The Next Steps Toward a Global AIDS Vaccine

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Despite significant global investment in education, counseling, and behavioral intervention campaigns to stem the transmission of human immunodeficiency virus (HIV) (*1*), the virus that causes acquired immunodeficiency syndrome (AIDS), HIV continues to spread uncontrollably throughout the world leaving devastating public health, social, economic, and political consequences in its wake. The World Health Organization (WHO) now estimates that by the year 2000, at least 40 million persons will be infected with HIV, with more than 10 million deaths attributable to AIDS. Thus, the development of a safe and effective AIDS vaccine has become an urgent international public health priority.

The first generation of candidate AIDS vaccines (that is, those currently in clinical trials) were produced in the mid to late 1980s, when there was significant optimism that a vaccine to prevent HIV would be no more difficult to develop than a vaccine for hepatitis B virus, which closely resembles HIV in its modes of transmission, and for which a successful recombinant vaccine had already been developed (*2*). These first generation AIDS vaccines were predominantly based on the envelope glycoprotein of HIV, which is the principal target for neutralizing antibodies (*3*). These vaccines were focused primarily on prevention of AIDS in North America and Europe by targeting a selected subtype of HIV that predominated in those regions of the world (*4*). Unfortunately, optimism for the potential success of the candidates quickly waned as the following information on the immunobiology and pathogenesis of HIV became available: the capacity for multiple subtypes of HIV to circulate concomitantly in different parts of the world (*4*, *5*); the capacity of the virus to infect by means of cell-free and cell-associated forms (*6*); the potential for selected regions of the envelope glycoprotein to induce immunosuppressive, immunopathologic, or infection-enhancing responses (*7*); and the inability of the first generation vaccines to stimulate or maintain the levels of immune responses likely to be effective against HIV (*8*). The National Institutes of Health AIDS Research Advisory Committee voted this past June to delay any consideration of efficacy trials for two of the leading candidate AIDS vaccines because of the lack of compelling data to suggest that there would be any significant likelihood of success (*9*). In this regard, William Paul, recently appointed director of the federal Office of AIDS Research which oversees the nation's AIDS research agenda, has called for an immediate reappraisal of the entire AIDS vaccine effort.

Scientists and policy-makers associated with the Federal Coordinating Council on Science, Engineering, and Technology's Committee on Life Sciences and Health, in an effort to provide guidance to vaccine manufacturers, have generated criteria for an "ideal" AIDS vaccine (*10*). Briefly, these criteria include the following.

1) The vaccine is safe.

2) The vaccine elicits a protective immune response in a high proportion of vaccinated individuals.

3) The vaccine stimulates both the cellular and antibody components of the immune system because HIV is transmitted by different routes (sexual, intravenous, and perinatal) and by different modes (as cell-free and cell-associated viruses).

4) The vaccine protects against different subtypes or variants of HIV because several variants of HIV are now circulating simultaneously in different geographic regions of the world.

5) The vaccine induces long-lasting protection because exposure to HIV may occur at long intervals after immunization, throughout an individual's sexually active lifetime.

6) The vaccine induces local immunity in the mucosa of the genital tract or rectum, which may be important to impede infection at the site or sites of sexually transmitted HIV infection.

7) The vaccine is practical (for example, with regard to the number of immunizations and cost) for worldwide delivery and administration).

Although the development of an "ideal" vaccine that achieves all of these criteria may be an unrealistic goal, the development of an effective AIDS vaccine that approaches these criteria is a distinct possibility. Moreover, the criteria highlight some of the important scientific and practical issues used in the decision-making process for determining whether any candidate AIDS vaccine shows sufficient promise of being effective that it warrants public sector support for large-scale efficacy trials. On the basis of these general criteria, and particularly points 4 and 5 above which highlight the goal of long-term protection against multiple worldwide variants of HIV, it is not likely that any of the first generation AIDS vaccines will progress any further toward licensure.

Rather than reviewing the scientific challenges for developing an AIDS vaccine and the status of improved second generation AIDS vaccines soon to be entering clinical trials [for review, see (*8*, *11*)], this Policy Forum focuses on four critical areas where intensified public sector efforts to facilitate private sector product development initiatives could significantly accelerate the timetable for the successful development of a safe and globally effective AIDS vaccine.

Providing incentives for expanded biopharmaceutical investment in AIDS vaccine development. Several groups, including the WHO, the U.S. National Academy of Sciences–Institute of Medicine, and the Rockefeller Foundation (*12*), have recently convened meetings aimed at identifying the principal obstacles to accelerating AIDS vaccine development and strategies for filling the gaps in the current worldwide effort. These sessions led to a generalized recognition that the current public policy environment is less than favorable for significant investment by the private sector toward the development of AIDS vaccines.

Currently, less than 10% of the total dollars spent on AIDS research is targeted to the development of AIDS vaccines (*12*). This is a result of several factors, including competing priorities for public sector research programs and economic disincentives for vaccine developers. Commercial manufacturers of vaccines face significant economic disincentives including liability, low profit margins compared with gains from therapeutics, and the potential of price controls. These concerns, when coupled with the scientific challenges of AIDS, have led some manufacturers to eliminate or scale back AIDS vaccine development programs.

To expand biopharmaceutical investment in AIDS vaccine development and thereby maximize the potential for success, we should establish the following public sector initiatives now: increased government funding of diversified global vaccine strategies, tax incentives for AIDS vaccine development, guaranteed purchase of an established quantity of the licensed AIDS vaccine to ensure a reasonable return on investment, orphan drug categorization and assistance with patent protection, and ex-

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clusion of AIDS vaccines from broad pharmaceutical price control legislation. More specifically, creative mechanisms of financial assistance to vaccine manufacturers developing AIDS vaccines could include cost-sharing for manufacturing facilities and construction of collaborative international clinical trial centers. Similarly, targeted tax incentives, particularly in the area of capital expenditures, would serve to shift risk-benefit considerations by the private sector toward greater investment in AIDS vaccine development.

The burden of liability for personal injuries associated with vaccines falls principally on vaccine manufacturers, providing another significant disincentive for the development of an AIDS vaccine (*13*). In May 1990 the Keystone Center convened a group of individuals from each of the major sectors to address this issue and proposed a no-fault compensation system aimed at decreasing the potential for costly litigation (*14*).

This recommendation was considered in the development of the National Vaccine Development and Compensation Act of 1992, introduced by Congressman Pete Stark, which addressed both AIDS vaccine clinical trial liability concerns as well as the more critical liability associated with the marketing of a licensed AIDS vaccine. Some states, such as Connecticut and California, have already enacted statutes limiting the liability of vaccine manufacturers (*15*). However, no legislation to this date has been enacted at the national or international level to significantly shift the burden of liability to a shared burden for all groups that would gain from the rapid development of an AIDS vaccine.

Establishing an international regulatory consensus of criteria for licensure of an effective AIDS vaccine. Scientists and policy-makers have realized that an effective but less than "ideal" vaccine [for example, one that is effective in preventing HIV (AIDS) in 50 to 60% of vaccinated persons instead of the 80 to 95% efficacy achieved for most licensed vaccines] could still have dramatic public health benefits (*16*). Thus, it is very important for commercial vaccine developers to have guidance from regulatory authorities on the levels of efficacy that a vaccine must achieve to be considered for licensure. For example, it is highly unlikely that a vaccine effective against a single subtype of HIV will ever be licensed either in the United States or elsewhere, given the epidemiology of HIV coupled with the mobility of the human population. In this regard, multiple subtypes of HIV have now been identified circulating simultaneously in several countries (*4*, *5*), and this trend will almost certainly continue to occur around the globe.

The efficacy of a global AIDS vaccine will likely be determined by large-scale field trials comparing the effect of the candidate vaccine to a placebo in different geographic and genetically diverse population groups, where different subtypes of HIV are already circulating. Thus, guidance from regulatory authorities on efficacy expectations will have a critical impact on the design of the field trial itself, particularly on sample sizes (the numbers of subjects to be immunized) necessary to determine vaccine efficacy. Is a target of 50 to 60% realistic for licensure? Is protection against 50 to 60% of the major circulating subtypes of HIV sufficient for licensure? Is protection for 1 year, with the requirement for an annual booster immunization sufficient for licensure? These questions and others could be addressed by the U.S. Food and Drug Administration, in collaboration with international regulatory authorities. An international regulatory consensus on the expected levels of vaccine efficacy would accelerate the timetable for licensing a globally effective AIDS vaccine, thereby expediting the accessibility of the vaccine to those worldwide population groups at highest risk for HIV infection.

Expanding the international capabilities to evaluate the efficacy of the best candidate AIDS vaccines. Given the logistical and scientific complexities associated with evaluating efficacy of a global AIDS vaccine, it is very unlikely that more than a few AIDS vaccine efficacy trials will be conducted in the next 10 to 15 years. At the logistical level, if a viable AIDS vaccine candidate were available today, one which potentially could elicit long-term protective immunity against a broad spectrum of HIV subtypes, it is very unlikely that multinational efficacy trials could be rapidly mobilized to evaluate efficacy. The epidemiologic, clinical, laboratory, and socio-political infrastructure required for undertaking large-scale AIDS vaccine efficacy trials simply does not exist at adequate levels in several regions of the world where a high incidence of HIV infection and diverse HIV subtypes currently occur. Although major national and international public sector agencies have recently begun establishing such infrastructure for AIDS vaccine trials, a significantly greater investment is necessary coupled with a more comprehensive level of international coordination. This includes obtaining verifiable incidence rates of HIV infection in potential trial populations, strengthening communication networks for data transmission and storage, training local personnel in clinical trial management, and conducting logistical phase 1 trials with other vaccines such as hepatitis B to test the adequacy of the infrastructure.

The cost of AIDS vaccine efficacy trials has been estimated to be in the range of $20 million to $60 million, depending on the sample size for the trial. The size of the trial depends on several conditions including the incidence of HIV infection in the population or populations being studied, the level of efficacy being sought, and the length of the study (*16*). For example, it has been estimated that for determining if a vaccine is 50% effective in a population with an annual HIV incidence rate of 4%, a 3-year clinical trial would require 1900 subjects. In contrast, if one is looking for a vaccine with 50% efficacy in a population with an HIV incidence rate of 1%, a 2-year clinical trial would require 13,700 subjects.

Although serological differentiation between vaccination and HIV infection can be achieved by selected diagnostic tests and will thus be monitored as one of the primary end points in AIDS vaccine trials, secondary end points (for example, prevention of viremia) may also be important for AIDS vaccine evaluation, because effective AIDS vaccines may ultimately prevent disease and not necessarily prevent initial infection (similar to licensed vaccines for other viral diseases). The secondary end points for AIDS vaccine efficacy trials remain in question because of the scientific uncertainties of identifying surrogate markers for disease progression and the length of clinical latency between asymptomatic infection and disease.

Small-scale safety and immunogenicity clinical trials of first generation AIDS vaccines are currently being conducted in the United States, France, Australia, People's Republic of China, and Thailand, with other phase 1 trials being planned for other countries in the near future (*17*). None of these products will likely enter efficacy trials either in the United States or elsewhere, because of their inability in phase 1 trials to induce or maintain the levels of immune responses likely to be effective against HIV. An opportunity now exists to redirect resources toward strengthening the international vaccine clinical trials infrastructure, so that valuable time is not wasted when the next generation candidate AIDS vaccines become available.

Improving mechanisms to facilitate information transfer to vaccine manufacturers. The domestic and international public health agencies have established numerous activities to facilitate the development of an AIDS vaccine. These activities often provide critical research leads for industries to apply toward product development. For example, the WHO Network for HIV Isolation and Characterization plays a prominent role in addressing the global HIV variability issue, one of the principal challenges in AIDS vaccine development. Similarly, the National Institute of Allergy and Infectious Diseases (NIAID) AIDS Vaccine Working Group reviews the latest data from

a series of NIAID contracted research activities, along with other available data, in an effort to set and prioritize the research agenda for NIAID's vaccine program. Vaccine manufacturers often must wait to review the data until it has been presented at a scientific meeting or published in a scientific journal, which can often cause delays of a year or longer. One way for the public sector to expedite AIDS vaccine development is to institute mechanisms for improved information flow to vaccine manufacturers, without jeopardizing the potential for academic researchers to publish their findings.

Conclusions. The urgency to develop a safe and effective vaccine to supplement ongoing counseling and behavioral intervention programs mandates that newly intensified public sector efforts be instituted to facilitate private sector product development initiatives. Resources should no longer be targeted to first generation vaccines that have little or no potential for success. Rather, efforts should be escalated to provide incentives for expanded biopharmaceutical investment, to establish an international regulatory consensus of criteria for licensure of an effective AIDS vaccine, to expand international capabilities for evaluating the efficacy of the best candidate AIDS vaccines, and to improve mechanisms to facilitate information flow from the public sector agencies to vaccine manufacturers. Although beyond the scope of this Policy Forum, it is also important to note that conservative estimates for the global market of an AIDS vaccine could well exceed 100 million people, making the cost of a global vaccination program in excess of $30 billion (*18*). Thus, policymakers in collaboration with AIDS vaccine manufacturers need to design effective financing strategies to maximize worldwide vaccine delivery and minimize significant lag periods between vaccine development and widespread distribution. Collectively, these efforts would markedly accelerate the potential for development of a safe and effective global AIDS vaccine.

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