Nairobi prostitutes face repeated exposure to HIV.

Whether and when an AIDS vaccine?

The level of scientific understanding required to develop a successful AIDS vaccine is still lacking, although the elements needed to pursue a practical and productive vaccine development program can be defined.

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In the first decade of HIV vaccine development, the independent discoveries in 1983–1984 of the HIV-1 virus that causes AIDS were followed by euphoric forecasts of an effective prophylactic vaccine that would be developed within two years. Yet, a decade later, there is still no vaccine and none in sight. In 1984, the rapid development of an AIDS vaccine seemed a realistic goal in light of the remarkable advances in molecular biology and a sophisticated appreciation of immunology. The highly effective hepatitis B virus vaccine, consisting of a recombinant-produced viral surface antigen, was licensed in 1986 and seemed to be the natural model for a vaccine against the phylogenetically related retrovirus that causes AIDS. It was held that the surface or envelope antigen of HIV (gp160) or its external (gp120) and transmembrane (gp41) components were considered to hold the most promise as effective viral antigens in an AIDS vaccine. Unfortunately, extrapolation from the hepatitis B model proved to be inappropriate because hepatitis B surface antigen is conserved, whereas HIV surface antigen exhibits marked variation. Despite this hypervariability, the dominant focus for HIV vaccine research in its first decade was fixed on a concept that a non-variable region could be found within the native surface antigen of HIV, especially in the hypervariable V3 loop, a principal neutralizing domain of the virus. Hand in hand with this misguided choice of target antigen was the unfortunate intent to achieve a high-level humoral (antibody) response. A high antibody level of broad antigenic specificity might have been of value if sterilizing immunity could have been attained. However, sterilizing immunity is seldom, if ever, achieved even by successful vaccines, and the host must also be able to remove small quantities of virus that breach the mucosal barrier. The tool of molecular genetics, which had been the central driving force in vaccine research in its decade, has now become subservient to the larger view of the biology of AIDS, especially because of progress made in understanding the pathogenesis of AIDS and because of important advances in immunology that were accomplished during the decade.

A year of transition

The year 1994 was a time of transition for AIDS vaccine research. The much-touted HIV surface antigen vaccines offered an insufficient promise to justify the large US-based phase III clinical trials required to establish efficacy, although plans are being pursued to conduct a protective efficacy trial(s) in an area(s) of the world where HIV infection rates are far greater[1]. I believe that the essential data required to judge whether a useful prophylactic vaccine will be probable or even possible are still missing, although it seems reasonable to expect that new initiatives being undertaken in basic and applied research will permit a meaningful prediction by the end of this century. Problems relating to the development of a vaccine against AIDS appear to be phenomenally difficult. HIV is very different from viruses against which successful vaccines have been developed (Table 1). The infrequent spontaneous recovery from HIV infections, progressive destruction of the immune system by diverse mechanisms and the remarkable capacity for antigenic change and immune escape of this virus, give serious cause to doubt whether a vaccine capable of coping with the antigenic diversity of the virus in nature and of stimulating sterilizing immunity will ever be developed. Compounding the problem is transmission of infection by infected cells and by free virus that is polytropic for host cells and has mandatory integration of proviral DNA into the host cell genome. The still incomplete knowledge of HIV pathogenesis and the lack of a reliable animal model combined with poorly defined correlates of immunity render it impossible to predict the protective efficacy of candidate vaccines.

Lessons from comparative biology

Despite the difference between HIV and other pathogenic viruses, studying mechanisms by which other viruses cause disease and of spontaneous recovery or immunoprophylaxis following vaccination can help provide guidelines for developing a prophylactic vaccine against AIDS (ref. 2).

Viral influenza is caused principally by two virus serotypes, A and B (ref. 7). The surface haemagglutinins of type A virus are also very variable in antigenic specificity (although the variation is relatively minor compared with the hypervariability of HIV) and therefore require world wide monitoring of the most prevalent virus variants, and annual or biennial change in the strain composition of the vaccine in order to maintain its effectiveness. Recent work has demonstrated that animals vaccinated with experimental DNA vaccines comprising highly conserved core antigens of circulating influenza viral strains were resistant to challenge by distant strains of virus from different epidemics[3,4]. These findings provide good evidence that single influenza vaccines of the future may provide protection from separated epidemic or pandemic eras and not be subject to the vagaries of the continuing antigenic changes that occur in the surface haemagglutinins of the virus in nature. It is hoped also that the conserved core antigens of HIV will therefore also give rise to vaccines that will circumvent the problems of hypervariability of the HIV envelope proteins.

Review of the pathogenesis of **hepatitis B** (refs 2,5) reveals the importance of clearance of infected hepatocytes by cytotoxic T cells and of neutralization of free virus by antibody. Clearance of infected cells is accomplished principally by cytotoxic CD8+ cells that specifically recognize the nucleocapsid protein core of the virus. A cytotoxic T-cell response is needed to remove infected liver cells but it can also cause severe damage to the liver if the number of infected cells is sufficiently large and the host immune response is excessive. Mutational changes in the nucleocapsid of the dominant virus population may bring about immune escape and clinical remission, although clinical exacerbation follows once an immune response against the immunologic specificity of the mutant virus develops.

The **measles** virus[2,6] like HIV, leads to anergy and an immune deficiency state that may open the way to opportunistic infections, especially when caused by exposure to a heavy dose of measles virus. However, the immune dysfunction or deficiency of measles, unlike that for AIDS, is nearly always reversible, and this reversion is spontaneous. In measles, as in hepatitis B, cytotoxic T cells are essential for clearance of infected cells. A premature shift from the initial cellular response to a humoral response may be important in promoting the immunodeficiency state in measles[7] and in allowing for establishment of the persistent carrier state seen in hepatitis B (refs 2,5).

Thus, the collective lessons learned from studies of comparative pathogenesis[2] of hepatitis B and measles, emphasize the need to achieve both humoral and cellular immunity (including memory cells), with memory, at the mucosal site of viral invasion and well in advance of the actual exposure to the virus. Furthermore, there is no reason to believe that sterilizing immunity can be practically attainable by a HIV vaccine, but there may only be a need for a low-level resident specific immunity to tip the balance in the favour of the host and make it possible to clear the early infection when the virus burden is still low and clearance still possible. A vaccine against HIV must surely include the broadest spectrum of immunologic determinants and the appropriate conserved elements of the nucleocapsid and matrix proteins and may also include certain non-structural proteins as well. Experimental live SIV (simian immunodeficiency virus) vaccines, attenuated through selective deletion, offered hope of inducing high-level immunity against homologous virus[8], although clearly the counterpart live HIV vaccines cannot be considered a viable possibility until real and perceived questions of safety have been resolved[9]. There may well be a special need to achieve and maintain an appropriate balance of immune responses against HIV so that both cellular and humoral immunity are obtained and retained. Such balance might be achieved by use of appropriate adjuvants and by managing appropriate cytokine responses to the vaccine.

Table 1 Hurdles in the way of developing an effective vaccine against AIDS

- Infrequent or rare spontaneous recovery from HIV infection+
- Progressive destruction, by HIV, of the host's immune and nervous systems, gut and other organs+
- Multiple mechanisms causing destruction of the host's immune system and opening the way for opportunistic infections+
- Many viral subtypes (clades) and antigenic hypervariability
- Transmission, by infected cells and free virus, via many routes
- Mandatory integration of the virus into the host cell genome
- Incomplete knowledge of viral pathogenesis
- Lack of reliable animal models and defined correlates of immunity
- Production of CNS disease in an immunologically sequestered site and induction of neoplastic disease

+These points are more properly aspects of AIDS pathogenesis, but are included here because of their relevance to the mechanisms that contribute to the disease and to vaccine development.

Second decade of vaccine development

Further HIV vaccine development will benefit greatly from what was learned during the first decade of HIV vaccine research and particularly from an evolving knowledge of the pathogenesis of HIV and other viruses, and a better understanding of immune function[10–13]. This is not to imply an abrupt alteration in what must be a continuing evolution in concept and practice, but rather to emphasize that many targets and objectives that were only minor during the first decade will become major in the second decade. Examples of objectives that demand particular attention are given in Table 2.

The importance of exploring the requirement of targeting particular and perhaps all antigens of the virus, with the intent to achieve broadest possible immunologic specificity, cannot be overstated (targets 1–3), and the requirement for a pre-established and intact immune response to achieve an earliest possible control of infection has been emphasized in the recent

demonstration that there is no true state of quiescence in HIV infection[10,11]. It is now clear that the virus and immune system are actively engaged in battle from the time of first infection and even during the period of so-called clinical latency. Clearly, it is not reasonable to hope for induction of sterilizing immunity by an AIDS vaccine any more than it is for vaccines against other viruses. Immunity need not be absolute, but the host immune system needs to be so perturbed as to be capable of quick response and effective removal of any and all virus that breaches the barrier on initial exposure to HIV in nature and at this time, even a modest immune response may be capable of ablating minor infection that would otherwise take over.

Sexual transmission of HIV is clearly the most serious threat to the majority of individuals and to the world population. Targets 4 and 5 address the need to establish a specific immunologic barrier at all mucosal surfaces that are likely points of entry for the virus. Simplicity and practicality are paramount for vaccine administration, and it is hoped that successful oral immunization or topical application to mucosal surfaces can be achieved. A continuing development of new methods for presenting and delivering vaccine antigens (target 6) suggests this may be possible.

Attention must also be focused on an effective balance between cellular and humoral responses to the virus. Different cytokine profiles have been recognized[14,15] as favouring one or another of these responses, and it is not beyond the realm of possibility that active or passive cytokine regulatory control can be artificially woven into the pattern of the initial and successive immune responses (targets 8 and 9). How an antigen is presented may be equally as important as which antigen(s) are presented. It will be remembered that the induction of T-helper memory will be initiated on first immunization, and that an inappropriate emphasis on either cellular or humoral immunity to the exclusion of the other may be difficult to alter at a later time. In considering cytokines, suppression of the virus may be achieved by development and passive administration of the soluble viral suppressive factor that is elicited by $CD8^+$ cytotoxic T cells in humans and monkeys[12,16].

Finally, the failure to define the markers for immunity in human HIV infection render it imperative to develop new and more reliable non-human animal models to test vaccines and to predict protective efficacy for human beings. Monkeys will likely continue to be the test animal of choice, and this work may be aided by studies using various transgenic and chimeric animal systems.

Table 2 Targets for achieving HIV vaccine

1. Broad group-specific immunity using conserved core, matrix, envelope and non-structural antigens.
2. Specific cytotoxic T-cell capability for clearing virus-infected cells.
3. Broad group-specific humoral immunity to clear free virus.
4. Resident and retained protective immunity at all sites of possible mucosal invasion by HIV.
5. Mucosal protective immunity, ideally by topical application or oral feeding.
6. Development and exploitation of presentation and delivery systems for simple and complex antigens, including technologies such as liposome presentation, microencapsulation, vectorology, and vaccination with recombinant polynucleotides.
7. Appropriate and retained balance in cellular and humoral immune responses.
8. Licensable immunologic adjuvants that provide appropriate immune responses, with memory.
9. Facilitation of appropriate balance between cellular and humoral responses through active and passive specific cytokine administration.
10. Development and application of more appropriate meaningful animal models and markers for protective immunity.

Achieving the goal

Ideally, new vaccines are developed in the laboratories of large pharmaceutical companies where a critical mass of scientists of diverse and necessary disciplines can be brought together under a single roof[17] to focus on specific objectives. In such an environment, there is direction and coordination of all facets of the initiative with continuous definition, determination and decision as to where the roadblocks lie and how they can be passed. Why is this not already happening?

In the early period following the definition of AIDS, some of the world's largest pharmaceutical companies and a far larger number of smaller biotechnology companies entered into HIV vaccine development with simplistic approaches and an enthusiasm that proved to be naively optimistic. Continued developmental efforts would require very substantial investment of limited resources and would constitute unjustifiable economic waste. Large industry therefore retreated with the intent of re-entering the field when a substantive science base had been established. Accompanying this withdrawal came calls in the scientific community for a return to basics[18] and a reanalysis of the situation[19].

Basic research at the academic level fuels the discovery and descriptive science from which practical applications develop. However, the traditional investigator-initiated research arising in individual laboratories is not an appropriate venue for targeted developmental research and provision needs to be made to direct at least part of the academic research budget to solving specific basic research problems that will facilitate targeted applications. Alternative approaches for developing an AIDS vaccine such as the so-called Manhattan Project have been proposed. This would create a major developmental effort under a single roof. There is no clear consensus that such a project would do more than achieve further waste, however, in view of the present incompleteness of the science base needed for developing a new and difficult vaccine. A further approach is to coordinate more closely the work of separate academic units using a self-directed committee to review, monitor, design and assign individual responsibilities. Such an organization has a precedent of success in the past. For example, the Vaccine Committee of the National Foundation for Infantile Paralysis developed a killed poliomyelitis vaccine during the 1940s and early 1950s, and the Commissions of the Armed Forces Epidemiological Board organized self-directed, contract-supported academic

units engaged to solve critical medical problems of the military during and after World War II. The successes of this approach might no longer be possible because of legal issues and conflicts of interest. Legal issues might be circumvented through an independent contractor chosen by competitive bid. It is important, however, that when the state of the science justifies the initiative, then existing private enterprise with requisite expertise may be expected to fulfill the need for practical development and for production of an AIDS vaccine.

Getting practical

The largest need for an AIDS vaccine is in the populations of the developing and transitional nations where resources, affordability, and simplicity for delivery became the overriding concerns. In particular, it is very important to consider the likely final cost of any vaccine project. There are five critical elements to bear in mind: (1) what is the retained protective efficacy in vaccinees, in the long term; (2) a single or only a few doses should be required for each individual; (3) the affordability of each dose must take account of local resources; (4) the vaccine must be a thermally stable as possible during transport and storage; and (5) administration to patients must be straightforward and preferably oral. With respect to pursuit of an oral-fed vaccine, very recent work describing the production of specific vaccine antigens in transgenic plants once the appropriate antigen epitopes have been defined may be relevant[20]. There is a rapidly evolving technical base that takes plant-derived vaccines well beyond speculative fantasy. No matter what kind of vaccine is developed, it must stand up to the scrutiny of a cost versus benefit analysis.

In summary

It is clear that the problem of developing an effective vaccine against AIDS presents unique difficulties that are compounded by an inadequate understanding of HIV pathogenesis and therefore makes it meaningless to attempt long-term predictions regarding the success or failure of the vaccine initiative. There is, however, the reasonable possibility that even a minor but appropriate perturbation of the host immune system in advance of exposure to HIV virus may tip the balance in favour of the host either by preventing infection entirely or by clearing the infection while it is still in its infancy. This hope may be of special promise for preventing mucosal infection that is the principal mode for HIV transmission.

Important buzz words for the current anti-HIV vaccine enterprise may be simplicity and frugality. Well-defined and straightforward approaches must also keep an eye on the practicality and costs of the vaccine. The wasteful pursuit of products of unestablished feasibility is an economically unsound and unacceptable practice.

While the first decade of AIDS research has not yielded a vaccine, nonetheless, there was an enormous amount learned about the virus, its pathogenesis and its immunology. In this respect, the second decade will benefit immensely from the achievements of the first. However, there has been an impediment to vaccine progress in the shape of governmental regulations and policies that function well for ordinary science but are inadequate when faced with the need for a huge and speedy response to handle emerging pandemics such as that seen with AIDS. The resources that have been committed to solve the AIDS problem have been inordinately small, and the financial restraints have severely restricted the conduct of a targeted vaccine initiative. Vaccines have been and continue to be one of the most cost-effective means for intervention in human medicine. The $125 million budgeted by the National Institutes of Health for AIDS vaccine research for 1995 seems wholly inadequate and seems almost insignificant in the face of the multi-billion-dollar annual cost of AIDS to the world economy and the increasing devastation of the world population in terms of loss of health. Only a targeted research initiative will help to fill in the gaps of knowledge still needed for meaningful pursuit of a program for vaccine development, and should, at least, clarify whether an adequate and practical vaccine is even feasible. I, for one, have an abiding bias, based on past experiences, that success can and will prevail.

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