Scientific and policy challenges to development of an AIDS vaccine

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24 years since the identification of HIV as the causal agent of AIDS, the pandemic continues to outpace attempts at control. The response to HIV/AIDS has been inadequate, and has consisted of crisis management rather than purposeful public health policies, because of the early silent spread of the virus, its high incidence in high-risk populations, its uniformly fatal outcome if not treated, and its global proliferation. However, an unprecedented commitment to control HIV has begun. In 2005, G8 leaders agreed to provide prevention and treatment to all those in need by 2010.1 But, however well intended, a universal treatment paradigm is unsustainable. UNAIDS predicts that more than US$9 billion will be needed in the next 2 years to fund AIDS treatment and care in the developing world alone.2 Estimates suggest that for each person who starts antiretroviral treatment, at least six people are newly infected with HIV.2 Thus, even if existing programmes are rapidly expanded, with increases in financing, infrastructure, and human capacity, the AIDS pandemic will continue to outpace efforts to curtail it unless we can substantially improve prevention strategies and their implementation.3

If we are to control and ultimately end the pandemic, a safe, effective, practical, inexpensive, globally accessible, preventive AIDS vaccine remains the best hope. Even an AIDS vaccine with only 50% efficacy, which covered only 30% of the target population, could avert up to a third of the HIV infections that would otherwise occur, and thus save tens of millions of lives.4 After a burst of attention in the mid-1980s, the search for a vaccine was largely neglected in the 1990s (eg, only about $160 million was spent worldwide in 1994).5 However, in the past few years investment has risen sufficiently to expand the vaccine development effort.6 Nearly $800 million is spent worldwide on research and development towards an AIDS vaccine every year.7

Development of an AIDS vaccine entails unique scientific challenges. The viral infection does not have many of the features that vaccinologists have traditionally used to design successful vaccines, such as induction of natural immunity to disease, known correlates of protection, and validated animal models. These novel scientific challenges demand a large-scale rational vaccine design effort, with increased and sustained financial investment in research and development, and innovative forms of scientific organisation and collaboration. Such an effort is beginning. However, we believe even greater scale, commitment, and innovation will be needed to solve the scientific questions that impede development and testing of improved vaccine candidates. We outline key scientific and policy questions that must be successfully addressed to accelerate development of a safe and effective AIDS vaccine.

Is an effective AIDS vaccine feasible?

Many scientists, including the editor of this journal,6 have asked whether an effective AIDS vaccine is feasible. Evidence in humans and in animal models suggests that immunological protection against immunodeficiency viruses is possible. For example, in the normal course of HIV infection, almost all people have robust and long-lasting immune control of the virus. Initial viraemia occurs at high levels but, with the induction of virus-specific CD8+ T-cell responses, HIV replication is suppressed and maintained at low levels for a long time. In rare individuals, known as elite controllers, HIV-specific cellular immune responses can suppress HIV replication to undetectable levels, sometimes for decades.7,8 In non-human primates, monkeys with depleted CD8+ T cells that are challenged with simian immunodeficiency virus (SIV) have no control of the infection and die rapidly.9,10 which suggests that early virus-specific cellular immune responses control virus replication. Vector-based candidate vaccines suppressed viral load and, in some cases, slowed disease progression in the macaque SIV and SIV–HIV chimera (SHIV) challenge models.11 Immunisation with a live attenuated SIV vaccine robustly protected macaques against subsequent challenge by mucosal or intravenous routes.12,13 Passive administration of broadly neutralising human HIV-antibodies protected monkeys against vaginal challenge with pathogenic SHIV.14,15 Taken together, these findings suggest that delivery of the correct combination of antigens in an effective formulation should enable induction of immunological protection in humans. Whether such protection can be turned into a practical, durable, safe, inexpensive vaccine can only be answered empirically through experimentation.

The primary goal of an AIDS vaccine is to prevent the establishment of persistent HIV infection. Although the correlates of protection against HIV remain undefined, achievement of this goal will probably entail induction of robust systemic (and potentially mucosal) immune responses, with production of antibodies that are high-affinity, long-lasting and broadly neutralising. Existing vaccine candidates have yet to elicit such responses. A secondary goal, which is actively under clinical investigation, is to lower the viral setpoint (the steady state of the viral load achieved after primary HIV infection) in the event of infection and thereby delay
progression to disease, most probably with strong cellular immune responses. An important corollary of either goal would be a reduction in transmission that would slow progression of the pandemic.

**Status of AIDS vaccine development**

The classic live attenuated vaccine approach, used to design vaccines for measles, mumps, and rubella, has not been suitable for HIV because of safety and regulatory concerns. A live SIV vaccine, attenuated by deletion of the nef gene (SIVΔnef), protected monkeys challenged with homologous pathogenic SIV more than 2 years after immunisation, and a retrospective analysis showed that live attenuated SIV was more protective than other vaccine types. However, SIVΔnef establishes a persistent state in the vaccinated host, can revert to virulence in some animals, and was pathogenic to neonatal macaques when given at high doses. An Australian cohort of patients who were naturally infected with nef-deleted HIV eventually had diminished CD4+ T cells and a slow progression towards AIDS. SIVΔnef establishes a persistent state in the vaccinated host, can revert to virulence in some animals, and was pathogenic to neonatal macaques when given at high doses. An Australian cohort of patients who were naturally infected with nef-deleted HIV eventually had diminished CD4+ T cells and a slow progression towards AIDS. For these reasons, live attenuation is not regarded as viable for design of an AIDS vaccine; however, the mechanisms of the protection conferred by the manipulation and attenuation of SIVs are under investigation, and could potentially be mimicked with safer human vaccine strategies.

The classic whole inactivated virus approach is not in use for development of an AIDS vaccine, since studies of such vaccines in SIV preclinical models showed insufficient efficacy. Production of HIV in transformed human cell lines would face strict regulatory challenges; the lability of the HIV virion would complicate large-scale production of whole inactivated vaccine with intact envelope glycoproteins; and it would be difficult to ensure that HIV preparations had been completely inactivated.

Only one vaccine, Vaxgen’s monomeric gp120, has progressed fully through efficacy trials. This candidate did not protect from HIV infection and had no effect on viral load in patients who did become infected.

**Candidate vaccines in the clinical pipeline**

More than 30 candidates, including prime-boost combinations, are in clinical trials. Approaches include nucleic acids, viral vectors, protein subunits, and synthetic peptides (figure 1). Two candidates are now in efficacy trials, with data expected by 2009. The first strategy consists of Sanofi Pasteur’s canarypox vector as a prime, with Vaxgen’s gp120 as a boost. This prime–boost candidate was shown in Phase I/II trials to be safe and immunogenic, with CD4+ T-helper responses and neutralising antibody responses against laboratory-adapted HIV isolates. However, the rationale for the trial has been actively debated, because the gp120 vaccine is not effective alone, the prime-boost combination induced less CD8+ cellular immune response than expected in Phase I/II trials, and preliminary data from small

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**Vaccines from HIV proteins**

- **Proteins**: The vaccine uses HIV proteins (e.g gp 120 on HIV’s surface) as immunogens.
- **Peptides**: The vaccine uses small pieces of HIV protein(s) as immunogens.

**Vaccines from whole HIV**

- **Whole inactivated HIV**: The vaccine contains killed HIV.
- **Live-attenuated HIV**: The vaccine contains weakened HIV.

**Figure 1: Approaches to AIDS vaccine designs**

**Vaccines from HIV genes**

- **Naked DNA**: The vaccine consists of HIV gene(s).
- **Viral vectors**: The vaccine consists of a weakened virus unrelated to HIV, into which HIV gene(s) are inserted. The virus delivers HIV gene(s) to human cells.
- **Bacterial vectors**: HIV gene(s) are delivered via weakened bacteria.

Combining different vaccine designs or different antigens could result in greater, broader, or more prolonged immune responses.
Panel 1: Three scenarios for the Ad5–HIV vaccine candidate in efficacy trials

Vaccine generates protective immunity in most patients, irrespective of pre-existing immunity to Ad5

If this vaccine was shown to prevent HIV infection or suppress viral load, Phase III licensure trials would probably be accelerated. The candidate vaccine could also be used to validate animal models, which would facilitate future candidate screening. As the first proof of benefit of an HIV vaccine in clinical trials, this outcome would be seen as a very positive result.

Vaccine suppresses viral load in a subset of vaccinated patients

If immunity was generated in those who were Ad5-naïve, but response in patients with high-titre pre-existing immunity was insufficient, the additional adenovirus vectors developed for this contingency, which are now in preclinical development (including low-seroprevalent serotypes and chimeric adenoviruses) would be accelerated. If immunity bore no relation to pre-existing immunity, a search for the correlate of immunity would begin. Other vaccines based on cell-mediated immunity would also be tested and improved, in an iterative process.

Vaccine does not reduce viral load, even in patients with robust cellular immune responses against HIV

This was the finding when Ad5-gag SIV vaccination was challenged with pathogenic SIV in macaques. In this scenario other candidates designed to stimulate cell-mediated immunity would probably only be considered for trials if they had quantitatively or qualitatively showed improvement in phase I and II trials and non-human primate challenge studies beyond Ad5. Vaccine discovery efforts would then focus on alternative approaches.

Vaccine candidates have been prioritised on the basis of the proportion of responders and the magnitude of responses in IFN-γ ELISPOT assays, but selection with single cytokines might not adequately identify cellular immune responses associated with protection. Better functional methods to test these responses are in development. Moreover, none of the candidates in the pipeline elicits broadly neutralising antibodies; only a few candidates induce early and local mucosal responses that might help to prevent establishment of persistent infection; and none have the level of protective efficacy recorded in human elite controllers or studies of live attenuated vaccines in non-human primates. We do not even have a clear rationale for the selection of specific HIV antigens for inclusion in vaccine candidates. Novel strategies for vaccine design are urgently needed.

Scientific challenges to AIDS vaccine development

Growing scientific knowledge about HIV and its pathogenesis enable a more rational approach to vaccine development. Panel 2 sets out some of the challenges. We believe that two key scientific problems—that stem from HIV’s hypervariability and its interaction with the immune system, including its propensity for immune evasion—must be solved in the design of an immunogen: (1) elicitation of broadly neutralising antibodies and (2) durable control of HIV infection.

Elicitation of broadly neutralising antibodies against HIV

Several multidisciplinary consortia, including our own, have focused on the difficult scientific challenge of elicitation of broadly neutralising antibodies against HIV. HIV uses a trimeric envelope (Env) complex, composed of gp120 and gp41 subunits, to bind and fuse to its target CD4+ T cell. Broadly neutralising antibodies from sera would probably need to either bind to the mature trimer and thereby prevent engagement of the CD4 receptor, or bind after receptor attachment and impede fusion. However, HIV avoids antibody-mediated neutralisation by several mechanisms, such as glycosylation of Env to prevent antibody access to essential binding sites; formation of trimers to shield epitopes exposed on monomeric surfaces; kinetic and spatial restraints to restrict antibodies to the membrane proximal exposed region; and highly immunogenic variable loops that might act as so-called immunodominant decoys to generate high titres of non-protective antibodies. Despite these defences vaccinologists have identified some broadly neutralising monoclonal antibodies against HIV, and solved the crystal structures in complex with Env. These broadly neutralising monoclonal antibodies provide important clues for vaccine development. They include b12, which recognises an epitope that overlaps the CD4 binding site; 2G12, which binds a complex of
oligomannose on gp120; 2F5; 4E10/Z13; and 447–52D, which recognise a conserved region of the V3 loop. A third strategy is to produce stable intermediates in the HIV binding process that present conserved epitopes to elicit CD4-induced antibodies. The final strategy is to produce epitope mimics of the broadly neutralising monoclonal antibodies, ascertained from structural studies of the MAb-Env complex.

A second important aspect of an immunogen capable of eliciting broadly neutralising antibodies is the induction and maintenance of antibody titres sufficiently high to blunt HIV infection. Passive administration of broadly neutralising monoclonal antibodies to non-human primates proved in principle that broadly neutralising antibodies could prevent the establishment of persistent infection, but suggested that high titres of broadly neutralising antibodies might need to be maintained for protection. However, these non-human primates did not have virus-specific cellular immunity; thus, protective antibody titres might not have to be so high when combined with effective cellular immunity. Once effective immunogens have been discovered, and tested in combination with those that elicit cellular immunity, novel adjuvants could also potentially be needed to achieve sufficiently high titres of broadly neutralising antibodies.

Progress towards elicitation of neutralising antibodies continues to be impeded by six factors, which are the subject of intensive work. We need information on the nature of the transmitted HIV isolate; a greater number of broadly neutralising monoclonal antibodies to inform immunogen design; structural information on the native trimeric Env complex; dedicated high-throughput antigen-design capacity; an in-vitro assay to accelerate immunogen screening; and effective linkages between efforts to design and formulate vaccines.

| Panel 2: Challenges to development of an AIDS vaccine |
| Virus |
| • HIV isolates worldwide are hypervariable |
| • HIV antigens required for protection remain undefined |
| • HIV infects, suppresses, and destroys key cells of the immune system |
| • Animal models for HIV/AIDS are inadequate |
| Immune response |
| • Natural immune responses do not eradicate HIV |
| • Correlates of protective immunity are undefined |
| • The role of innate immunity is poorly explored |
| • Superinfection with a second isolate of HIV is possible |
| HIV transmission and pathogenesis |
| • Multiple forms: HIV is transmitted as cell-free and cell-associated virus |
| • Multiple routes: HIV is transmitted sexually, intravenously, and orally (by breastfeeding) |
| • HIV replication cycle includes integration into the host-cell genome |
| • Short window of opportunity: regardless of route of transmission, HIV rapidly targets gut-associated lymphoid tissue, then amplifies and seeds to other lymphoid organs |
| • HIV incidence, time to setpoint, and required follow-up combine to make AIDS vaccine efficacy trials very complex and long (4–5 years) |

Figure 2 shows the four main vaccine-design strategies that have been proposed to elicit broadly neutralising antibodies against HIV. The first is to generate a candidate that mimics the shape of the mature trimeric Env complex on the virion’s surface. The second is to produce antigen molecules that focus the immune response on cross-reactive immunodominant non-neutralising epitopes. A third strategy is to produce stable intermediates in the HIV binding process that present conserved epitopes to elicit CD4-induced antibodies. The final strategy is to produce epitope mimics of the broadly neutralising monoclonal antibodies, ascertained from structural studies of the MAb-Env complex.

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Production of antigen molecules that mimic the shape of HIV’s surface proteins

Production of antigen molecules that better express the neutralising epitopes

Production of stable intermediates in the HIV-binding process that present conserved epitopes to which a neutralising antibody could bind and inhibit HIV infection

Production of mimetopes, antigens that mimic the shape of epitopes that bind antibodies known to broadly neutralise HIV

Figure 2: Current strategies to design vaccines to generate broadly neutralising antibodies
Control of HIV infection
Suppression of viral load sufficient to slow disease progression and lower infectiousness would both benefit individuals and protect public health. Natural history studies have shown that a viral load of less than 1500–2000 HIV RNA copies per mL of plasma reduced HIV transmission. The design of immunogens for control of HIV infection therefore consists of both the identification of the requisite antigens and their formulation and delivery in a vaccine to provide control of HIV infection.

HIV’s wide genetic variability is due primarily to its rapid replication rate, high mutation rate, and propensity for recombination. An effective AIDS vaccine will need to protect against the divergent strains of HIV in circulation worldwide, and will need to recognise either conserved sequences or a cocktail of protective antigens. Antigens targeted by existing candidates vary according to factors such as the HIV protein from which they are derived; the size of antigenic inserts; antigen modification strategies; source of antigen (newly-transmitted or older virus strain); and other strategies such as inclusion of consensus, ancestral, or mosaic sequences.

Natural history studies do not provide clear direction for selection of vaccine antigens. Data from patients with chronic HIV-infections show that gag, pol, and nef are targets for CD8+ T-cell-mediated immune responses. The breadth of such responses to gag is reportedly important in control of HIV infection, whereas Env-specific cell-mediated immune responses were associated with higher viraemia. The most important control conferred on non-human primates in the live attenuated SIV model included nearly all SIV antigens in the vaccine. Multiantigenic SIV vaccines with gag, tat, rev, and nef provided greater control of SIV infection than SIV gag-only vaccines.

Systematic clinical trials and non-human primate studies will probably be needed to identify the antigens needed for protection. SIV-challenge studies in non-human primates with standard vectors and variation in antigenic inserts for comparison against the live attenuated SIV vaccine could assess whether addition of specific SIV antigens improved protection. Similar studies could be designed to assess novel antigenic designs, including consensus, ancestral, toggle, and mosaic antigens.

The selection of a vaccine strategy for delivery of the requisite antigens poses a major dilemma for vaccine developers. Without defined correlates of immune protection, Phase I/II safety and immunogenicity trials must rank candidates on the basis of immunological assessments that might not equate to control of infection. Similarly, SIV protection studies in non-human primates have both virological and immunological limitations for comparison with HIV infection in people. Some investigators have focused on whether the protection conferred by live attenuated SIV is due to the composite of SIV antigens in the vaccine, its replication-competence, its tropism for gut-associated lymphoid tissue, or other mechanisms. Each of these hypotheses is testable, both in models of SIV in non-human primates and in clinical trials, by the systematic development and assessment of vaccine candidates.

Screening test of concept (STOC) trials, which test the efficacy of AIDS vaccine candidates in individuals at high risk of HIV infection, could aid in generation of preliminary efficacy data to guide the prioritisation process. The primary endpoint of a STOC trial is reduction in viral load setpoint in individuals who acquire HIV. These trials are designed to detect with sufficient power a minimum 1·0 log10 reduction in viral load using the Wilcoxon rank-sum test based on 30 HIV infections. For a population with a 3% incidence of HIV infection every year, about 600–700 participants would need to be enrolled in a STOC trial. Together with HIV phase I/II trials for safety and immunogenicity, and SIV protection studies, STOC trials could accelerate comparisons of prime-boost versus single modality vaccines, multiantigen versus single antigen vaccines, replicating versus non-replicating vectors, and mucosal versus intramuscular delivery.

Policy challenges to AIDS vaccine development
As with any product-oriented effort in research and development, timelines are long and failure rates for individual products are high. Progress relies on sustained financial and political support and policy conditions such as regulatory frameworks and incentives for scientific innovation. More funding is needed for fundamental investigator-driven research, applied research, product development, and clinical testing. Long-term financing commitments for AIDS, such as the Global Fund to Fight AIDS, TB and Malaria and the US President’s Emergency Plan for AIDS Relief represent advances, but largely benefit existing efforts for prevention, treatment, and social mitigation. Similar long-term commitments are needed for new and better tools such as vaccines, microbicides, barrier methods, improved diagnostics, and treatments. New financing mechanisms for the purchase and distribution of vaccines, such as the International Finance Facility for Immunization and the pilot Advance Market Commitment for pneumococcal vaccines, show political will and innovation, and could be tapped to support AIDS vaccine development.

Another challenge is that small biotechnology companies, which generate a large proportion of innovations in health product development, do not have sufficient incentives or resources to invest in AIDS vaccines, because of high scientific risks and the uncertain commercial returns associated with interventions for which the highest need is in resource-poor countries. Funding mechanisms such as public–private partnerships and the NIH’s Small Business Innovation Research Program should expand support to encourage these small companies to join the AIDS vaccine effort. Traditional push mechanisms that reduce the cost of research and...
development, such as subsidies for research, tax credits, and liability protection, are being supplemented by synergistic pull mechanisms that increase revenues, such as market guarantee mechanisms, tax credits on sales, and intellectual property incentives.

Accelerated trials need to move as rapidly as possible into cohorts with the highest incidence of HIV/AIDS so that preliminary efficacy can be established. As most of these cohorts are in stigmatised high-risk groups or in developing countries, vaccine investigators will need expertise in working with these populations to ensure community outreach and participation, informed consent procedures, and high standards of care for trial participants. More developing countries should participate in AIDS vaccine development partnerships, with active involvement of their scientific leaders. Since the readiness of vaccine candidates for clinical assessment tends to be sporadic, long-term vision will be needed to support AIDS vaccine research sites—eg, epidemiological studies could be designed for populations in which it is later planned to test specific AIDS vaccines, or other products such as microbicides or vaccines (or even combinations of various prevention methods) could be tested with these populations during the period before candidate vaccines become available. Such a strategy should enable sustained investment in human resources, capacity building, and equipment at such sites.

Help for countries with a high rate of HIV infection to acquire the ability to more quickly review and approve vaccine trials should increase the capacity for clinical testing. In Rwanda, Zambia, and India shared learning between testing sites accelerated approval and enrolment times. Sharing experiences across vaccine trial sponsors should further increase speed. But in all countries regulatory challenges are likely to accompany approval criteria for vaccines with low efficacy or trials with unconventional clinical endpoints such as lowered viral setpoint and consequent delayed disease progression. The potential ability of replicating viral vectors to mimic the effects of live attenuated vaccines suggests that such vectors should be developed and moved rapidly into clinical trials. This will raise tough issues for regulatory agencies that will have to develop specific guidelines for testing of such vectors and reassess their risks and benefits.

The way forward

HIV could be the most formidable adversary for vaccine development yet, because of unique scientific challenges: uniformly fatal outcome, the absence of natural immunity, the virus’s genetic variability, and its ability to target the immune system. The correlates of protection against HIV remain undefined, but an effective AIDS vaccine will probably need to generate both broadly neutralising humoral immunity and sustained cellular immunity to more than one HIV epitope to deal with genetic variability.

A renewed effort based upon rational vaccine design is beginning with a doubling of resources during the past 5 years. Major AIDS vaccine research agencies have come together as the Global HIV Vaccine Enterprise,26 and have launched collaborative initiatives such as the International AIDS Vaccine Initiative’s Neutralizing Antibody and Live Attenuated Consortia, the NIH’s Vaccine Research Center and Center for HIV/AIDS Vaccine Immunology, the Gates Foundation’s Collaboration in AIDS Vaccine Discovery, EuroVacc, and the South African AIDS Vaccine Initiative.

AIDS vaccine research now needs to be integrated into overall AIDS and public health priorities, so that increases in funding will be sustained. To solve these difficult scientific challenges, we must recruit new institutions and technologies into the existing global AIDS vaccine research and development effort, even if they have no track record in AIDS vaccine research. Scientific methods and expertise from different disciplines, such as systems biology, nanotechnology, genomics, proteomics, glycobiology, molecular immunology, and structural biology, and from the intersections between such disciplines, will be crucial. Progress could be accelerated by creation of incentives for innovation, participation of novel players, and informed risk-taking.

Moreover, the repetitive attempts to base a vaccine on the cellular immunity approach need to be complemented by strategic efforts to find solutions to the challenges of how to elicit neutralising antibodies and control HIV infection. We also need to understand whether mucosal immune responses are necessary for protection; if so, we need to learn how to best elicit such responses. These systematic attempts to solve the most urgent scientific challenges must be supplemented by an iterative process to move promising candidates into clinical testing to establish and improve efficacy. This combination of rational vaccine design and coordinated scientific empiricism represents the beginning of a renaissance in AIDS vaccine development, and offers the greatest potential for shortening the time to a safe and effective vaccine.

Contributors

Both authors revised and edited the manuscript, and have seen and approved the final version.

Conflict of interest statement

As senior management of IAVI, we are committed to and actively involved in the development of safe, effective, and accessible AIDS vaccines.

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References

Viewpoint


