including increases in CD8+ T cells and eventually neutralizing antibodies, only partially control infection. As a result, in the absence of effective vaccination or therapy, a slow and continued depletion of CD4+ T cells ensues and there is a progression to AIDS. A vaccine that prevents the establishment of chronic infection would probably need to induce immune responses that halt the local expansion of HIV, prevent dissemination of HIV to distal lymphatic tissue within the first week or two, or both. A vaccine that acts at later stages might still reduce or prevent the destruction of CD4+ T cells, help control infection, and prolong disease-free survival. Adapted from Haase with the permission of the publisher.[1]

## EARLY FOCUS ON MONOMERIC ENVELOPE PROTEINS

Efforts to develop an effective vaccine began soon after HIV was identified. Using the same paradigm that formed the basis for successful development of a genetically engineered vaccine against hepatitis B, most vaccine developers focused on recombinant forms of the viral envelope, which is the target of neutralizing antibodies in HIV-infected persons. The hypothesis was that antibodies directed against the envelope would bind, neutralize, and clear HIV particles before infection became established.

Soluble forms of the external glycoprotein 120 (gp120), all or portions of the uncleaved gp160 precursor protein, and envelope peptides were tested for safety and immunogenicity in more than two dozen phase 1 clinical trials.[10] Gp120 that had been produced in mammalian cell lines induced the highest level of neutralizing antibodies in laboratory assays that used HIV grown and tested in immortalized T lymphocytic cell lines. However, later experiments demonstrated that the antiserum failed to neutralize primary isolates of HIV grown and tested in fresh peripheral-blood mononuclear cells.[11,12] Because the clinical significance of these laboratory assays was unknown and be-



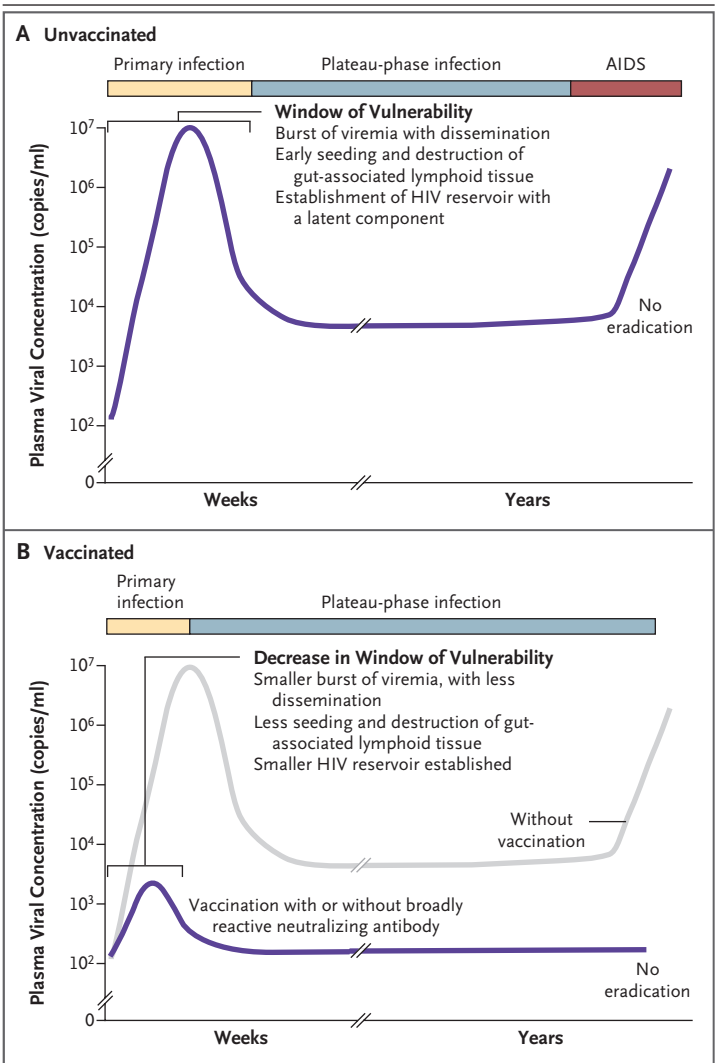



**Figure 2. Course of HIV Infection in Unvaccinated Persons and the Hypothetical Course of Infection in Vaccinated Persons.**

Panel A shows the course of infection in unvaccinated persons. The primary stage of HIV infection (yellow) starts with a burst of viremia, dissemination of the virus, early seeding and destruction of gut-associated lymphoid tissue, and establishment of a viral reservoir with a latent component (window of vulnerability). HIV levels in plasma then decline to a set point that lasts from months to years. Eventually, in the absence of effective therapy, the virus escapes immune control and AIDS results (red). Panel B shows the hypothetical course of infection in vaccinated persons. A T-cell vaccine might decrease the burst of viremia and dissemination that occurs in primary infection (yellow), preserving gut-associated lymphoid tissue, diminishing the viral reservoir, decreasing virus levels at the set point, and increasing the length of time that viral levels are controlled (blue).

cause gp120 protected chimpanzees from HIV infection, two phase 3 trials were undertaken. The vaccines failed to protect healthy subjects from HIV infection.[13,14]

Basic research on the HIV envelope has since provided several clues in the effort to determine why induction of antibodies that neutralize primary isolates of HIV is so difficult.[15] The envelope on the virion surface exists not as a monomer but as a trimer. Immunogenic regions of the monomer are occluded in the native trimer on the virion surface. The envelope protein is cloaked with numerous N-linked glycans, undergoes considerable conformational change on binding to the cell-surface CD4 receptor, and exposes sequences that are highly variable.[16,17] The potential effect of antibodies directed against variable regions is negated by the emergence of these so-called escape variants.[3,18] Furthermore, high levels of neutralizing antibodies may be required to prevent infection.[19-21] On a positive note, highly conserved epitopes do exist, as evidenced by the derivation of broadly neutralizing human monoclonal antibodies from HIV-infected persons, although such antibodies are rare.[15]

## T-CELL IMMUNITY IN THE CONTROL OF HIV INFECTION

An improved understanding of the pathogenesis of HIV infection and the immune responses that contribute to the control of HIV replication has led to increased attention to T-cell immunity. CD8+ cytotoxic T lymphocytes, key effectors of cellular immunity, recognize viral peptides bound to major-histocompatibility-complex (MHC) molecules on the surface of virus-infected cells.[22] Numerous studies support the importance of T-cell–mediated immune responses in the early and subsequent control of both HIV infection in humans and simian immunodeficiency virus (SIV) infection in nonhuman primates.[10,23] Cytotoxic T lymphocytes can kill or suppress cells infected with HIV in the laboratory,[24] and the emergence of these lymphocytes correlates with early containment of viremia.[2] The qualitative nature of CD8+ T-cell responses may be key to the control of HIV infection.[25] In monkeys that were depleted of these cells and then infected with HIV, the virus was never controlled, and the progression of the disease was accelerated.[26] However, latently infected cells survive cytotoxic-T-lymphocyte surveillance. When those latently infected cells become activated, they produce virions that infect new cells before the initial cells die or are cleared. Thus, cytotoxic T lymphocytes help control the infection but do not clear HIV reservoirs completely.

### T-CELL VACCINES

Animal models of HIV infection have proved to be very valuable in exploring the mechanisms whereby vaccines that induce primarily T-cell responses might have an effect on viral infection and disease. Regardless of the route of exposure, SIV infection in rhesus macaques is characterized by a burst of viremia and follows a course similar to that of HIV infection in humans. Studies have demonstrated that CD4+ memory T lymphocytes in gut-associated lymphoid tissue undergo massive destruction during the first few weeks of infection with SIV, as observed recently in HIV infection.[27-31]

Immunization of nonhuman primates with vaccines that induced primarily T-cell responses resulted in a blunting of the initial burst of viremia, a reduction in virus levels at the set point, a decrease in the total virus produced during the early stage of infection, or a combination of these changes.[32-34] Disease progression was delayed in many of these animals, and the delay correlated with the level of vaccine-induced T-cell responses. Immunization with one candidate vaccine preserved memory CD4+ T cells throughout the body, and this preservation was associated with an improved long-term outcome.[32,35] Peak viral levels were reduced by a factor of approximately 10, and peak levels of infected memory CD4+ T cells by approximately 75%.

The question arises whether a vaccine that does not prevent infection but reduces HIV levels and preserves uninfected memory CD4+ T cells would benefit the recipient. Cohort studies of the natural history of HIV infection have shown that viral levels at set point are inversely correlated with disease progression. A reduction of only one-half log of viral RNA resulted in slowed disease progression. If natural-history and animal-model studies prove to be predictive, people who receive T-cell vaccines before infection might remain disease-free for a prolonged period, and antiretroviral therapy, which can be burdensome and have serious side effects over time, might be delayed (Fig. 2B).[36]

Furthermore, if initial infection is blunted and memory CD4+ T cells in gut-associated lymphoid tissue are preserved, strong, vaccine-induced, T-cell–mediated immune responses might draw down viral reservoirs by destroying HIV-infected cells before new viral particles are released. Most studies in nonhuman primates have used levels of challenge virus that have been high enough to infect all control animals after a single exposure. In contrast, the probability of HIV infection has been estimated at 0.00007 to 0.0028 per coital act, depending on the stage of disease and in the absence of antiretroviral therapy in the transmitting partner, although this probability is increased in the presence of herpes simplex virus type 2 infection.[37,38] Nonhuman primates become infected when repeatedly challenged intrarectally with levels of virus that are typical of those found in the semen of men with acute HIV infection. In one such experiment, animals immunized with a T-cell vaccine had a reduced per-exposure probability of becoming infected as compared with controls.[39] If such results are reproduced with other pathogenic challenge viruses, this would suggest that a potent T-cell vaccine may delay or provide some protection from infection.

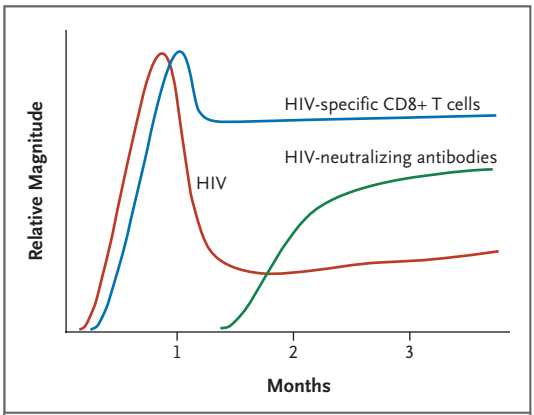



**Figure 3. Immune Responses to HIV Infection, Showing Plasma HIV Levels, HIV-Specific CD8+ T Cells, and HIV-Neutralizing Antibodies.**

If T-cell vaccines prove to benefit individuals, it will also be important to explore their public health utility. Studies have suggested that the HIV epidemic is driven largely by transmission of virus by people with high viral loads.[37,40-42] People in the early and late stages of disease, when viral levels are generally highest in untreated patients, are more likely to infect their partners than those whose viral levels are controlled. Vaccine-induced immune responses that blunt initial viremia and better control virus levels could reduce infectiousness and reduce the spread of HIV, although this would depend on a number of variables, such as the efficacy of the vaccine, durability of protection, vaccine coverage, and effect on risk-taking behaviors.[43,44]

**Table 1. Candidate Vaccines Currently in Clinical Trials.***

| Candidate and Trial Phase | Components (Clade) | Countries Hosting Trial | Developers, Sponsors, Collaborators |
|---|---|---|---|
| Canarypox plus envelope, phase 3 | gag, pro, env (E) plus gp120 (B, E) | Thailand | NIAID, Sanofi Pasteur, Thailand Ministry of Public Health, U.S. Army Medical Research and Materiel Command, VaxGen |
| Ad5, phase 2b | gag, pol, nef (B) | Dominican Republic, Haiti, Jamaica, Peru, South Africa, United States | HIV Vaccine Trials Network, Merck, NIAID |
| DNA plus Ad5, phase 2 | gag, pol, nef (B), env (A, B, C) plus gag, pol (B), env (A, B, C) | Kenya, Haiti, Jamaica, Rwanda, South Africa, Tanzania, Uganda, United States | HIV Vaccine Trials Network, International AIDS Vaccine Initiative, NIAID, U.S. Army Medical Research and Materiel Command |
| Canarypox plus lipopeptides, phase 2 | gag, pol, nef, env (B) plus cytotoxic T lymphocyte epitopes (B) | France | ANRS, Sanofi Pasteur |
| DNA plus protein, phase 1 | T helper epitopes from gag, pol, vpr, nef (B) | Peru, United States | HIV Vaccine Trials Network, NIAID, Pharmexa-Epimmune |
| DNA plus peptides, phase 1 | gag (B) multiple T-cell epitopes (plus or minus IL-15 or IL-12 adjuvant or GM-CSF) | Brazil, Thailand, United States | HIV Vaccine Trials Network, NIAID, Wyeth |
| DNA–PLG plus envelope, phase 1 | gag, env (B) plus oligomeric gp140 (B) | United States | HIV Vaccine Trials Network, NIAID, Novartis |
| Anthrax-derived polypeptide-HIV gag fusion protein, phase 1 | gag (B) | United States | Avant Immunotherapeutics, Walter Reed Army Institute of Research |
| DNA plus modified vaccinia Ankara, phase 1 | gag, pol, nef, tat, env (C) | United States | Aaron Diamond AIDS Research Center, International AIDS Vaccine Initiative |
| Modified vaccinia Ankara, phase 1 | gag, pol, nef, tat, env (C) | India | Indian Council of Medical Research, International AIDS Vaccine Initiative |
| Fowlpox plus modified vaccinia Ankara, phase 1 | gag, pol, nef, tat, rev, env (B) | Brazil, United States | HIV Vaccine Trials Network, NIAID, Therion Biologics |
| Adeno-associated virus, phase 1 | gag, pr, rt (C) | Belgium, Germany, India, South Africa, Zambia | International AIDS Vaccine Initiative, Targeted Genetics |
| Venezuelan equine encephalitis viral replicon, phase 1 | gag (C) | Botswana, South Africa, United States | AlphaVax, HIV Vaccine Trials Network, NIAID |

* Ad5 denotes adenovirus type 5, PLG polylactide co-glycolide, GM-CSF granulocyte–macrophage colony-stimulating factor, NIAID National Institute of Allergy and Infectious Diseases, and ANRS French Agence Nationale de Recherches sur le SIDA.

### COMPLICATING FACTORS

There is optimism that a T-cell vaccine could be beneficial in helping to control HIV infection, but several factors complicate the evaluation of such vaccines and suggest that we should proceed with caution. First, licensure will probably require demonstration that the initial diminution of viremia results in a clinical benefit in the individual, meaning that it will delay the development of AIDS or the need to initiate antiretroviral therapy. Furthermore, T-cell–mediated control of infection may not prove to be complete. The disease eventually progressed in some immunized and protected macaques, probably as a result of changes in critical T-cell epitopes that enabled the virus to escape immune recognition.[45] Deciding whether the level and durability of T-cell–mediated protection observed in clinical trials are sufficient to seek or grant vaccine licensure will challenge vaccine developers and regulators alike.[46]

With respect to the public health value of a T-cell vaccine, additional phase 3 or phase 4 studies would be required to determine whether vaccination reduced the spread of HIV in the com-

munity. In addition, a vaccine that delayed but did not completely prevent disease would not serve as a stand-alone preventive measure. If such a vaccine were licensed, the medical community would need to deliver it as part of a broader HIV-prevention program to reduce, if not eliminate, high-risk practices. Otherwise, the individual and public benefit could be counteracted by an increase in exposure to HIV.

**Table 2. Novel Approaches to the Design of Envelope Immunogens.**

| |
|---|
| Mimic native trimer on virion surface |
| Redirect immune responses to conserved conformational epitopes |
| Add disulfides or other amino acids to stabilize conformational epitopes |
| Bind envelope to CD4 or CD4-mimetic peptide |
| Remove carbohydrate residues or entire carbohydrate side chains |
| Redirect responses away from variable epitopes |
| Remove one or more variable loops |
| Add carbohydrate side chains to hide variable regions |

### RESEARCH ISSUES

Several vaccines that induce primarily T-cell responses are currently in phase 1 and phase 2 clinical trials (Table 1).[10,47] A recombinant canarypox vector combined with a gp120 boost is being evaluated in about 16,000 subjects in a community-based phase 3 trial in Thailand. A recombinant, nonreplicating adenovirus vector is in two phase 2b trials that will each enroll 3000 people at high risk for HIV infection. There is skepticism that either of these vaccines will be effective in the prevention of HIV infection. The canarypox vector–gp120 combination does not induce broadly neutralizing antibodies, whereas the adenovirus vector expresses only internal viral proteins that are recognized by the immune system only after productive infection. However, these trials will also evaluate whether immunization affects the early viral load in subjects who become infected with HIV despite repeated counseling. Modeling studies have suggested that even a vaccine that does not provide adequate protection against infection might alter the course of the epidemic.[48] Finally, immune responses to the HIV genes that are inserted into the adenovirus vector may be affected by prior immunity to adenovirus; investigation of this and alternative vectors is ongoing.[10,49,50]

The development of a vaccine that induces broadly neutralizing antibodies remains a high research priority. The existence of broadly neutralizing monoclonal antibodies provides hope that an immunogen that reliably induces protective antibodies can be designed. Numerous approaches using various immunogens are currently under investigation but have yet to yield more than incremental improvements over gp120 (Table 2). The recent observation that two broadly reactive monoclonal antibodies to the HIV envelope are polyspecific and react with phospholipids such as cardiolipin suggests that some species of HIV antibodies, like autoimmune antibodies, may be controlled by B-cell tolerance mechanisms.[51-53] Innovative adjuvants or immunogens might be capable of circumventing tolerance pathways and inducing more broadly reactive antibodies. Ensuring the safety of such approaches will be critical. In addition, understanding and counteracting the mechanisms responsible for the delay in the appearance of neutralizing antibodies may lead to more rapid and effective immune responses. Finally, a thorough analysis of the sequence of transmitted viruses and the structures of their envelopes may yield clues to help guide vaccine design.

Research on innate immunity could influence the design of future HIV vaccines. Innate immune responses occur early and, unlike adaptive responses, are neither antigen-specific nor durable. Natural killer cells are cytolytic cells that are key mediators of innate immunity and the first responders to viral infection.[21] Natural killer cells also secrete cytokines and chemokines that help drive virus-specific adaptive immune responses. The recent report of a form of adaptive immunity that is independent of T cells and B cells and is mediated by natural killer cells is the first observation of innate immune memory in a higher vertebrate (the mouse).[54] Improving our understanding of how innate immunity is turned on and off could lead to strategies that augment innate responses or make them more durable. Immune responses that more effectively slow or blunt the primary stage of HIV infection might increase the window of opportunity for clearing HIV before latent reservoirs become established. An improved understanding of the role of toll-like receptors in triggering innate-immune-response pathways could also suggest approaches to augment induced immune responses.[55]

## CONCLUSIONS

A vaccine that conforms to the classic paradigm of viral vaccines remains the goal of efforts to develop

an HIV vaccine. Such a vaccine would induce immune responses that prevented the establishment of HIV infection by clearing virus before latent viral reservoirs were produced. This goal may not be realized with first-generation vaccines. The development of an HIV vaccine may diverge from the classic paradigm for viral vaccines. There is optimism that even a less-than-perfect vaccine could benefit both individual recipients and the at-risk community. By blunting the initial burst of viremia and reducing virus levels, such a vaccine could prolong the disease-free period and also reduce transmission. If licensed, such a vaccine will have to be delivered as part of a comprehensive, multifaceted, prevention program.

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