AIDS VACCINE BLUEPRINT 2008

A Challenge to the Field,
A Roadmap for Progress
IAVI's mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world.

Imagine a World Without AIDS

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IAVI gratefully acknowledges the valuable contributions of our colleagues who made it possible to accurately assess the field and provide recommendations to catalyze change to improve AIDS vaccine development. IAVI, as a member of the Global HIV Vaccine Enterprise, sought feedback from members of the Enterprise Coordinating Committee and selected members of IAVI’s Scientific and Policy Advisory Committees, as well as a number of thought leaders in the field. Their input was invaluable—although in the end, the responsibility for the report remains with the IAVI team.

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The quest to develop an AIDS vaccine is at a pivotal moment. Scientific evidence supports the idea that an AIDS vaccine is possible. However, the high-profile failure in September 2007 of an AIDS vaccine candidate in an advanced trial has generated a broad consensus among those working in the field that it is time to evaluate carefully where and how best to direct the available finite resources. The International AIDS Vaccine Initiative (IAVI) has, through its biennial Blueprints begun in 1998, monitored the state of the global AIDS vaccine effort. In this latest installment (available in full at www.iavi.org/blueprint2008), we challenge the field to reset both expectations and focus.

The ultimate goal remains the same: development of a safe, effective, preventive AIDS vaccine that can be licensed and made accessible to all, throughout the world (Figure 1). We must acknowledge, however, that while AIDS vaccine research has yielded enormous advances in knowledge (Table 1), it has also provided many lessons in humility. Achieving our ideal result will take more time and ingenuity than any of us originally imagined.

Although we have evidence of feasibility in animal models, studies have yet to demonstrate that an AIDS vaccine candidate benefits humans. While it may appear obvious, the next major advance on the way to the ultimate goal will be the first demonstration that a candidate benefits humans, either by preventing HIV infection or by delaying the onset of disease in those who become infected after vaccination through exposure to the virus. This proof of benefit, even if it does not lead directly to a licensed vaccine, would demonstrate the feasibility of an AIDS vaccine. This intermediate achievement would help to solve key riddles that have impeded advances, give researchers a platform on which to improve, and attract investment and creative energy to the field.

How, then, to achieve this intermediate goal? This Blueprint proposes that those of us engaged in the quest for an AIDS vaccine divide our mission into components that are more readily attainable than the ultimate prize—a finished vaccine—or even than the intermediate goal of proof of benefit in humans. In suggesting what some of those components should be and laying out a roadmap of tangible proposals on how to achieve them, IAVI, as a founding partner of the Global HIV Vaccine Enterprise, hopes to stimulate discussion among all stakeholders about the way ahead and to promote a resetting of priorities. Stakeholders could tackle the goals and milestones that most closely align with their core capabilities.
The World Needs an AIDS Vaccine

How an AIDS Vaccine Would Work

Vaccines are a highly effective way to train the immune system to combat pathogens. Researchers are currently exploring multiple strategies in an effort to develop an effective AIDS vaccine.

1. **To generate an immune response against HIV**, researchers are looking at different ways of introducing into humans harmless pieces of the virus, known as immunogens, that cannot cause HIV infection. Some approaches involve using other viruses, bacteria, or DNA as vectors for HIV immunogens.

2. **Following vaccination**, the immunogens are captured by cells, such as dendritic cells, and are presented on their surface. These cells then travel to the lymph nodes where they trigger cellular and antibody immune responses against the virus.

3. **Lifelong protection** against a pathogen is possible because of activation of the adaptive immune responses, which results in immunological memory. Memory T and B cells are generated in response to a vaccine, just as they are during an actual infection, and persist in the body. Inducing memory T and B cells will be critical for vaccine-induced protection against HIV.

4. **Vaccine-induced memory cells** become activated when the immune system encounters the actual virus—in this case HIV—in the future. Memory cells allow the immune system to respond much more rapidly and robustly, enabling the immune system to block the establishment of an infection.

Figure 1 Immune responses after vaccination
We consider two of the Blueprint recommendations especially noteworthy. The first is practical: to shift resources away from the majority of vaccine candidates currently in the pipeline on the basis of their probability of success, and steer those freed resources toward solving the key scientific problems impeding the development of an improved pipeline. The second is strategic: in addition to increasing efforts to discover how to induce broadly neutralizing antibodies to HIV, to use rational design to strengthen the effort to discover how to effectively induce cell-mediated immunity to HIV. This would entail greater exploration of potentially more effective viral vectors for the delivery of HIV immunogens, including replicating vectors, the development of which raises novel questions for regulatory agencies. It would also entail ramping up efforts to determine what HIV antigens (i.e., what pieces of HIV) should be included in an AIDS vaccine. Until now, the field has focused more on how to deliver such antigens, and less on which antigens are required.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Key Findings in AIDS Vaccine Design and Development</th>
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</table>
| **First Wave 1983-1994** | - Human immunodeficiency virus (HIV) identified as the cause of AIDS  
  - First demonstration of antibody and cell-mediated immune (CMI) responses against HIV  
  - HIV Env (gp120) protein identified as the primary target for antibodies  
  - CD4 identified as the primary host cell receptor for HIV  
  - Diagnostic assays developed that measure antibody and CMI responses to HIV  
  - First clinical trial of an AIDS vaccine candidate  
  - First viral vector-based AIDS vaccine candidate designed  
  - HIV genetic hypervariability first described  
  - Simian immunodeficiency virus (SIV) discovered  
  - Prime-boost vaccination strategy for HIV proposed  
  - First-generation Env-based vaccines elicit antibodies that neutralize laboratory-adapted HIV strains but not circulating primary isolates  
  - Clinical centers established in the developing world provide HIV incidence and genetic sequence diversity data  
  - Live-attenuated SIV protects against disease after challenge with pathogenic SIV  
  - First AIDS vaccine trials in the developing world conducted |
| **Second Wave 1995-2007** | - Broadly neutralizing monoclonal antibodies against HIV identified  
  - CCR5 identified as co-receptor for HIV  
  - Refined and validated assays developed to measure viral load and CMI responses against HIV  
  - HIV-specific CMI responses correlated with viral control  
  - Broadly neutralizing monoclonal antibodies against HIV protect against challenge with chimeric simian/human immunodeficiency virus (SHIV)  
  - Scientific consortia established to focus on HIV neutralizing antibody problem and other specific research problems  
  - First efficacy trial of Env-based vaccine fails to protect against HIV infection or suppress viral load  
  - Structures of broadly-neutralizing monoclonal antibodies bound to Env determined  
  - HIV shown to deplete CD4+ T cells and amplify in gut-associated lymphoid tissue (GALT) very early after infection  
  - Efficacy trial of leading vaccine candidate designed to elicit CMI responses shows no evidence of effectiveness |
The World Needs an AIDS Vaccine

The AIDS pandemic is one of the greatest global health crises of our time. In the 25 years since HIV was first identified as the cause of AIDS, an estimated 23 million people have died of the disease and 33 million more are currently living with HIV. Almost 7,500 people become infected with HIV everyday.

The world’s response to HIV and AIDS must be comprehensive, encompassing education, prevention, treatment, care, and support, and must include strategies to further increase access to life-prolonging treatment for all who need it. With the same urgency, there must be more investment to develop better technologies for the future: drugs and diagnostics for treatment, microbicides, and other methods for prevention, in particular vaccines that can control or, better yet, prevent HIV infection. Vaccines are the most effective public health measure for controlling epidemic infectious disease; millions around the world owe their lives to them.

HIV, however, is the most formidable pathogen for which vaccine development has ever been attempted. In 25 years we have come to know more about the basic biology of HIV than any other pathogen. Yet an AIDS vaccine remains elusive. This is due primarily to the scientific challenges that HIV poses for vaccine development.

### TABLE 2 Scientific Challenges in AIDS Vaccine Development

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Description</th>
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| **HIV is a retrovirus**                         | • HIV integrates its genetic material into human chromosomes inside the cells it infects.  
• HIV establishes a persistent and lifelong infection within the first 7 to 10 days after infection.  
• This gives only a brief window of opportunity for vaccine-mediated immune responses to act. |
| **HIV does not induce protective immunity**     | • There is no documented case of recovery from HIV infection.  
• The correlates of protection in HIV infection remain unknown.  
• Without a correlate of protection, the field does not have a validated marker to determine whether one candidate is more effective than another. |
| **HIV is hypervariable**                        | • HIV has an error-prone reverse transcriptase that, combined with a rapid replication rate, leads to a high mutation rate.  
• HIV has a high capacity for recombination.  
• HIV hypervariability enables "immune escape".  
• Hypervariability renders HIV a moving target—by the time a vaccine candidate has been designed and tested, the virus might well have mutated significantly. |
| **HIV has immune evasion mechanisms**           | • The virus outer surface protein and neutralizing antibody target, gp120, is especially well adapted to avoid the immune system:  
  ◦ it is decorated with a dense matrix of carbohydrates that shield it from neutralizing antibodies;  
  ◦ its binding sites to the main host cell receptor (CD4) are normally concealed from neutralizing antibodies;  
  ◦ it has decoys to shift the immune response away from generating broadly neutralizing antibodies.  
• HIV targets the very immune cells that are needed to keep infection at bay. |
| **HIV infects humans**                         | • There are no ideal animal models for HIV infection and AIDS.  
• The best surrogate animal model is the SIV/rhesus macaque model, but SIV is not HIV and macaques are not humans. |
| **HIV is a sexually transmitted infection**     | • HIV infects by multiple routes (genital tract, rectal, oral, intravenous) and forms (cell-free and cell-associated virus), so robust mucosal immunity may be required.  
• Sexually-active adolescents through to the elderly can be infected, so an effective vaccine will have to induce durable, long-term protective immunity. |
including the brief window of opportunity for a vaccine to work (Figure 2) before HIV establishes a lifelong infection, and the enormous variability of HIV circulating worldwide (Figure 3).

Despite these challenges, scientific research suggests that an AIDS vaccine is attainable. Studies show that broadly neutralizing antibodies from HIV-infected individuals can completely protect nonhuman primates (NHPs) from infection with immunodeficiency virus. Furthermore, nonhuman primates vaccinated with a weakened or live-attenuated form of SIV, HIV’s simian cousin, are protected from disease when exposed to matching strains of SIV. In humans, the immune system naturally keeps HIV in control for a decade or more before symptoms of disease emerge, and certain HIV-infected individuals called elite controllers manage that feat for decades. This suggests that HIV is vulnerable to the weapons of the immune system, so if we can better understand the specific weapons and specific vulnerabilities of HIV that are at play, we should be able to design a vaccine that will give the immune system the necessary, definitive advantage.
The history of AIDS vaccine development may be viewed as two waves, with some overlap, with a third wave just now beginning. During the first wave, scientists followed a path similar to the one that led to the successful hepatitis B vaccine: identify the part of the virus (called the antigen) that elicits neutralizing antibodies, purify it, and formulate it to create an agent called an immunogen that is capable of eliciting similar antibodies in the body.

After evidence emerged suggesting this approach would not work, a second wave of AIDS vaccine development, beginning in 1995, marked a shift away from antibodies to the other arm of the immune system, cell-mediated immunity (CMI). The antibody arm of the immune system destroys pathogens before they take hold in the body. The CMI arm dispatches T cells to destroy cells in the body that have been infected by a successfully invasive pathogen. Some researchers hoped candidates designed to activate the CMI arm would prevent HIV infection. Others thought a more realistic goal would be reduction in the amount of virus (i.e., viral load) circulating in people who became infected after vaccination (Figure 4). This reduction would delay the onset of disease and decrease infectiousness. Today, nearly all of the approximately 30 AIDS vaccine candidates in the clinical pipeline (Table 3) are focused on CMI responses, creating a consensus among researchers that the field has swung too far in one direction.

The announcement in September 2007 of the failure in a Phase IIb trial of Merck’s CMI candidate, considered by many as the best candidate in the pipeline, can be seen as the beginning of a third wave. The field is now focusing more on finding answers to key questions that impede AIDS vaccine development. There is a new emphasis on basic research to gain a better understanding of the underlying principles fundamental to HIV and its interaction with the human immune system. In translational research, the third wave has seen an increased focus on solving the HIV neutralizing
### TABLE 3  AIDS Vaccine Candidates in Clinical Trials

<table>
<thead>
<tr>
<th>Protein Prime + Vector Boost</th>
<th>Phase III</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Canarypox Clades B, E, gp120 prime</td>
<td>US Department of Defense, Ministry of Public Health Thailand, National Institute of Allergy and Infectious Diseases, That AIDS Vaccine Evaluation Group, sanofi pasteur, VaxGen</td>
<td></td>
</tr>
<tr>
<td>DNA Vectors +/- Vector Boost</td>
<td>Phase I/II</td>
<td></td>
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<tr>
<td>Clade B’C + Electroporation</td>
<td>International AIDS Vaccine Initiative, Ichor, Aaron Diamond AIDS Research Center</td>
<td></td>
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<tr>
<td>DNA polyepitopic, MVA boost</td>
<td>Epimmune Pharmexa, Bavarian Nordic</td>
<td></td>
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<tr>
<td>Clade B, MVA boost</td>
<td>GeoVax, US Military HIV Research Program</td>
<td></td>
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<tr>
<td>Multiclade A, B, C, Ad-5 boost</td>
<td>National Institute of Allergy and Infectious Diseases</td>
<td></td>
</tr>
<tr>
<td>Multiclade A, B, C, MVA boost</td>
<td>Karolinska Institute</td>
<td></td>
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<tr>
<td>Clade B’C, MVA boost</td>
<td>Johns Hopkins University, Guangxi, Changchun Baike</td>
<td></td>
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<tr>
<td>Clade C, NYVAC boost</td>
<td>EuroVacc, Agence national de recherches sur le sida et les hépatites virales</td>
<td></td>
</tr>
<tr>
<td>Clade B + IL-12, IL-15, peptide boost</td>
<td>Wyeth</td>
<td></td>
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<tr>
<td>DNA Clade C, MVA boost</td>
<td>South African AIDS Vaccine Initiative</td>
<td></td>
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<tr>
<td>DNA Clade A, E, FPV boost</td>
<td>The HIV Netherlands Australia Thailand Research Collaboration</td>
<td></td>
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<tr>
<td>Pennvax-B</td>
<td>University of Pennsylvania, VGX Pharmaceuticals</td>
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<tr>
<th>Viral Vectors</th>
<th>Phase I/II</th>
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<tbody>
<tr>
<td><strong>Adenovirus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad-6 Clade B</td>
<td>Merck</td>
<td></td>
</tr>
<tr>
<td>Ad-35 Clade A, +/- Ad-5 (prime or boost)</td>
<td>National Institute of Allergy and Infectious Diseases, Vaccine Research Center</td>
<td></td>
</tr>
<tr>
<td>Ad-26 Clade A</td>
<td>National Institute of Allergy and Infectious Diseases, Harvard University</td>
<td></td>
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<tr>
<td><strong>Poxvirus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALVAC-HIV</td>
<td>National Institute of Allergy and Infectious Diseases, sanofi pasteur</td>
<td></td>
</tr>
<tr>
<td>MVA Clade A, E</td>
<td>Walter Reed Army Institute of Research</td>
<td></td>
</tr>
<tr>
<td>MVA multiantigen</td>
<td>Bavarian Nordic</td>
<td></td>
</tr>
<tr>
<td>MVA Clade C</td>
<td>International AIDS Vaccine Initiative</td>
<td></td>
</tr>
<tr>
<td>Vaccinia multiclade (DNA &amp; protein cocktail)</td>
<td>St. Jude Children’s Research Hospital</td>
<td></td>
</tr>
<tr>
<td><strong>Proteins</strong></td>
<td>Phase I/II</td>
<td></td>
</tr>
<tr>
<td>Gp140 Clade C mucosal</td>
<td>St. George’s, University of London</td>
<td></td>
</tr>
<tr>
<td>C-terminal p17, full p24, fragment of gp41 with polyoxidonium adjuvant</td>
<td>Institute of Immunology, Moscow</td>
<td></td>
</tr>
<tr>
<td>Adjuvanted Gag, Pol and Nef</td>
<td>GlaxoSmithKline</td>
<td></td>
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The World Needs an AIDS Vaccine

antibody problem. But a vaccine that elicits antibodies alone probably won’t suffice; studies with other retroviruses in which both prevention and control have been achieved indicate that both neutralizing antibodies and CMI responses are required. Thus, CMI approaches must still be improved. New strategies, greater innovation, and a long-term commitment will be required for success.

LOOKING FOR CLUES THROUGH GENE TRANSFER

A recent innovative concept now in preclinical testing aims to use vector-mediated gene transfer to maintain large amounts of broadly neutralizing antibody over long periods of time.

1 IDENTIFICATION
A broadly neutralizing antibody (NAb) (or antibodies) that can neutralize a majority of the HIV strains worldwide is selected.

2 INSERTION
The genes that code this NAb are inserted into a vector to create a delivery system.

3 INJECTION
After injection, the vector establishes itself in the body.

4 PROTECTION
The vector produces a constant supply of NAb in the blood to prevent infection on exposure.

Source: Dr. Philip R. Johnson Research Laboratory, The Children’s Hospital of Philadelphia

Figure 5 A novel approach to antibodies
1. Solve the HIV Neutralizing Antibody Problem

An AIDS vaccine is unlikely without a solution to the HIV neutralizing antibody problem. Most vaccines work by neutralizing the virus with antibodies. However, scientists have not yet determined how to elicit antibodies that neutralize the many strains of HIV worldwide. Although significant progress has been made (Figure 6), we believe the pace of discovery is too slow, given the urgency to develop an effective vaccine. A paradigm shift is required in terms of the scale of resources, time commitment of leading researchers, new ideas, and innovation from within and outside the field. We propose the scaling up of programs at consortia, laboratories, and discovery centers that focus on the HIV neutralizing antibody problem, and that they receive long-term funding commitments. These programs should aim to achieve a preliminary goal of identifying and advancing to clinical trials an immunogen that neutralizes a substantial proportion of circulating HIV strains, a suggested initial benchmark being at least 50 percent of moderately resistant HIV isolates. The full Blueprint lays out specific milestones we believe should be undertaken to reach this goal.

2. Solve the HIV Cell-Mediated Immunity Problem

One of the lessons of the Merck trial is that inducing effective CMI responses will be more challenging than originally envisioned and perhaps as challenging as solving the neutralizing antibody problem. A number of tacks are called for:

- **Determine the mechanisms responsible for control of HIV infection by elite controllers.** A major gap exists between the resources devoted to studying elite controllers and the attention that should be paid to them. As with the neutralizing antibody problem, we propose building on established programs that focus on studying the control of HIV infection and ensuring that they have comparable long-term support. An important aim of these programs would be to define what sites on HIV the T cells (CD4+ and CD8+) of elite controllers are targeting to control infection.

- **Determine the mechanisms responsible for control of SIV infection by live-attenuated SIV.** Live-attenuated SIV is the only vaccine approach that consistently provides a thousand-fold reduction in viral load when the test animal is challenged with the same (homologous) strain of SIV from which the vaccine was made. There is no serious consideration given to developing a live-attenuated AIDS vaccine because of the possibility that the attenuated virus could revert to its disease-causing form. Live-attenuated SIV is used as a model to understand how the immune system in nonhuman primates is helped by the administration of live-attenuated SIV, so that this information can be used to design improved AIDS vaccine candidates for humans. A significant problem...
has been securing the resources required to conduct these studies on a large scale. The Blueprint proposes the dedication of sufficient numbers of nonhuman primates to AIDS vaccine discovery and development to allow the conduct of large-scale studies that can reach statistical significance. Programs should aim to determine the mechanism by which live-attenuated SIV protects nonhuman primates against SIV.

- Implement a new clinical research program to determine the optimal immunogens for eliciting cell-mediated immunity. Much of the focus of AIDS vaccine clinical research has been on vectors and delivery systems for immunogens, rather than on what the optimal immunogens are themselves. Some questions can be addressed using immunogens currently in hand. But as new leads come from elite controllers, live-attenuated SIV models, and other studies, additional immunogen development and testing in humans will be necessary. Dedicated clinical research should now be undertaken to systematically assess the required immunogens. The field should aim to develop and to systematically test in clinical trials a set of immunogens to optimize CMI responses against HIV.

3. Improve the Pipeline

- Broaden and rationalize approaches to vectors for use in AIDS vaccines. It is likely that the impressive level of protection afforded by live-attenuated SIV is at least partly due to its replicative nature, since SIV that has been genetically engineered so that it is limited to a single cycle of infection is not nearly as protective (Figure 7). Thus, the Blueprint recommends accelerating the development of live replicating vector-based vaccines, which have received little attention in the field so far (Figure 8). Accelerating their development will raise novel questions for regulatory agencies, making risk-benefit calculations particularly important. It is also vital to prioritize among replicating as well as non-replicating vectors. A preliminary goal for the field would be to advance to clinical development AIDS vaccine vectors that demonstrate improved efficacy against SIV challenge compared to the Merck Ad5 candidate.

- Conduct small efficacy trials on leading candidates that achieve predetermined criteria. In AIDS vaccine research, human efficacy data is essential, especially since there are no validated animal models and since scientists do not know the correlates of protection for HIV (i.e., the specific immune responses that must be present to protect an individual.

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LEARNING FROM THE LIVE-ATTENUATED MODEL
This figure shows composite results of various SIV challenges in nonhuman primates. An understanding of the workings of live-attenuated SIV and the limitations of single-cycle SIV may help guide AIDS vaccine design. Live-attenuated SIV vaccine, which is persistently replicating, reduces viral load to undetectable levels and protects from SIV infection. Single-cycle SIV vaccine (SIV that has been altered to replicate only once) provides marginal suppression of viral load and thus is not protective. This suggests replication is important for an effective AIDS vaccine.

![Figure 7 The benefits of replication](image-url)

Evans DT, et al. J. Virol. 79, 7707, 2005
from infection). Relatively small Phase IIb trials, including Screening Test of Concept (STOC) trials—which can be set up rapidly and completed quickly and can determine whether a candidate vaccine provides benefit—would provide initial efficacy data while maximizing resources. Such trials and a prioritization of candidates to test in them would greatly benefit from the development of universally accepted, pre-determined criteria for advancing candidates from Phase I to small efficacy trials. We suggest that candidates entering human efficacy testing should, at the very least, elicit stronger or differing T-cell responses in humans, show better efficacy in nonhuman primates than the Merck Ad5 candidate, or meet the antibody neutralization criteria described earlier. One of the lessons of the Merck trial was that the common way of measuring a vaccinee’s response to a CMI candidate—by the gamma interferon ELISPOT test—did not accurately predict whether the candidate would be efficacious. Assays that are more predictive of a vaccine candidate’s actual effect on the immune system need to be developed and validated in these small efficacy trials.

- Trim the product development pipeline of less promising candidates. Most of the AIDS vaccine candidates in the current pipeline test DNA and viral vectors, alone and in combination, with the goal of stimulating CMI responses to suppress viral load. We believe stakeholders should review their portfolios and drop candidates considered to have a low probability of success. Resources should
then be redirected toward more promising approaches or toward solving the key scientific challenges. Preclinical and clinical comparison against the Merck Ad5 vaccine would facilitate prioritization and should be encouraged. It is imperative that the global clinical pipeline encompass a spectrum of scientific hypotheses and eventually include candidates that elicit broadly neutralizing antibodies against HIV; stimulate mucosal immunity; perform as well in SIV models as the live-attenuated SIV vaccine; and combine effective neutralizing antibody responses with robust and durable CMI responses.

4. Sustain the Effort

- **Ensure adequate and appropriate clinical research and trial capacity.** It is essential to have sufficient clinical capacity to conduct Phase I and small efficacy trials, as well as to ramp up to large-scale efficacy trials in case of promising leads. Clinical trial centers can’t simply be turned on and off. Stakeholders in the global AIDS vaccine effort should undertake assessments of clinical trial capacities and make the necessary corrections to ensure that gaps between trials neither waste resources nor disillusion investigators, staff, and communities. In periods between AIDS vaccine trials, the talent and infrastructure already existing at clinical trial centers could be applied to clinical research for AIDS vaccine discovery, trials of vaccines against other diseases, and trials of other AIDS prevention technologies. Despite significant investment over the past two decades, there are still only a limited number of centers in developing countries with validated laboratories and good clinical practice capable of conducting clinical research programs relevant to AIDS vaccine discovery. To foster advances in clinical research, particularly in those countries, ethical and regulatory systems must be strengthened and streamlined, and training must be carried out to ensure appropriate capacity of clinical research teams.

- **Establish incentives to enhance innovation in AIDS vaccine discovery and development.** Moving beyond existing strategies and seeking true innovation will be vital to successful AIDS vaccine development. Advances in biomedical science provide many potentially useful tools. However, given market forces, there is little incentive for companies that create those technologies to use them in the AIDS vaccine field. The AIDS vaccine field would also profit from closer integration with the basic immunology field, with efforts to develop other vaccines, and with many of the cross-disciplinary fields that are transforming biology, such as systems biology and computational biology. Recently, a number of innovation programs have been established by key stakeholders in the field. However, the resources for fostering innovation remain quite limited. Thus, the Blueprint recommends building on existing programs to proactively identify novel technologies that offer promise to the AIDS vaccine field and create incentives for their use.

- **Train the next generation of AIDS vaccine scientists.** The challenge of an AIDS vaccine requires that the brightest young scientists enter the field, bringing new energy, ideas, and enthusiasm. Measures should be undertaken to attract such scientists from all over the world. These measures should include training initiatives, such as establishing AIDS vaccine research graduate and post-doctoral fellowships for young investigators worldwide, and the fostering of career development, mentoring, and leadership opportunities. There should be specific incentives for young investigators from low- and middle-income countries who can contribute research and build research capacity in their home countries, as well as influence policymakers, civil society, and the wider community to support AIDS vaccine research.
• Sustain and enhance financing for AIDS vaccine research and development (R&D). The stability, flexibility, and appropriate allocation of AIDS vaccine financing are as important as the quantity of funding. The field must ensure AIDS vaccine funding is matched to R&D needs in size, duration, and flexibility through an analysis of needs and enhanced advocacy efforts. Achieving the goals and milestones of this Blueprint will require long-term and flexible funding built on renewed commitments from existing donors and contributions from new sources. This financing will need to be medium-term in nature (5 to 10 years) to provide the stability and flexibility needed in the discovery and development process.

• Establish a mechanism to monitor progress in the AIDS vaccine field. Finally, to monitor progress in the AIDS vaccine field, beginning in 2009, the field should limit duplicative meetings. It should establish an annual meeting to monitor and update progress towards a safe and effective AIDS vaccine, including the achievement of milestones proposed in this Blueprint. We consider that the proliferation of meetings each year cuts into time better spent on research and that one major meeting focused on accountability would be a superior use of time.*

*Annual HIV and AIDS Vaccine Related Meetings: AIDS Vaccine 2008; 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; CROI; Immunology; Annual Meeting of the American Association of Immunologists (AAI)/Experimental Biology 2008; Mucosal Immunity and HIV/AIDS Vaccines; Challenges of Global Vaccine Development; World Vaccine Forum; Cancer Vaccines/Adjuvants/Delivery for the Next Decade (CVADD 2008); Clinical Update in Infectious Diseases (11th Annual); 21st International Conference on Antiviral Research; HVTN Conference; CHAVI Annual Meeting; CAVD Annual Meeting; Phacilitate’s 7th Annual European Vaccine Forum; 11th Annual American Society for Gene Therapy Meeting; American Society for Virology; HIV Implementers - Scaling Up Through Partnerships: Overcoming Obstacles to Implementation; BIO 2008 Annual International Convention; American Society for Reproductive Immunology (28th Annual); DNA Vaccines 2008, The Gene Vaccine Conference; 2nd International Symposium on Genetic and Immune Correlates of HIV Infection and Vaccine-Induced Immunity (GIC HIV); 35th Annual Meeting and Exposition of the Controlled Release Society; 9th International Veterinary Immunology Symposium; JP Morgan H&Q 26th Annual Healthcare Conference; Pharmaceutical Strategy Series’ Sixth Annual R&D Executive Summit (part of Molecular Medicine Tri-Conference); HIV Vaccines: Progress and Prospects; Molecular Approaches to Vaccine Design, CSHL.
As challenging as the frontier ahead undoubtedly is for the AIDS vaccine field, those of us who are committed to it know that we have only one choice: to keep advancing. The promise of an AIDS vaccine is too great to leave any other option. A vaccine offers the world’s best hope for not just easing the AIDS pandemic, but ending it. The past has shown us the power of vaccines to change the course of human history. Vaccines often take decades to develop (Table 4). Failure—sometimes of a spectacular sort—virtually always precedes success. We at IAVI believe in the power of science to solve human problems, in persistence, and in the learning opportunities afforded by failure. We believe that creating an AIDS vaccine requires a global effort employing the talents, resources, and passions of scientists, donors, policymakers, activists, advocates, and other stakeholders from both the developing and developed worlds. We offer this Blueprint energized by the chance to work on an enormous scientific challenge at a moment of great dynamism, grateful for the opportunity to work with and alongside the many other stakeholders around the world who are committed to an AIDS vaccine, and eager for what we hope will be a productive debate on the suggestions made here.

**TABLE 4** To Create a Vaccine: Always Years, Sometimes Decades

Most licensed vaccines took at least several decades to develop; the world still awaits other vaccines.

<table>
<thead>
<tr>
<th>Infectious agent (disease)</th>
<th>Agent linked to disease</th>
<th>Vaccine licensed in U.S.</th>
<th>Years elapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bordetella pertussis (whooping cough)</td>
<td>1906</td>
<td>1948</td>
<td>42</td>
</tr>
<tr>
<td>Poliovirus (polio)</td>
<td>1908</td>
<td>1955</td>
<td>47</td>
</tr>
<tr>
<td>Measles virus (measles)</td>
<td>1953</td>
<td>1963</td>
<td>10</td>
</tr>
<tr>
<td>Hepatitis B virus (hepatitis)</td>
<td>1965</td>
<td>1981</td>
<td>16</td>
</tr>
<tr>
<td>Haemophilus influenzae (meningitis)</td>
<td>1889</td>
<td>1981</td>
<td>92</td>
</tr>
<tr>
<td>Salmonella Typhi (typhoid fever)</td>
<td>1884</td>
<td>1989</td>
<td>105</td>
</tr>
<tr>
<td>Varicella zoster virus (chickenpox)</td>
<td>1953</td>
<td>1995</td>
<td>42</td>
</tr>
<tr>
<td>Rotavirus (diarrheal disease)</td>
<td>1973</td>
<td>2006</td>
<td>33</td>
</tr>
<tr>
<td>Human papillomavirus (cervical cancer)</td>
<td>1981</td>
<td>2006</td>
<td>25</td>
</tr>
<tr>
<td>HIV (AIDS)</td>
<td>1983</td>
<td>–</td>
<td>25+</td>
</tr>
<tr>
<td>Human cytomegalovirus (birth defects, mononucleosis)</td>
<td>1960</td>
<td>–</td>
<td>48+</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis (tuberculosis)</td>
<td>1882</td>
<td>*</td>
<td>126+</td>
</tr>
<tr>
<td>Plasmodium spp. (malaria)</td>
<td>1880</td>
<td>–</td>
<td>128+</td>
</tr>
</tbody>
</table>

* Although BCG vaccine is effective and widely used in children, no highly effective licensed vaccine against adult tuberculosis is currently available.
The next major advance on the way to the ultimate goal of an effective, licensed AIDS vaccine will be the first demonstration that a candidate AIDS vaccine provides benefit in humans. To achieve this intermediate goal, IAVI believes the field must achieve a series of tangible milestones that will solve both the neutralizing antibody problem and the question of how to control HIV infection.

Solving the neutralizing antibody problem will involve identifying and characterizing new broadly neutralizing monoclonal antibodies against HIV from infected individuals, determining their binding sites and structure, and high throughput design, and testing of immunogens that elicit broadly neutralizing antibodies in people.

Controlling HIV infection will involve: determining the antigens and immunologic mechanisms responsible for control of HIV infection by elite controllers and/or for control of SIV infection by live-attenuated SIV in nonhuman primates; implementing a clinical research program to determine the optimal immunogens for eliciting CMI responses against HIV; and broadening and prioritizing approaches to vectors for use in AIDS vaccines.

All of these approaches will require that the appropriate infrastructure is available to speed AIDS vaccine discovery, including clinical trial research and capacity, and human and financial resources.

Figure 9 Steps toward the ultimate goal
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