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Toward an AIDS Vaccine

Bruce D. Walker^{1,2*} and Dennis R. Burton^{3*}

A quarter century of scientific discovery has been applied to developing an AIDS vaccine, yet this goal remains elusive. Specific characteristics of the virus, including the extreme genetic variability in circulating viral isolates worldwide, biological properties of HIV that impede immune attack, and a high mutation rate that allows for rapid escape from adaptive immune responses, render this a huge challenge. However, evidence of protection against AIDS viruses in animal models and control of HIV in humans under certain circumstances, together with scientific advances in understanding disease pathogenesis, provide a strong rationale and objective paths to continue the pursuit of an effective AIDS vaccine to stem the global epidemic.

Twenty-five years ago, a report in this journal of the discovery of a pathogenic human retrovirus (1) led to great optimism that a solution to an emerging lethal epidemic was at hand. This discovery, along with subsequent key confirmatory reports the following year (2–5), firmly established human immunodeficiency virus (HIV) as the causative agent of AIDS and prompted then U.S. Health Secretary Margaret Heckler to publicly proclaim at a news conference on April 23, 1984, that a preventive HIV vaccine could be expected to be available for testing within 2 years.

A quarter of a century later, HIV continues to wreak havoc on a global scale, with the most devastating consequences seen in the most impoverished nations. Despite tremendous advances in the development of life-extending anti-HIV medications and in understanding of how HIV causes disease, there have already been more than 25 million deaths. Nearly a billion dollars is spent globally on HIV/AIDS research annually, and yet the sobering reality is that at present there are no promising candidates for an HIV vaccine. The most recently tested vaccine, a collaboration between Merck and the National Institutes of Health (NIH), is only the second candidate HIV vaccine to complete efficacy testing in humans; despite considerable hope, the outcome may have been worse than simple failure. Not only did the vaccine not protect against infection, nor contain virus replication in those who became infected, apparently it increased susceptibility to infection in persons who had preexisting antibodies to the adenovirus vector used to deliver the HIV vaccine antigens (6). The failure of this vaccine has led some leaders in the field to question whether an AIDS vaccine is feasible given what is currently known (6).

This review will address the quest for an HIV vaccine in the broader context of why collective efforts and steady progress by two generations of

committed scientists have failed to deliver on the early promise of an effective AIDS vaccine and suggest paths forward to attain this elusive goal.

Vaccines That Work and Why

Since Edward Jenner's success with smallpox immunization in 1796, there have been dramatic immunization-related reductions in disease incidence for a number of viral diseases including

which is the original Salk killed poliovirus vaccine, used in the first widespread polio vaccination campaigns in the mid-20th century. A third approach employs exposure of the immune system to recombinant viral proteins alone, as in the current highly successful hepatitis B vaccine.

The goal of each of these vaccination strategies is to have an immunologic barrier in place that will prevent infection or, failing that, minimize symptoms of disease caused by virus infection. Successful vaccines have typically been generated against pathogens for which the immune response thwarts serious disease in a substantial fraction of those infected. Remarkably, knowledge of how vaccine barriers function to protect against infection and/or disease remains limited. What is known is largely built upon observations from animal models but, although these are widely accepted as relevant to human vaccines, direct mechanistic evidence for how any vaccine works in humans is sparse.

The main gatekeeper in most vaccination strategies is thought to be neutralizing antibody (Fig. 1). Preexisting serum or mucosal antibody induced by an earlier infection or through vac-

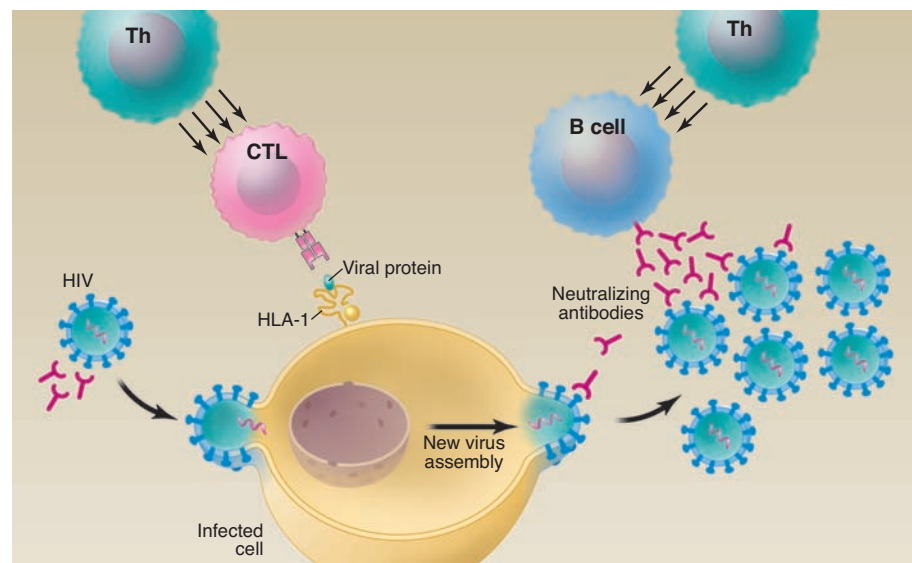


Fig. 1. Adaptive immune responses in HIV infection. HIV infection of cells can be prevented by antibodies that can neutralize free virus before progeny viruses are produced, can neutralize newly released virions from infected cells, and can act against infected cells. CTLs act once a cell becomes infected by recognizing processed viral proteins presented in the context of HLA class I molecules at the cell surface through the T cell receptor of the CTL. Coordination of CTL and neutralizing antibody responses is mediated by CD4⁺ T helper (Th) cells.

polio, measles, mumps, rubella, hepatitis B, and influenza. For each of these, protection has been achieved by mimicking infection with the pathogen and thereby establishing immunologic memory that can rapidly respond should an actual infection occur. This has been perhaps best achieved with the use of live attenuated virus vaccines, such as the mumps and measles vaccines, which infect the host but do not cause disease and elicit strong and long-lasting immune responses. A second successful approach involves the use of killed virus vaccines, an example of

sterilizing immunity against several viruses in experimental animal models. Realistically, for most human

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vaccines, antibodies are unlikely to provide sterilizing immunity; rather, they limit the initial burst of virus replication such that it can then be contained by ongoing immune responses without substantial disease symptoms—the most likely mechanism for most successful vaccines.

The most important second line of defense is the cellular immune response, particularly cytotoxic T lymphocytes (CTLs). Immunization with the appropriate T cell–inducing vaccine generates a population of memory T cells that can rapidly expand in the first days after infection. These expanding CTLs kill infected cells by recognizing foreign viral proteins that bind to developing human leukocyte antigen (HLA) class I molecules and are displayed at the cell surface, providing a signal that the cell should be eliminated (Fig. 1). Lysis of a virus-infected cell before the assembly of mature progeny virions leads to elimination of the virus, which undergoes rapid degradation in the extracellular milieu in the absence of the protective outer envelope. CTLs also release antiviral cytokines, which may act to limit the impact of progeny virions already produced (7). Many live attenuated vaccines elicit both neutralizing antibodies and CTL, the combination of which is likely to be necessary for rapid elimination of the virus or successful immunologic containment preventing the development of disease. CTL can also be induced by killed virus and recombinant protein vaccines through cross-priming when these vaccine antigens are taken up by professional antigen-presenting cells. Even in the case of vaccines that induce neutralizing antibodies, CTL may also be induced by the infection and contribute to preventing symptomatic disease. Optimal coordination of both neutralizing antibody and CTL responses requires induction of virus-specific CD4 T cell responses (Fig. 1).

Unique Challenges for HIV Vaccination

The tremendous global success with other viral vaccines raises the question as to why HIV vaccine development has been so difficult. Many of the difficulties lie in distinct properties of this virus compared with other viruses (Table 1). Foremost among these is HIV's enormous sequence diversity. Because of an error-prone reverse transcriptase, a high propensity for recombination, and an extremely rapid turnover in vivo, HIV's

Table 1. Properties of HIV that hinder vaccine development.

Sequence diversity
Infection of critical immune cells
Immune avoidance
Masking of neutralization epitopes
MHC down-regulation
Immune escape through viral mutation
Counter-immunoregulatory mechanisms
Latency

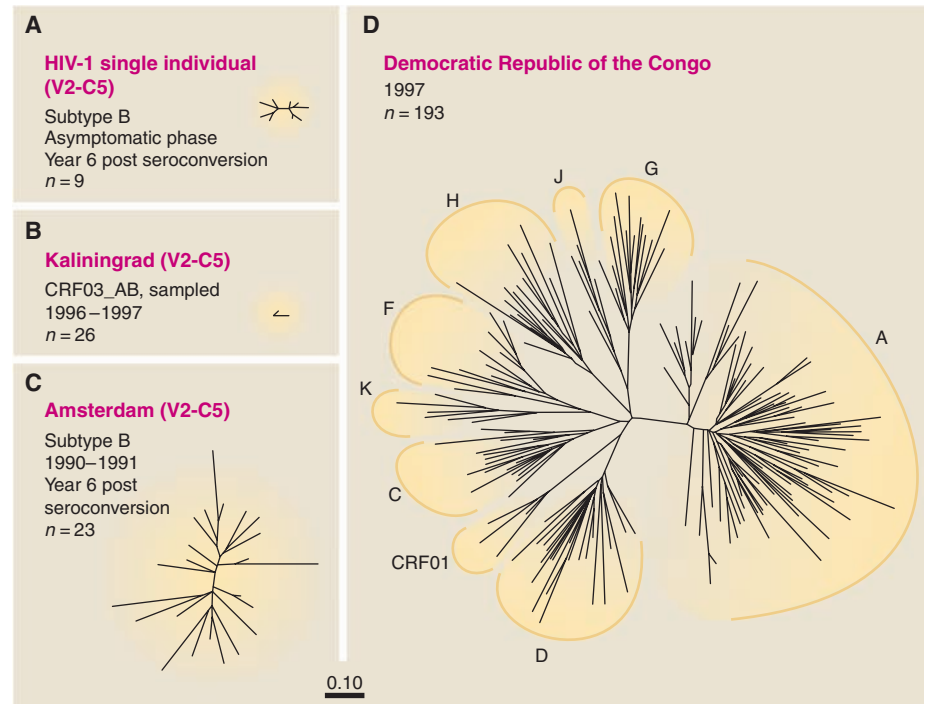


Fig. 2. Representations of HIV diversity under differing circumstances. A comparison of the evolutionary distances of DNA encoding HIV-1 partial envelope gene sequences (C2–V5) through phylogenetic analysis is shown in a “tree” representation. (A) Tree based on nine sequences taken from an asymptomatic individual 73 months after seroconversion of a subtype B infection. This tree is the result of a typical example of sampling of inpatient diversity at one time point. (B) Tree based on HIV-1 circulating recombinant form CRF03_AB sequences derived from samples taken from 26 Kaliningrad individuals. The Kaliningrad epidemic represents a unique situation in which a recombinant form of the virus spread explosively through a population of intravenous drug users and all viruses were extremely closely related to their most recent common ancestor. These samples were collected in 1997 to 1998, less than a year after the strain had been introduced to the population. Drawn at this scale, the tree appears as a dot because of the lack of diversity. (C) Tree based on sequences representing a subtype B epidemic, sampled from 23 individuals residing in Amsterdam in 1990 to 1991. (D) Tree based on HIV-1 V2-C5 sequences sampled in 1997 from 193 individuals residing in the Democratic Republic of the Congo. This is a remarkably diverse set. The HIV-1 subtypes are labeled, and the full spectrum of diversity found in the HIV-1 M group is represented by the epidemic occurring in this region. All panels show maximum likelihood trees generated using a REV model and allowing for rate variation at different sites (23). The genetic distance scale bar is shown. [From (8, 52)].

capacity for mutation and adaptation is enormous (8). There are three different groups of HIV globally (M, N, and O), and group M is further subdivided into nine distinct subtypes and numerous additional circulating recombinant forms. Viruses even within the same HIV-1 subtype may differ by up to 20%, and in places such as Africa where there are multiple subtypes, circulating viruses can differ within the highly variable envelope protein by up to 38% (Fig. 2). Indeed, the amount of HIV diversity within a single infected individual can exceed the variability generated over the course of a global influenza epidemic, the latter of which results in the need for a new vaccine each year. With more than 33 million people currently infected with HIV, and the need for a vaccine that simultaneously protects against all potential exposures, HIV sequence diversity alone represents a staggering challenge.

A further hurdle to AIDS vaccine development is that HIV is an infection of the immune system, specifically targeting CD4⁺ T lympho-

cytes. Within days of exposure, massive infection and loss of memory CD4⁺ T cells ensues, particularly within the gut-associated lymphoid tissue (9, 10) where most of these cells reside. The loss of these cells, which are critical for coordinating effective immune responses, results in considerable immune impairment within the first weeks of HIV infection. Furthermore, bacterial translocation across a damaged intestinal mucosa may even help to drive ongoing CD4⁺ T cell activation and facilitate viral replication, which is most efficient in activated cells (11).

Yet another challenge is that HIV has evolved strategies to avoid immune elimination. Particularly notable examples include the accessory protein Nef, which down-regulates molecules of the major histocompatibility complex (MHC) that are crucial for T cell recognition of infected cells (12, 13), and surface envelope proteins, which incorporate multiple features to avoid antibody recognition (14). HIV also rapidly establishes a latent reservoir of infected lymphocytes by inte-

gration of its genetic material into the host chromosome. This represents one of the greatest challenges because this is an irreversible process that occurs immediately after infection and ends only with the death of the infected cell (15). The virus is immunologically silent in this latent reservoir, but production of infectious virus particles may be subsequently initiated if cells become activated at a later time. The stability of this reservoir means that lifelong infection of the host is maintained, even in the face of potent anti-HIV medication.

All of these features of the virus mean that an optimal HIV vaccine will need to recognize a huge array of diverse viruses, and with sufficient speed to prevent the establishment of a latent reservoir. Failing this, it will need to augment natural immune responses so as to prevent the early wholesale destruction of the CD4 cell population and immunologically suppress virus for the lifetime of the individual, without allowing for immune escape. Such enormous challenges are made even more important by the lack of understanding of the immune responses that can control HIV replication.

The Neutralizing Antibody Problem

A huge gap in HIV vaccine development is the failure to generate an immunogen to elicit effective neutralizing antibodies. Only one antibody-based AIDS vaccine has been taken through efficacy trials thus far, using the gp120 subunit protein as an immunogen, and this vaccine candidate did not elicit antibodies neutralizing field isolates of HIV, did not prevent infection, and did not affect subsequent viral load (16).

Why has there been so much difficulty in generating an immunogen able to elicit neutralizing antibodies to HIV? To be effective, antibodies must bind to structures on the surface of the virus known as spikes, composed of the gp41 transmembrane protein and the heavily glycosylated gp120 surface protein, which exhibit enormous sequence variation among different viruses (Fig. 3). An effective vaccine must therefore induce antibodies able to bind and neutralize not just one or a few viral species, as might be the case with poliovirus, for example, but the millions of different viruses representative of the global pandemic (8). To date, no immunogens have been developed that elicit such broadly neutralizing antibodies (bNAbs). In fact, natural infection, in most cases, does not do much better: Antibodies generated in natural infection clearly exert selection pressure, yet are typically unable to cross-neutralize variants that rapidly arise *in vivo* (17, 18). On the other hand, a few human monoclonal antibodies (mAbs) that neutralize a broad spectrum of circulating HIV isolates *in vitro* have

been derived from infected persons. When these mAbs are passively administered, either systemically or topically, to monkeys that are subsequently challenged with a hybrid AIDS virus that bears HIV spikes and is infectious for monkeys [i.e., simian-human immunodeficiency virus (SHIV)], complete protection against

response will probably be required to control infection. Because the set-point level of viremia after infection predicts both disease progression and the likelihood of subsequent transmission, a vaccine that did not protect against infection could still be effective if it induced sufficient immune responses to dramatically

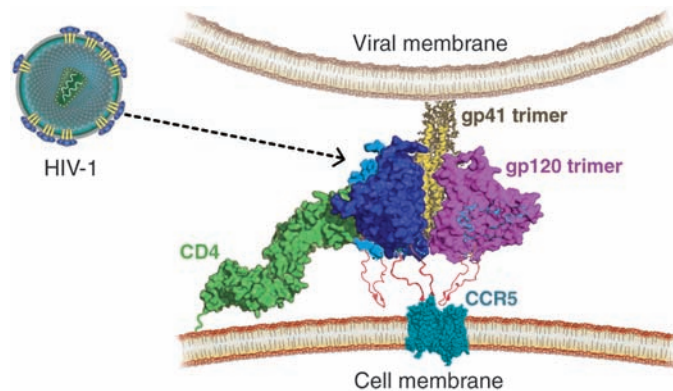


Fig. 3. Schematic of the HIV-1 envelope spike interacting with its cellular receptors on a target cell. Gp120 of the spike interacts with CD4 (shown in green) on T cells leading to conformational changes that allow interaction with the chemokine receptor CCR5. Further conformational changes are triggered in the spike leading to fusion of viral and target cell membranes and transmission of viral genetic material into the target cell. Neutralizing antibodies interrupt the viral entry process by binding to the envelope spike before CD4 binding or after CD4 binding but before fusion. [Modified from (53)].

mucosal challenge can be achieved, although the amounts of antibody required are generally high (19).

Broadly neutralizing antibodies appear to be very difficult to induce through immunization because of the molecular nature of the HIV surface spike. This is a compact structure heavily camouflaged by sugars in which conserved surfaces, like the CD4 binding site that interacts with the viral envelope and is a target of bNAbs, are either buried and very difficult for antibodies to access or only form through conformational changes after gp120 binding. In addition, the viral spike is an unstable structure that is difficult to generate in recombinant form. Indeed, many of the antibodies generated in natural infection target virion debris that forms after disintegration of the mature envelope trimer (20, 21). The ability to generate bNAbs with vaccines has been so poor thus far that most vaccinologists agree that an HIV vaccine able to induce sterilizing immunity will not be possible without some fundamental new breakthroughs. Currently, there are no neutralizing antibody vaccine candidates in advanced clinical trials.

T Cell Immunity and an HIV Vaccine

The second major gap in HIV vaccine development is a failure to identify the nature of T cell responses that could best contribute to vaccine protection against HIV. Should the antibody gatekeepers fail to completely prevent infection, as seems likely, then an effective T cell

lower the steady-state viral load should a vaccinee become infected (Fig. 4). Indeed, at a set-point plasma viral load of 1000 to 2000 RNA copies/ml (lower by a factor of about 30 than the median viral set point after infection), the chances of disease progression and of transmission are markedly diminished [reviewed in (22)]. In the absence of vaccines that induce a neutralizing antibody response, it is understandable that the field has focused on exploring vaccines to induce T cell responses alone (“T cell-only vaccine”).

The rationale for a T cell-based AIDS vaccine stems from data in monkey models and in humans indicating that CTLs play a role in control of HIV. Although these cells do not prevent infection because they only target virus after a cell becomes infected,

their effects on infection are considerable. For example, depletion of CTLs in monkeys with acute or chronic simian immunodeficiency virus (SIV) infection has been shown to lead to a marked increase in viral load (23). In infected humans, there are strong linkages between certain HLA class I alleles and viral control, whereas other class I alleles are associated with more rapid disease progression (24, 25). Because CTLs recognize infected cells by interaction with viral peptides bound to surface HLA class I molecules, the association between HLA alleles and disease outcome has provided strong evidence that CTL responses contribute substantially to immune control during infection. CTL responses exert sufficient pressure on the virus to lead to the emergence of “escape” viruses that have mutations occurring within or adjacent to the peptide sequences recognized (26–28). Further evidence for the importance of the anti-HIV activity of CTLs comes from studies that indicate that CTLs from infected persons can effectively contain HIV replication *in vitro* (7, 29, 30). Crucial for the evolution of the HIV vaccine field were studies that showed strong protection by T cell-based vaccines in a particular monkey model (SHIV 89.6P): Whereas control animals rapidly developed disease on virus challenge, vaccinated animals that had a vaccine-induced CTL response, as measured by assays quantifying surrogate markers of CTL function such as interferon- γ (IFN- γ) Elispot, became infected but had a relatively low set-point level of viremia, with most not progressing to disease

(31, 32). Together these findings provided a rationale for exploring a T cell–only vaccine.

The STEP Trial and the Future of AIDS Vaccines

Based on the monkey model results, the STEP trial (6), the first test of efficacy of a T cell–only vaccine, was initiated in 2004 using recombinant adenoviruses to express HIV Gag, Pol, and Nef proteins. Why the vaccine failed to provide evidence of protection has been widely debated. The simplest explanation is that the vaccine-induced CTL responses were of insufficient magnitude and/or breadth to substantially impact HIV replication in humans. It is worth noting that the hybrid SIV-HIV virus used for challenge, as well as the selection for particular MHC alleles in the monkey model used to support the STEP trial, was considered by some not to be representative of human infection (33, 34). Indeed, an alternative model that had been thought more representative, using animals of differing MHC types and challenge with a pathogenic SIV strain, failed to show protection even for homologous challenge, i.e., when the vaccine and challenge strain are identical (35). In humans, of course, challenge is heterologous.

It should also be noted that the strength of vaccine-induced CTL responses, as estimated in surrogate assays such as the IFN- γ Elispot used in the STEP trial, may not provide a robust indication of functional antiviral activity as compared with more direct measurement of antiviral activity: the cytotoxic killing of cells by CTL. Not only does the IFN- γ Elispot assay fail to directly assess CTL function, but it uses peptide-pulsed cells, meaning that the multiple steps in antigen processing and presentation normally required to sensitize infected cells *in vivo*, or the effects of viral proteins on these processes, are not taken into account. Numerous population-based studies have shown that IFN- γ Elispot responses in infected humans have no correlation with control of viremia (36, 37), raising questions about its suitability as a sole correlate for moving T cell–based vaccines forward. Furthermore, monkeys protected against a robust SIV challenge with live attenuated SIV vaccines have only modest CTL responses when assayed by IFN- γ Elispot assays, underscoring the lack of understanding of immune responses required for an effective vaccine (38).

Overall, it appears that there is still much to be learned about what constitutes functional CTL responses and how to elicit such responses. Other immunologic parameters that are more burdensome to assess may be critical for immune con-

trol and may not have been assessed in the STEP trial. In phase I studies preceding the STEP trial, the breadth of the CTL responses induced by the vaccine was quite narrow, with a median of one Gag peptide epitope targeted per vaccinee and a median of three responses per person when responses to all three expressed vaccine proteins were examined, far less than the median of 14 observed in the context of natural infection, which fail to prevent disease progression (37). Moreover, the specificity of responses may matter: The breadth of the Gag-specific response, but not other responses, is associated with lowering of viral load in chronic infection (39). Studies in infected humans suggest that avidity (the amount of viral peptide required at the cell surface to sensitize cells for lysis) may be key, with lower avidity responses lacking potent antiviral function and being less effective at killing infected cells (29). A function of CTLs that has been associated with *in vivo* containment of virus replication is the ability of these cells to proliferate when they encounter cognate antigen (40). Also important may be the breadth and magnitude of responses at the mucosal level, which may also have been suboptimal in the

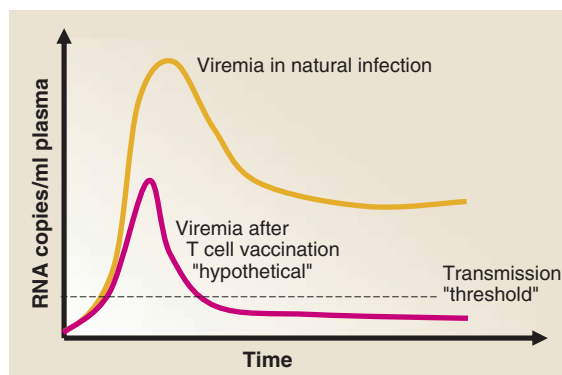


Fig. 4. Potential effect of vaccination on HIV load. After T cell vaccination, peak viral load as well as the set-point level of viremia would hopefully be reduced. The chances of transmission would be expected to be reduced (albeit still possible) at a viral load of 1000 to 2000 copies. Likewise, at very low viral loads, the rate of progression in the vaccinee who becomes infected would ideally be markedly diminished.

STEP trial. Given the many limitations described above, the STEP trial does not provide a definitive answer regarding the potential utility of the T cell–only vaccine concept. Perhaps most crucially, the STEP trial provides little insight regarding the potential success of a vaccine that induces both bNAbs and functional CTLs.

Recommendations for Immediate Attention

The unique challenges posed by HIV, the lack of clear understanding of what constitutes an effective immune response, the inadequacy of current assays to evaluate these responses, and the HIV vaccine failures of the past emphasize that the route forward to developing an effective vaccine is by no means straightforward. Some would

argue it is probable that a vaccine will not be available for use for many years to come. Nevertheless, there is room for optimism. First, for example, long-term vaccine-mediated protection from AIDS virus infection has been achieved in animal models, albeit with live attenuated AIDS virus vaccines considered too dangerous to pursue in humans (41, 42) but demonstrating nonetheless that durable control is attainable. Second, there are some infected individuals who do generate broadly cross-reactive neutralizing antibodies, and these antibodies have been shown to be able to provide sterilizing immunity when infused in animal models of mucosal AIDS virus challenge (19). Finally, there is a subset of infected persons, who have been termed “elite controllers,” who maintain virus load below the limits of detection by the most sensitive commercial assays available, some now for more than 25 years (22). How this is achieved in these individuals is still being investigated but is likely associated with immune control of virus. There are thus reasons to be hopeful.

Several critical issues can be identified to accelerate the development of an effective vaccine:

Solve the neutralizing antibody problem. This problem has not yielded to the more conventional approaches, meaning that a more rational approach based on molecular understanding of the HIV envelope spike structure and its interaction with bNAbs might be the way forward. Key components of this strategy are (i) determination of the specificities responsible for broad neutralization in a wide selection of different individuals, (ii) isolation and characterization of panels of monoclonal bNAbs, (iii) determination of the structure of intact functional HIV spikes alone and in complex with bNAbs, and (iv) rational design and high throughput evaluation of immunogens until a useful set, able to induce serum antibodies capable of neutralizing a majority of circulating viruses, is derived. Such an approach will entail an understanding of the relationship between antigenicity and immunogenicity at a level far deeper than currently exists. There are many variants of this approach, and alternate strategies should also be explored in parallel.

Define the correlates of T cell–mediated control of HIV. Although the first efficacy trial of a T cell–based vaccine failed, despite the induction of HIV-specific CTLs, this does not mean that the entire concept is flawed. Rather, it may be that the T cells induced were suboptimal in their antiviral effect. A critical next step is to develop methods to assess the antiviral efficacy of CTL, akin to the antibody neutralization assay, rather than relying on IFN- γ Elispot assays (30). Not all CTL responses are created equally in terms of the ability to inhibit virus replication (29, 43, 44), and it is critical to define the antigens that elicit the most potent responses. Efforts also need to be expanded to define the role of virus-specific CD4 T helper cell responses in durable HIV containment. Further, given concerns from the recent Merck/NIH vaccine trial, it must be determined

to which extent such responses induced by a vaccine, either directed at HIV or at a vaccine vector, may add fuel to the fire by causing CD4 T cell activation.

Determine mechanisms of HIV control in cases where these occur. Apparent durable control of HIV occurs in about one in 300 persons infected with HIV, and control of SIV occurs in macaques vaccinated with attenuated virus or treated with antiretroviral drugs shortly after infection. Despite some evidence for the involvement of CTL responses, there is strikingly little that is definitively known about mechanisms of control in these cases. Unraveling the mechanisms involved in these cases should be a high priority because this may facilitate the design of immunogens able to elicit the corresponding protective responses.

Define the role of innate immunity in viral containment. The innate immune response also serves as an important first line of defense against viruses, but little is known about its contribution to vaccine success. Accelerated efforts to define the contribution of the innate immune response to HIV control and to determine how innate immune mechanisms can be exploited for adjuvant development and to induce immunologic memory with a vaccine must be a clear priority.

Make best use of animal, particularly monkey, models. There is still no consensus about the most appropriate animal model for HIV vaccine evaluation. Although the SIV mac239/macaque model correctly predicted the failure of the STEP trial (45), it would need to predict a success to be a fully validated model. Nevertheless, a strong argument can be made that this is the best available model at this time, and a reasonable current requirement for any immunogen seeking to be advanced into human trials is that it be able to suppress viral load by a minimum of about 1 to 2 logs (peak and set point) compared with control animals in this model (46). At the same time, vigorous exploration of immunization and protection should proceed in macaques and other animal models to further understanding of potential vaccine candidates.

Define the mechanisms of action of successful human vaccines. Remarkably, there is little consensus as to the precise mechanisms that create a vaccine-induced barrier to infection and/or disease for any of the current successful human vaccines. Antibody induction has been used as a surrogate for immunogenicity, and neutralizing antibodies are presumed to be involved, but the relative contributions of neutralization versus other effector arms remain undefined. Substantial additional work needs to be done on the science of immunization and in exploring the roles of molecules such as interleukin-10 (IL-10) and other immunoregulatory mechanisms in controlling the magnitude of immune responses (47, 48).

Explore alternative approaches to "vaccination." Traditional vaccine approaches have failed thus far, and although rational design

toward a traditional vaccine must be pursued, novel approaches should also be encouraged. The possibility of nonclassical routes to antibody-mediated protection, such as inducing antibodies to the chemokine coreceptor or providing bNAbs passively via a viral vector or stem cell transformation, should also be considered, as should efforts to reverse the integration process (49).

Test candidate vaccine efficacy in humans only when well-defined criteria are met, and test in smaller cohorts. It is critical for the field to establish firm go/no-go criteria to advance products into human efficacy testing. Only vaccines that are clearly superior in immunogenicity and in animal protection studies to previous failed vaccines should be advanced into efficacy trials. Moreover, vaccine candidates should be tested in small screening test of concept (STOC) trials (50) that are by necessity performed in areas of high HIV incidence, requiring a global commitment to this strategy.

Support innovation, interdisciplinary research, and new blood. Given the lack of success thus far, one of the most important issues to address is the need for innovation. The current constraints on NIH funding have a negative impact on innovative research, as study sections tend to take fewer informed risks when funding is tight, despite potential greater rewards. This is particularly a problem for more junior investigators attempting to obtain their first funding. Given the expected long route to an AIDS vaccine, it is critical not to lose this next generation of committed scientists. Funding agencies have the critical task of continuing to support basic innovative scientific discovery and to guard against investing in premature product development. Moreover, restrictions imposed by foundations funding AIDS vaccine research can have an unintended impact of thwarting innovation, to the extent that funding is highly project and milestone driven, which may inhibit rapid changes in direction needed to adapt to an ever-changing body of knowledge. We believe great success would result from a model in which the investment is made in people rather than projects, particularly including scientists from diverse fields not currently engaged in HIV vaccine research, allowing them to focus totally on the task at hand. Given the magnitude of the global crisis, an approach free from traditional academic and private sector constraints seems highly warranted.

Conclusions

With few exceptions, even the most critical and skeptical of scientists, who have stressed the difficulties of developing an HIV vaccine, feel that this is no time to give up (51). However, far more selectivity than hereto in advancing immunogens to large-scale clinical trials is required. The mantra of "the only way we will know if it is likely to be effective is to try it in humans" is not appropriate given the current state of knowledge. Trust in science, making full use of the tool kit that is provided by modern molecular biology, immunology, virology, structural biology, chemistry, and

genomics is crucial. There is a critical need to understand how other vaccines work with a level of detail that has never been necessary for pathogens less adapted to immune evasion. The way forward is without question very difficult and the possibility of failure high, but the global need is absolutely desperate, and this is an endeavor that must be pursued, now with greater passion than ever.

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