

AIDS VACCINE BLUEPRINT 2006

Actions to Strengthen Global Research and Development



A partner of the Global HIV Vaccine Enterprise

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IAVI’s mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world.

IAVI gratefully acknowledges the valuable contributions of its colleagues that made it possible to assess the field and provide recommendations to catalyze change to improve AIDS vaccine development. IAVI, as a founding member of the Global HIV Vaccine Enterprise, sought feedback from members of the Enterprise Coordinating Committee, selected members of IAVI’s Scientific and Policy Advisory Committees, and a number of other 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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LIST OF ABBREVIATIONS

AAV.....	adeno-associated virus
ABL.....	Advanced BioScience Laboratories
ACH2.....	Australian Centre for HIV and Hepatitis Virology Research
Ad5.....	adenovirus type 5
ADARC.....	AIDS Vaccine Advocacy Coalition
AIDS.....	acquired immunodeficiency syndrome
AMC.....	advance market commitment
ANRS.....	Agence Nationale de Recherches sur le Sida
ARCSHS.....	Australian Research Centre in Sex, Health and Society
AVIP.....	AIDS Vaccine Integrated Project
BMGF.....	Bill & Melinda Gates Foundation
CAB.....	community advisory boards
CAVD.....	Collaboration for AIDS Vaccine Discovery
CBO.....	community-based organization
CCR5.....	chemokine receptor 5
CHAVI.....	Center for HIV/AIDS Vaccine Immunology
CMI.....	cell-mediated immune
CRI.....	Children's Research Institute
CSIR.....	Council of Scientific and Industrial Research
DBT.....	Department of Biotechnology
DNA.....	deoxyribonucleic acid
EDCTP.....	European and Developing Countries Clinical Trials Partnership
ELISPOT.....	enzyme-linked immunosorbent spot
EU.....	European Union
GALT.....	gut-associated lymphoid tissue
GCLP.....	good clinical laboratory practices
GCP.....	good clinical practices
GDP.....	gross domestic product
GSK.....	GlaxoSmithKline
GTU.....	Gene Transport Unit
HIV.....	human immunodeficiency virus
HPV.....	human papillomavirus
HVTN.....	HIV Vaccine Trials Network
IAVI.....	International AIDS Vaccine Initiative
IBSA.....	India, Brazil, and South Africa
ICH.....	International Conference on Harmonisation
ICMR.....	Indian Council of Medical Research
LDC.....	least developed countries
MRC.....	Medical Research Council
MUVAPRED.....	Mucosal Vaccines for Poverty-Related Diseases
MVA.....	modified vaccinia ankara
NAC.....	Neutralizing Antibody Consortium

Continued on next page

List of Abbreviations, continued

NACO	National AIDS Control Organization
NGO	non-governmental organization
NIAID	US National Institute of Allergy and Infectious Diseases
NIH	US National Institutes of Health
NOE	Networks of Excellence
OECD	Organization for Economic Co-operation and Development
PAVE	Partnership for AIDS Vaccine Evaluation
PPP	public-private partnerships
R&D	research & development
SAAVI	South African AIDS Vaccine Initiative
SBIR	small business innovation research
SHIV	simian human immunodeficiency virus
SIV	simian immunodeficiency virus
TB	tuberculosis
TGEN	Targeted Genetics Corporation
UNAIDS	Joint United Nations Programme on HIV/AIDS
USMHRP	US Military HIV Research Program
VCT	voluntary counseling and testing
VEE	Venezuelan equine encephalitis
VRC	Vaccine Research Center
VSV	vesicular stomatitis virus
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

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Twenty-five years after the first five cases of a novel immunodeficiency disease were described, the AIDS pandemic has become the greatest global public health crisis since the Black Death in the Middle Ages. Although the ideal global response to HIV/AIDS must be a comprehensive approach that includes education, prevention, treatment, and care, the only way to end this epidemic is to develop a safe, accessible, and preventive vaccine.

The ultimate goal is an AIDS vaccine that prevents infection from the wide spectrum of globally diverse HIV isolates and is applicable for use in the developing world, where the need is the greatest (Figure 1, Figure 2). However, a vaccine that suppresses viral load and slows progression to AIDS or suppresses and blunts transmission of HIV would have significant public health impact (Figure 3). To achieve that, a host of scientific, public policy, and political actions must be taken in a coordinated, interlinked fashion to make all of the necessary resources available (Figure 4). While scientific challenges continue to be the main obstacle in the search for an AIDS vaccine, countless examples of successful technology breakthroughs show that judicious policy changes and political will matters enormously. It is vital to enlist political leadership, non-governmental organizations, community groups, and a range of strategic coalitions that can amplify and reinforce support for AIDS vaccines.

Through its series of biennial AIDS Vaccine Blueprints begun in 1998, the International AIDS Vaccine Initiative (IAVI) has monitored the state of the global AIDS vaccine effort. This year, as a partner of the Global HIV Vaccine Enterprise (the Enterprise), IAVI endeavors to take a comprehensive look at the achievements and challenges facing science and policy efforts and to make a series of integrated recommendations that will move the field closer to achieving its goal of an effective AIDS vaccine.

THE AIDS VACCINE LANDSCAPE

Though the challenges in developing an AIDS vaccine are numerous, scientists think that it is possible. This conviction is based, in part, on observations from the field:

- A small number of individuals remain uninfected despite evidence of repeated exposure to HIV;
- Robust anti-HIV cellular immune responses found in some rare individuals suppress viral load to undetectable levels;
- In the normal course of HIV infection, cellular immunity suppresses the viral load for a substantial period of time, often a decade;

- Monkeys immunized with live-attenuated vaccines are completely protected against matching strains of simian immunodeficiency virus (SIV), which normally causes AIDS in monkeys; and
- Broadly neutralizing antibodies against HIV can completely protect monkeys from infection with a homologous hybrid simian/human immunodeficiency virus (SHIV).

There have been several milestones in AIDS vaccine design and development, marking progress in our understanding of the HIV virus and ways to design an effective vaccine against it, as well as in our ability to conduct efficient AIDS vaccine clinical trials in a wide variety of settings, including in developing countries badly affected by the AIDS pandemic (Table 1). Informed risk-taking and scientific empiricism—assessing vaccine candidates in human trials on the grounds of testable scientific hypotheses—have been fundamental to successful vaccine development for polio, measles, mumps, rubella, pertussis, and other diseases (Figure 5) and have led to a number of AIDS vaccine candidates in clinical trials (Table 2, Table 3, Figure 6). Data from these clinical trials will not be available until 2008 and are eagerly anticipated by the field. Two approaches are currently being tested in large-scale efficacy trials: the sanofi-aventis-VaxGen Phase III trial to induce cellular-helper and humoral immune responses and the ongoing Merck Phase IIb trial that is the first real test of a candidate that induces cellular-cytotoxic mediated immune responses in the majority of vaccinees. The results of these trials will have significant impact on the AIDS vaccine pipeline (Table 4), since virtually all of the current vaccine candidates primarily generate such responses. While induction of cell-mediated immune (CMI) responses may be an important component in protective immunity against HIV, global resources need to be devoted to candidates that elicit other potentially protective immune responses such as neutralizing antibodies and mucosal immunity.

Since the XV International AIDS Conference in Bangkok, July 2004, steps have been taken towards the implementation of a more integrated vaccine design effort. Three of the founding members of the Enterprise have launched programs to design vaccines to elicit broadly neutralizing antibodies, elucidate the correlates of protective immunity, and address the scientific challenge of HIV variability:

- The Bill & Melinda Gates Foundation established the Collaboration for AIDS Vaccine Discovery (CAVD), a network of 11 vaccine-

discovery consortia focused on designing AIDS vaccines that elicit durable and broad-spectrum cellular, neutralizing antibody, and mucosal immune responses, supported by five centralized facilities that provide standardized laboratory analysis and statistical support;

- The US National Institute of Allergy and Infectious Diseases (NIAID) established the Center for HIV/AIDS Vaccine Immunology (CHAVI) to study the virologic, genetic, and immunologic responses to acute HIV infection, to elucidate correlates of human protection through a range of human and nonhuman primate studies, and to translate this knowledge into the design of AIDS vaccines; and
- The International AIDS Vaccine Initiative (IAVI) expanded its Neutralizing Antibody Consortium (NAC) to focus on solving the neutralizing antibody problem, establish new consortia to elucidate the correlates of protective immunity, and establish an industrial-style AIDS Vaccine Development Laboratory to provide enhanced capabilities for the field in process development, systematic optimization and prioritization of candidate vaccines, and new approaches to vaccine design.

Although the overall funding landscape in AIDS vaccine development has substantially improved, increasing to \$759 million in 2005 (Figure 7), a comparison of investment in preventive AIDS vaccine R&D as a percentage of GDP highlights that countries are not contributing equally (Figure 8). In addition, though pharmaceutical and biotechnology companies are playing a part in AIDS vaccine research and development today, they are only contributing 10% of the total spending from their own resources. Policy discussions have focused on mechanisms such as “push” and “pull” incentives to reduce the risk of early-stage investment in R&D and to ensure viable markets for AIDS vaccines (Figure 9). We now need to implement and evaluate the most promising incentive mechanisms to see if they can improve investments and accelerate results in AIDS vaccine R&D.

The geography of the AIDS vaccine research and development has also evolved significantly in recent years. The number of developing countries conducting AIDS vaccine trials continues to increase, with four additional countries beginning trials (China, India, Rwanda, and Zambia) since 2005. There is a need to carry out R&D in a variety of epidemiological settings where populations are different and a variety of HIV isolates are circulating. It is also important to recognize the potential contributions of emerging biomedical research and manufacturing capabilities in innovative developing countries such as Brazil, China, India, and South Africa.

CHALLENGES FACING AN AIDS VACCINE

Despite a more favorable policy environment, significant scientific progress, and over 30 clinical trials under way, the goal of a safe, effective, preventive, and globally accessible AIDS vaccine remains elusive. This is due primarily to the scientific challenges (Table 5) and the related operational and policy challenges.

HIV Hypervariability: HIV is hypervariable, both within HIV-infected individuals and on a population basis (Figure 10, Figure 11), which poses several problems for vaccine developers:

- HIV is a moving target; thus, by the time a candidate has advanced to large-scale efficacy trials, which currently takes several years, the target HIV antigens in the vaccine may no longer match the antigens in the circulating virus strains where the efficacy trials are conducted;
- No candidate in the current clinical pipeline has been capable of neutralizing the wide spectrum of HIV isolates circulating worldwide, and the candidates may only be effective against challenge with a homologous virus; and
- Attempts to design vaccines directed at conserved regions of the virus may not be completely effective, based on analogous studies in nonhuman primates.

Neutralizing Antibodies: HIV is able to evade neutralizing antibodies upon infection due to several factors, including:

- The virus outer surface protein is decorated with a dense matrix of carbohydrates;
- The virus binding sites to the host cell receptors (CD4) are shielded from neutralizing antibodies; and
- Decoys shift the immune response away from generating broadly neutralizing antibodies.

Broadly neutralizing antibodies are not generated in the majority of naturally occurring HIV infections, so the standard vaccinology strategy of mimicking natural infection to induce a neutralizing antibody response may not be an effective strategy against HIV. In order to successfully address this issue, scientists have developed novel ways to induce a neutralizing antibody response against HIV (Figure 12).

Retrovirus: HIV is a retrovirus that integrates its genetic material into the human genome and establishes a persistent and lifelong infection. After

this integration, the resting HIV-infected cells appear no different from uninfected cells and avoid immune defense mechanisms. The goal for an AIDS vaccine is to prevent the genome integration and establishment of persistent infection, which occurs within the first seven to ten days after HIV exposure. This brief window of opportunity creates challenges for optimizing the magnitude, durability, and localization of vaccine-induced immune responses.

Animal Models: There is currently no ideal animal model for AIDS since HIV/SIV pathogenesis and major histocompatibility antigens differ between nonhuman primates and humans. AIDS vaccine researchers have to rely on surrogate animal models but the predictive value of these models will remain uncertain until they are validated and protection of humans is demonstrated by an AIDS vaccine candidate in clinical trials.

Correlate of Protective Immunity: In many other viral infections, persons can be identified who become infected with the pathogen, spontaneously generate immune responses, and clear the infection. Analysis of these individuals leads to identification of a correlate of protective immunity, which facilitates vaccine development. For HIV there is no documented case of “recovery” from infection and the immunological correlates of protection remain unknown. In the absence of a correlate of protection the field does not have a validated marker for determining whether one vaccine candidate is a significant improvement over another. It is unclear whether one or more of innate, neutralizing antibody, cell-mediated, or mucosal immune responses is required for eliciting protective immunity (Figure 13). In particular, mucosal immunity may be required to prevent the earliest stages of HIV infection.

HIV Antigens: It is still unclear which HIV antigens are needed to induce protection (Figure 14), so vaccine designers are creating candidate vaccines to test multiple HIV antigens in different combinations. But the field as a whole has not systematically tested different antigens in the same vector in either clinical or preclinical studies. Until some efficacy is achieved in human clinical trials and/or systematic studies are undertaken in nonhuman primates, this question will remain unanswered.

Clinical Trials: The only completed AIDS vaccine efficacy trials took four to five years, and the ongoing efficacy trials are expected to take three to four years before key data are available. New strategies to accelerate clinical development of AIDS vaccines are necessary, including enhancing regulatory and ethics review board capacity in the developing world and accelerating the

testing of candidate AIDS vaccines in persons at high risk for HIV infection.

Funding: Currently there are significant funding shortfalls in certain key areas, especially to support a large-scale rational vaccine design effort. Resource needs will also expand as more vaccine candidates enter later-stage clinical trials. Sustained and flexible funding is also vital since developing an effective AIDS vaccine will be a long-term undertaking and new priority activities will emerge as the field advances. Funders’ and stakeholders’ expectations need to be carefully managed to match the reality of AIDS vaccine development.

Engaging the Private Sector: A number of pharmaceutical and biotech companies are currently involved in AIDS vaccine research but greater engagement will be vital to expedite success in the field. The private sector holds much of the needed expertise to create an AIDS vaccine, including product development, manufacturing, and commercialization. This experience must be harnessed to minimize the time needed to discover, develop, and distribute a vaccine.

Building an Enabling Environment in Developing Countries: The environment for AIDS vaccine R&D in developing countries has improved but further progress in ethical and regulatory systems is required. AIDS prevention and treatment services, including voluntary counseling and testing, and community awareness building, need to be reinforced at all trial sites.

Each problem in itself is not unique to HIV and it is important to note that vaccines have been developed successfully for other viruses facing many of these same challenges. However, the combination of these together provides the major obstacle to accelerating AIDS vaccine development and requires a number of new approaches to shorten the timeline for success. The recommendations below build upon the Enterprise process, focusing on initiatives to address key scientific challenges and integrating these efforts to create a more effective enabling environment to accelerate AIDS vaccine R&D.

ADDRESSING THE CHALLENGES

Scientific empiricism alone is unlikely to yield an effective vaccine. An integrated approach that incorporates rational vaccine design to address key scientific challenges to improve antigen development along with a more streamlined evaluation and testing procedure is required to accelerate AIDS vaccine development. In addition to the formidable scientific barriers to more rapid progress in AIDS vaccine R&D existing today, there are also major policy obstacles which must

be overcome in order to speed scientific progress. This report recommends a series of new initiatives with five-year interim milestones, which, if reached, would likely and significantly advance the search for an effective AIDS vaccine.

Integrated Program for Accelerating AIDS Vaccine Development: There needs to be a coordinated paradigm shift to move more novel candidates targeting different immune responses into the pipeline and to accelerate feedback on their efficacy. The required components of this paradigm shift are: rational vaccine design applied towards resolving the unanswered questions and translating answers into novel vaccine candidates; coordinated scientific empiricism to test only those candidates that are significantly better than the leading candidate in the pipeline; and accelerated clinical trials to yield efficacy and safety data to prioritize within the field. This shift in focus must be supported by policy choices that make available the necessary resources—sufficient and flexible funding and expertise—to successfully develop an AIDS vaccine.

Building upon the collaborative stakeholder alliances established through the Enterprise process, a Rational Vaccine Design Effort, patterned after industrial-scale efforts in drug discovery, should be implemented and adequately resourced. This effort should be focused on solving the key scientific challenges, designing improved candidates, and accelerating the development of these candidates through an industrial-like, milestone-driven series of closely coordinated programs. This requires:

- Closely linked multidisciplinary scientific teams, dedicating the vast majority of their time to solving the AIDS vaccine challenges;
 - Implementation of rigorous industrial project and portfolio management systems to monitor progress and shift resources accordingly;
 - Core resources and enabling programs, including high-throughput tools and procedures adapted from drug discovery efforts, where appropriate;
 - Dedicated nonhuman primate facilities with adequate resources for comparison and prioritization of candidate vaccines; and
 - Access to a dedicated vaccine development infrastructure, including process development and manufacturing capability for translating leads to the clinic.
- Phase I trials of candidates which qualitatively or quantitatively are superior to the current leading candidate vaccines should be conducted in small numbers (<50) of subjects at sites where Phase II trials would be conducted;
 - Candidates that fulfill the criteria should be advanced immediately to Phase II trials of about 500 subjects at high risk for HIV infection, such as discordant couples or people living in areas where HIV incidence rates exceed 4% per year and there is a strong track record of compliance in clinical trials. The expected 20–25 new infections per year would be comprehensively assessed for anti-HIV immune responses, viral load at acute infection and set point, and host genetics. This would greatly speed the collection of efficacy data and allow for many candidates to be tested at the same cost as a

A number of organizational models—additional scientific consortia, the creation of a dedicated AIDS vaccine R&D company, or more effective linkages with established biotech and pharmaceutical activities—could achieve significant scientific and operational synergies and make available industry skills, management techniques, and accountability.

A Collaborative Scientific Empiricism Effort should focus on the design and clinical efficacy testing of candidates that qualitatively or quantitatively improve upon the best current candidates and eliminate the unnecessary duplication that currently plagues the AIDS vaccine pipeline. The focus must be on candidates that hold promise for improving upon the levels of protection likely to be conferred by those currently in the pipeline, are capable of generating persistent and long-lived immune responses against HIV, or target potentially protective responses other than CMI, such as mucosal immunity or neutralizing antibodies. Criteria have been developed to advance candidates into clinical trials, and parallel sets of small trials in subjects at high risk for HIV infection should be conducted to provide crucial preliminary assessments of efficacy. Linked closely with the Rational Vaccine Design Effort, this combination of approaches could significantly improve the pipeline of candidates in the next five years (Figure 15).

The field needs to establish a new model for accelerating AIDS vaccine trials, because the current model follows the standard paradigm for all other vaccine trials and does not allow for the accelerated testing and prioritization of candidates. Given the urgency of the AIDS pandemic, the following new model should be established:

single Phase IIb trial in the current funding paradigm; and

- Based on preliminary efficacy data from these proposed accelerated Phase II efficacy trials, an algorithm must be established for terminating work on the candidate, modifying/improving the candidate, or advancing the candidate to Phase III trials.

Financing a dynamic global R&D program requires flexible, long-term resource allocations to diverse areas of research and product development and different types of organization/coordination, which match the evolving needs of R&D. Donors must also be prepared to make commitments to fund several generations of progressively better vaccines. Clear targets must be agreed upon for spending, and an equitable burden-sharing formula should be created, which governments of developed and developing nations can agree upon and abide by, to contribute to the global AIDS vaccine R&D movement.

In order to increase the engagement of pharmaceutical and biotechnology companies, their R&D investment risk needs to be reduced. A variety of “push” and “pull” incentive mechanisms are needed to lower the cost of R&D and to ensure viable markets for future AIDS vaccines. A number of innovative proposals have been developed and discussed. These include, for instance, tax benefits, expedited regulatory approvals, price and quantity purchase guarantees, and intellectual property protections. The time has come for the most promising of these incentives to be taken from the drawing board, adopted by governments, and evaluated for their effectiveness. Additionally, novel forms of partnership and product development schemes should be created to tap private sector expertise in areas such as high-throughput technologies, project management, process development, and manufacturing.

Capacity Building to Pave the Way for the Future of AIDS Vaccine Development:

In order to effectively capitalize on the recommendations discussed above, the capacity to allow for rapid advancement of clinical trials and the political environment to support research and access have to be carefully established and fostered.

Establishing Vaccine Trial Networks of Excellence in developing countries by enhancing existing centers and creating new centers will fully utilize resources and provide maximum long-term benefit to the local communities. These networks should be able to conduct the required clinical research and multiple Phase IIb and III AIDS vaccine trials, as well as have the capacity to

conduct vaccine trials for other diseases such as tuberculosis and malaria. Key components include: clinical trial capacity; accredited and validated laboratory capacity; data management; epidemiology expertise; training facilities; community linkages; and national and international support. Vaccine Trial Networks of Excellence incorporating agreed-upon standards to enable multicenter clinical trials should be established in the regions of eastern Africa, southern Africa, western Africa, India, China, Russia/Eastern Europe, Southeast Asia, Latin America, and the Caribbean, where circulating HIV isolates vary.

Training the next generation of scientists is critical to maintaining the momentum and progress in the development of a safe and effective AIDS vaccine. New training initiatives must be established—in association with the Rational Vaccine Design Effort and new Vaccine Trial Networks of Excellence—through the establishment of postdoctoral fellowships in areas crucial to HIV research. Careers and training also need to be made available to scientists and other technical staff in developing countries through long-term funding of Networks of Excellence.

Improving the environment for AIDS vaccines in developing countries by engaging the national leadership and community-based organizations to build support that leads to improved volunteer enrollment and compliance can also help to facilitate research, development, and future access. Health and other AIDS prevention and treatment services in the surrounding communities, including voluntary counseling and testing and AIDS drug therapy, should be brought to high standards of quality and availability.

Preparing today for rapid vaccine approval and uptake of an effective AIDS vaccine will help to minimize any possible lags in vaccine availability between developed- and developing-country populations. This requires estimating demand, building systems to deliver a vaccine that is likely to be recommended for adolescents and adults, and devising financing schemes that will ensure access to those who most need it.

Critical Actions to Build and Sustain Long-Term Political Support and Commitment:

Implementing the recommendations outlined above will require enormous commitment from many groups, from grassroots to global, and this commitment must be sustained until vaccines are accessible to all those who require them. Policy research is critical in providing a solid base for advocacy, and the relevance of AIDS vaccines to other issues should be emphasized to engage a wider range of constituencies. Ultimately, those allocating resources must be convinced and engaged for the long term. Recent political

statements reflect the awareness and priority these countries assign to AIDS vaccines, but more needs to be done to turn these declarations into real resources and tangible results.

With 40 million infections worldwide, AIDS is the pandemic that will define our current generation. Governments, institutions, and organizations will be judged by their response. The world's best hope to end this pandemic is a preventive vaccine. However, it will take a significant shift in the way R&D is funded, organized, and conducted and the way policy is implemented if we are to successfully galvanize the resources, talents, and sense of urgency needed to drive rapidly towards a vaccine.

An AIDS vaccine is possible. As President Bill Clinton said in his Morgan State University commencement address in 1997, "It is no longer a question of whether we can develop an AIDS vaccine, it is simply a question of when. And it cannot come a day too soon." *AIDS Vaccine Blueprint 2006* outlines a series of initiatives—improving the pipeline through rational vaccine design and enhanced scientific empiricism efforts, accelerating product testing by creating a new paradigm for AIDS vaccine clinical trials, and building capacity, particularly in developing countries—that will speed the creation of an AIDS vaccine for the world. Given the 14,000 new HIV infections that occur daily, the impact of these recommendations could save millions of lives.

The AIDS pandemic has become the greatest global public health crisis since the Black Death in the Middle Ages. In 2005 alone, 4.1 million people were newly infected with HIV and 2.8 million died from AIDS worldwide, with approximately 95% of these in the developing world. Sub-Saharan Africa has been hit the hardest. AIDS has dramatically reduced life expectancy, created an unprecedented orphan crisis, and fostered social and political instability—AIDS has become a true development issue. In Asia and Eastern Europe, particularly in the ex-Soviet bloc nations, new and burgeoning HIV epidemics threaten to dwarf the sub-Saharan African crisis in the coming decades in the absence of effective AIDS prevention and control programs.

Ideally, the global response to HIV/AIDS must be a comprehensive approach that includes education, prevention, treatment, and care. The world needs to continue to develop creative strategies for accelerating access to life-saving treatment for all those in need. At the same time and with equal urgency there must be investment to develop better technologies for the future: drugs and diagnostics for treatment and, in particular, vaccines that offer the best chance of ending the epidemic.

Historically, vaccines have been the greatest success story in the prevention and control of infectious diseases; achievements include eradication of smallpox, progress towards elimination of polio and measles, and control of diseases such as tetanus, diphtheria, and whooping cough. Though the challenges in developing an AIDS vaccine are numerous, scientists think that it is possible. This conviction is based, in part, on observations from the field:

- A small number of individuals remain uninfected despite good evidence of repeated exposure to HIV;
- Robust anti-HIV cellular immune responses found in some rare individuals can suppress viral load to undetectable levels, slowing the progression of disease and inhibiting HIV transmission;
- In the normal course of HIV infection, cellular immunity suppresses the viral load for a substantial period of time, often a decade;
- Monkeys immunized with live-attenuated vaccines are completely protected against matching strains of simian immunodeficiency virus (SIV), which normally causes AIDS in monkeys; and

- Broadly neutralizing antibodies against HIV can completely protect monkeys from infection with a homologous hybrid simian/human immunodeficiency virus (SHIV).

Based on these observations, an AIDS vaccine that elicits antibodies to neutralize a broad spectrum of circulating HIV subtypes, elicits cell-mediated immune responses to blunt viral load to undetectable levels, and is as effective in preventing HIV infection as are live-attenuated vaccines in monkeys should be achievable.

The development and recent licensure of a human papillomavirus (HPV) vaccine for the prevention of cervical cancer, now known to be caused by a sexually transmitted agent, is the most recent biomedical triumph and provides important insights for AIDS vaccine development. Fundamental knowledge of HPV pathogenesis came from years of basic research supported by public sector agencies throughout the world. Application of this knowledge towards vaccine design took a further 16 years and the expenditure of several hundred million dollars by private industry, which has the critical skills and infrastructure for successful product development. Such partnership between publicly funded basic research and privately funded vaccine development has been crucial to recently licensed vaccines. Ensuring significant industrial involvement is a prerequisite for successfully developing a safe and effective AIDS vaccine.

A second key element critical to successful vaccine development is scientific empiricism coupled with the willingness to take informed risk. This was most radically demonstrated in 1798 at the birth of vaccinology when Edward Jenner made the critical observation that milkmaids, who were regularly exposed to the cowpox virus, did not suffer the scourge of smallpox. He noted that “what renders the Cow Pox so extremely singular is that the person who has been thus affected is for ever after secure from the infection of the Small Pox.” Jenner then tested his hypothesis by “vaccinating” a young boy with cowpox and subsequently exposing him to pus from smallpox patients.

Ever since, scientific empiricism has been the basis for the science of vaccinology—the design and testing of vaccine candidates in human trials on the grounds of testable scientific hypotheses. Of course, today placebo-controlled clinical trials, regulatory guidelines, and informed consent practices have replaced Jenner’s radical methods. Nevertheless, informed risk-taking and scientific empiricism were fundamental to successful vaccine development for polio, measles, mumps, rubella, pertussis, and other diseases, and will remain

important elements in the search for a safe and effective AIDS vaccine.

Scientific empiricism alone, however, is unlikely to yield an effective AIDS vaccine. The scientific challenges that HIV poses are too great and need to be addressed systematically. An integrated approach incorporating rational vaccine design to address key scientific challenges is required. Rational vaccine design is conceptually analogous to rational drug discovery efforts familiar in the pharmaceutical industry. For AIDS vaccine development, rational vaccine design includes iteratively designing and screening candidate vaccines by scientific methods until predetermined criteria are reached. The rational vaccine design effort would then feed better candidates into the scientific empiricism model, improving the pipeline and speeding the development of an effective AIDS vaccine.

There is now a resurgence in the biomedical science arena, one which has the potential to provide renewed energy and commitment to the global AIDS vaccine effort. This is due to a convergence of many factors, including the establishment of new alliances and initiatives covering the spectrum from scientific directives to funding streams, such as public-private partnerships that have provided new incentives for collaboration and partnership. In the research arena,

the development of new high-throughput technologies for immunogen design and screening will significantly augment rational vaccine design and will be critical for successfully developing and delivering a safe and effective AIDS vaccine.

Additionally, a spectrum of policy decisions are crucial—from ensuring sufficient financing to streamlining regulatory systems, from agreeing to standards of care for clinical trials to prioritizing the strengthening of health systems to support research. Underpinning all of this is the requirement for sustained political commitment by decision makers and activists.

Through its series of biennial AIDS Vaccine Blueprints begun in 1998, the International AIDS Vaccine Initiative (IAVI) has monitored the state of the global AIDS vaccine effort. This year, as a partner of the Global HIV Vaccine Enterprise (the Enterprise), IAVI endeavors to take a more comprehensive look at the recent achievements and the challenges facing science and policy efforts, and to make a series of integrated recommendations that will move the field closer to achieving its goal of an effective AIDS vaccine. This Blueprint reaffirms that innovation, speed, flexibility, and informed risk-taking, complementing creative science and rigorous product development, are key attributes required to develop and license an AIDS vaccine for the world.

SECTION 2 The AIDS Vaccine Landscape

2.1 • GOALS FOR AN AIDS VACCINE

Classically, vaccines prime the immune system to recognize and protect against a disease caused by a virus or other infectious agent. To have a significant public health impact on the AIDS pandemic a vaccine must be both effective against the wide diversity of global HIV isolates and useful in the developing world, where the need is greatest. In this context, there are three potential goals for an AIDS vaccine.

The first is to prevent establishment of persistent HIV infection. Most successful vaccines, like the one against measles, generate neutralizing antibodies and cell-mediated immune (CMI) responses against the invading pathogen but do not prevent infection. Rather,

they train the host immune system to curtail infection and consequently to prevent disease (Figure 1). Polio vaccines generate neutralizing antibodies against poliovirus and block infection from spreading to the nervous system, preventing paralytic polio. HIV is a retrovirus that persistently infects and integrates into the host cell genome, where it resides for the life of the host (Figure 2). During the first 7–10 days after infection, HIV amplifies in gut-associated lymphoid tissue and seeds the cells of the lymphoid organs. Preventing this initial spread throughout the body is the ultimate goal for an AIDS vaccine. So far this has not been achieved, either in preclinical studies of candidate vaccines or in clinical trials of the one candidate that has completed efficacy testing.

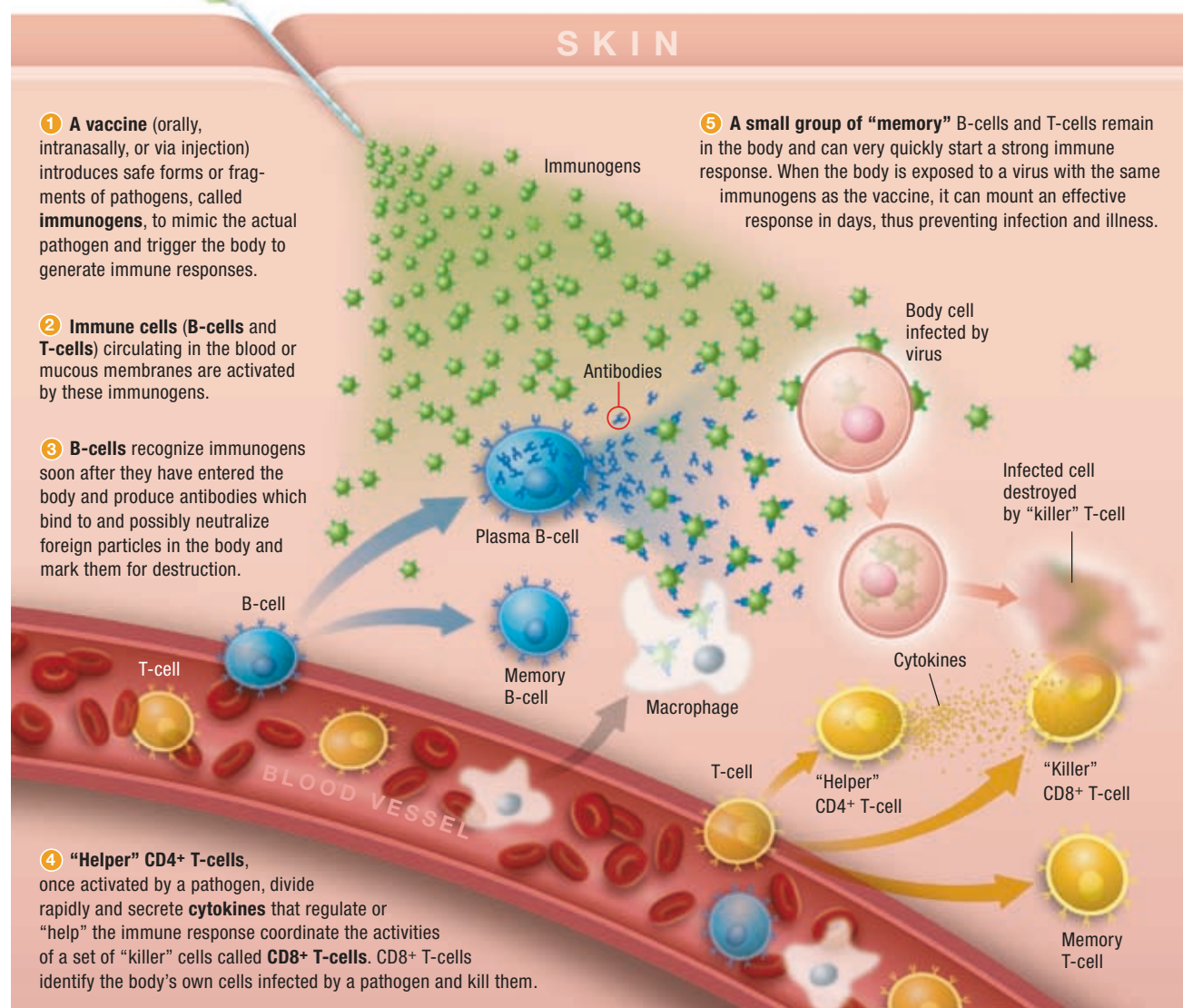


Figure 1 How Vaccines Work Against Viruses

The second potential goal is to significantly suppress viral load and slow the progression to AIDS in vaccinees if they become infected by HIV. The current clinical candidates focus primarily on induction of CMI responses against HIV and it is thought that the best they could achieve is this second goal. The approach is based on observations correlating levels of HIV-specific CMI responses in humans with lower viral loads and on studies in nonhuman primate models of AIDS that indicate some CMI-based vaccines can suppress viral load and slow progression to AIDS.

The third potential goal for a vaccine is to significantly reduce transmission of HIV, providing a public

health benefit. Building upon epidemiological data showing an inverse relationship between viral load and HIV transmission, mathematical models of the HIV epidemic have shown that even a partially effective vaccine could have a dramatic public health benefit (Figure 3).

It is important to note that while developing an AIDS vaccine that meets the goals outlined above is a scientific challenge, the resources required to do so—funding, technical, and human resources—will only be available if political will supports it. An enabling political environment is necessary to provide the mobilization of resources required to conquer this pandemic (Figure 4).

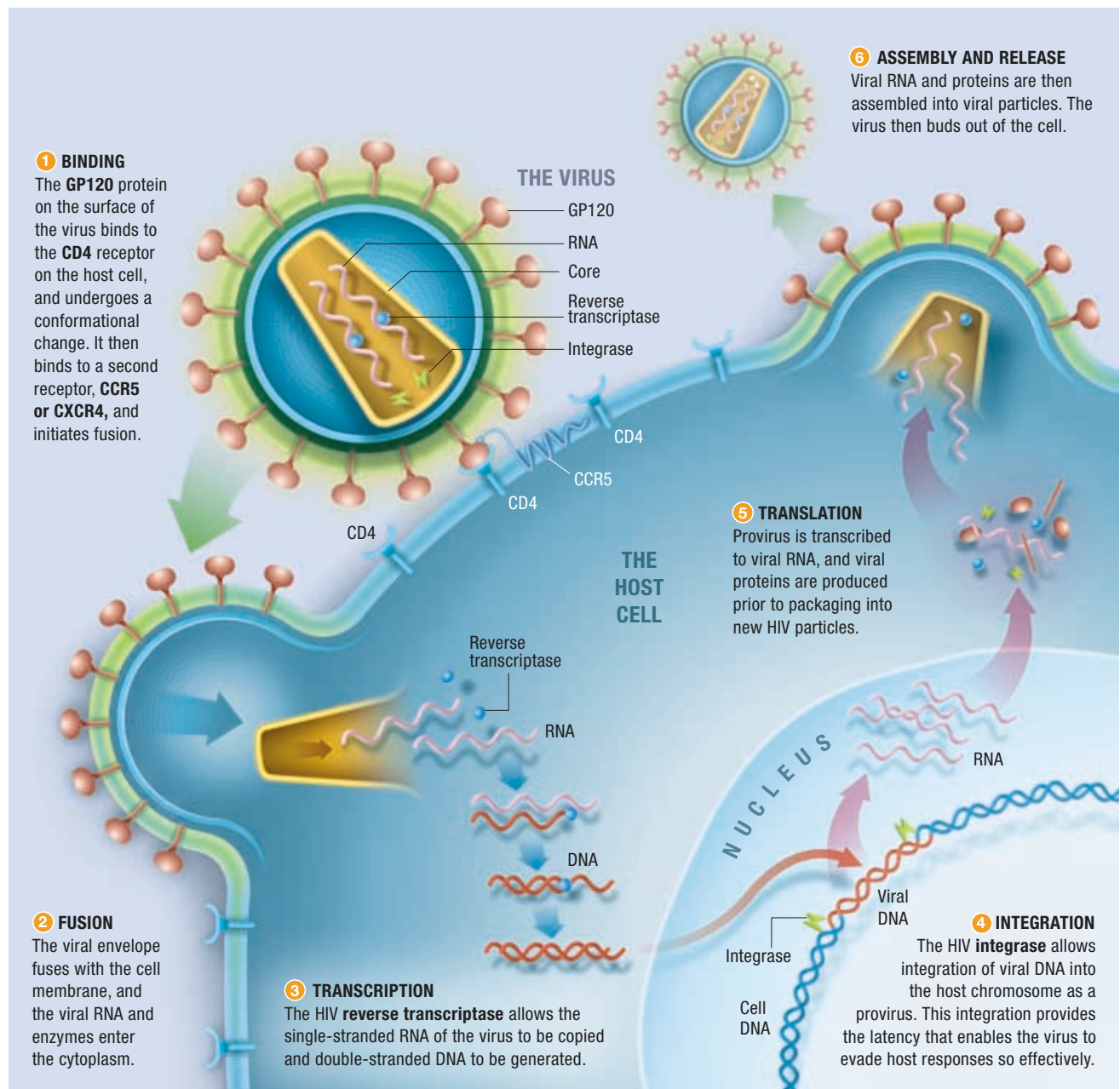


Figure 2 The HIV Replication Cycle

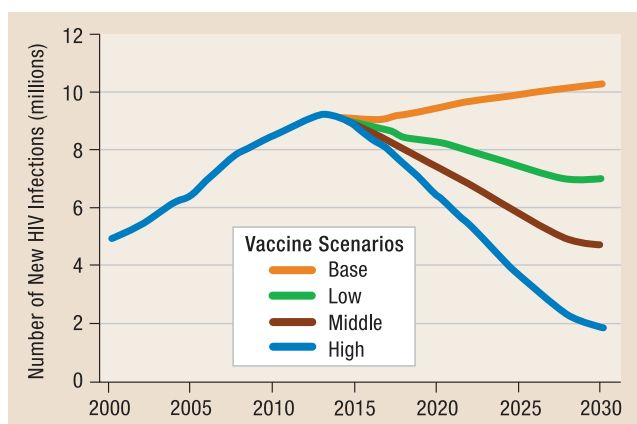


Figure 3 The Impact of an AIDS Vaccine on New HIV Infections

This model illustrates three different vaccine impact scenarios, as well as a “base scenario” showing the predicted course of the epidemic without a vaccine. The low scenario assumes a vaccine efficacy of 40%, which is probably at the low end of efficacy that would be considered acceptable by health authorities for implementation. Moderate (60%) and high (95%) efficacies are modeled in the middle and high scenarios, respectively.

2.2 • SCIENTIFIC EMPIRICISM AND AIDS VACCINE DEVELOPMENT

Much of the progress towards an AIDS vaccine to date has been driven by scientists working in a traditional “scientific empiricism” model. One of the hallmarks of the scientific empiricism model is to advance novel vaccine concepts to human efficacy trials, which remain the ultimate test of a vaccine concept and provide the unique opportunity to determine correlates of protective immunity. Figure 5 shows the major steps in AIDS vaccine development based on a scientific empiricism model, including the three phases of clinical trials to assess safety, immunogenicity, and efficacy, and Figure 6 provides an overview of AIDS vaccine designs. This model for AIDS vaccine development has now led to a number of candidates in clinical trials* (Table 1, Table 2), with those candidates in efficacy trials described in Table 3.

Important achievements have been made in AIDS vaccine design and development (Table 1), but there is still a very long way to go. Both the importance and limitations of the scientific empiricism model with respect to AIDS vaccine development are highlighted in Tables 2 and 3.

Vaccine concepts that significantly improve upon the current pipeline should continue to advance to efficacy trials. However, excepting a few subunit vaccines, virtually all of the vaccine candidates now in the pipeline focus on eliciting CMI responses against

HIV. While induction of such responses is likely an important component of a protective immune response against HIV, global resources also need to be devoted to candidates that elicit other potentially protective immune responses, in particular neutralizing antibodies.

The rationale for advancing cellular-based candidates to efficacy trials is based on studies in humans and monkeys that demonstrate an important role for CMI responses in suppressing viral load. But while the leading vaccine candidates do induce relatively robust CMI responses there is a lack of data on whether these particular vaccine-induced cellular responses correlate with protection against HIV infection or disease progression. This is partly due to limitations of the only validated assay, ELISPOT, that is currently routinely used to assess CMI responses in vaccine trials. It is unknown whether the magnitude or quality of ELISPOT responses correlates with protection and, in fact, several nonhuman primate protection studies have shown no such correlation.

The lack of immune correlates is compounded by the current limitations of animal models for HIV/AIDS—different host species, testing a related but distinct virus (SIV/SHIV vs. HIV), using different doses of infecting virus (much higher in monkeys to ensure that non-vaccinated animals become infected), and trying different routes of infection (rectal, vaginal, intravenous).

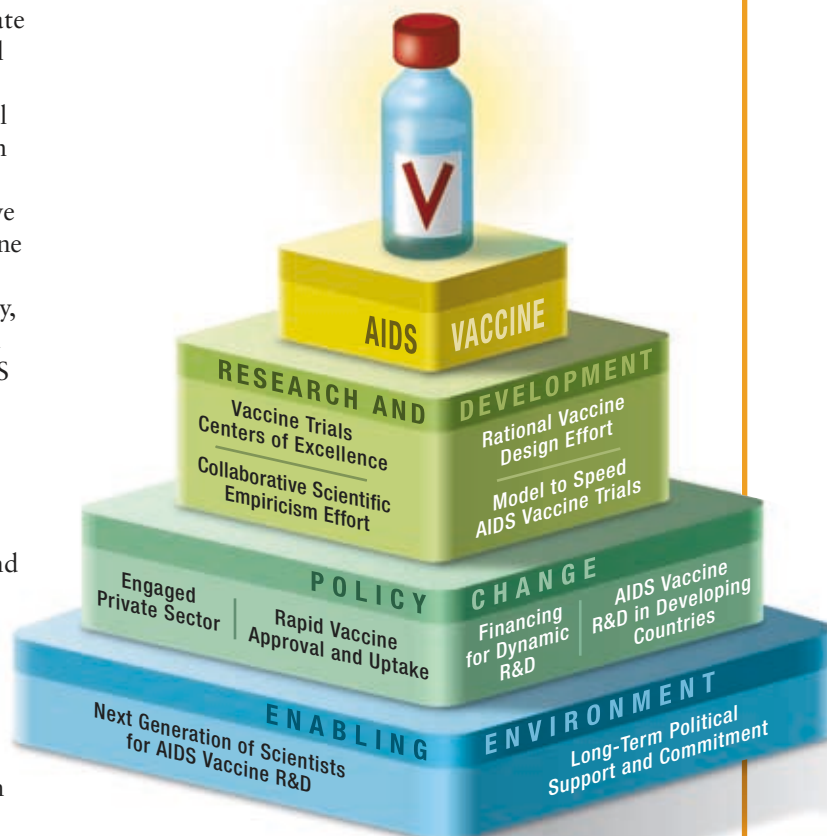


Figure 4 Elements Required to Accelerate an AIDS Vaccine

* Note that details on the vaccine candidates in the clinical pipeline can be found at www.iavireport.org/trialsdb.

Table 1	Key Milestones in HIV Vaccine Design and Development
1981–1989	First cases of a syndrome that later would be termed acquired immunodeficiency syndrome (AIDS); HIV identified as the cause of AIDS; CD4 identified as primary host cell receptor for HIV; assays developed to measure antibody and cell-mediated immune responses to HIV, to diagnose infection; first clinical trial of a candidate HIV vaccine; first viral-vector-based HIV vaccine designed; HIV variability identified; simian immunodeficiency virus (SIV) discovered; prime-boost vaccine strategy for HIV proposed.
1990–1999	Live-attenuated SIV protects against challenge with pathogenic SIV; CCR5 identified as co-receptor for HIV; first-generation HIV envelope-based vaccines elicit neutralizing antibodies against laboratory-adapted strains of HIV, but not against circulating primary isolates; discovery of broadly neutralizing HIV monoclonal antibodies; first HIV vaccine trials conducted in the developing world; more refined and validated assays developed to measure viral load and cell-mediated immunity against HIV; HIV-specific cell-mediated immune responses correlated with viral control; sites established in the developing world provide HIV incidence and HIV genetic sequence diversity data.
2000–present	Broadly neutralizing monoclonal antibodies against HIV protect against challenge with chimeric simian/human immunodeficiency virus (SHIV); first efficacy trial of gp120 fails to protect against HIV infection or suppress viral load; HIV is found to deplete CD4 central memory cells and amplify in gut-associated lymphoid tissue (GALT) early after infection; adenovector-based vaccine (Merck) advances to proof of concept Phase IIb trial.

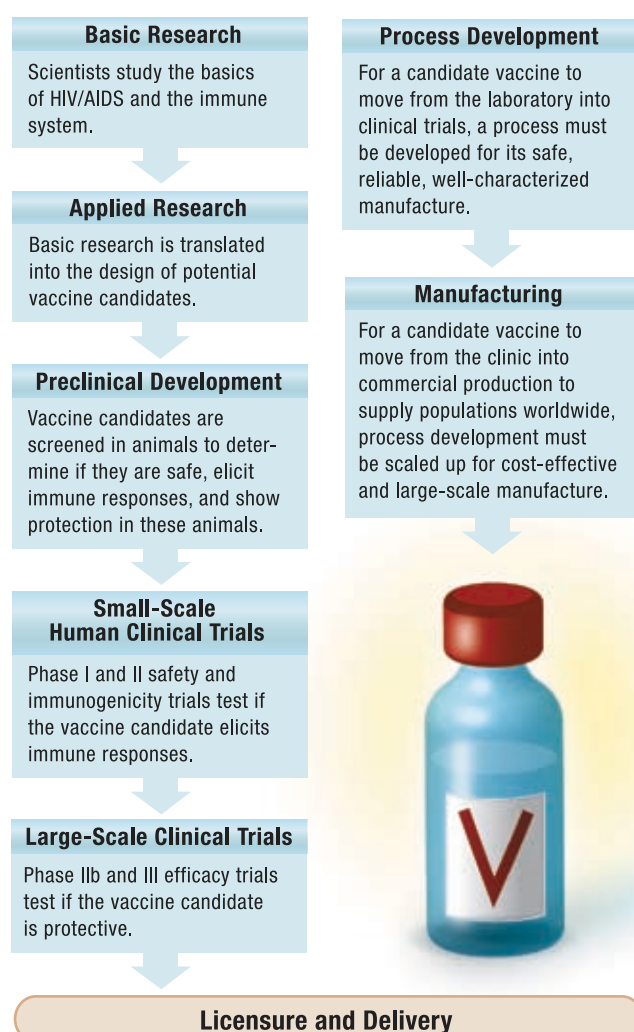


Figure 5 AIDS Vaccine Research and Development

These limitations render predictions from SIV studies in monkeys to AIDS vaccine trials in humans problematic. Until a candidate vaccine demonstrates protection in humans and these data are related back to analogous studies in the monkey model, questions regarding the relevance of animal models will persist.

Collectively, these scientific challenges highlight a need to establish new strategies to overcome them (Rational Vaccine Design) in order to fuel the pipeline with new and interesting vaccine concepts to test in efficacy trials (Scientific Empiricism).

Only one vaccine concept—based on a cell-mediated approach—has completed Phase III efficacy trials, and this failed to demonstrate efficacy (VaxGen, gp120; see Table 3). In 2008–2009, data from two additional trials will be available and are eagerly anticipated by the field. Sanofi-aventis-VaxGen has a Phase III trial to induce cellular-helper and humoral immune responses. Additionally, Merck is conducting a Phase IIb trial of its adenovirus-based candidate, the first real test of a candidate that induces robust cell-mediated immune responses in the majority of recipients. It is hoped that this will translate either to some degree of protection from infection or at least suppression of viral load that ameliorates disease progression in vaccinees who become infected incidentally (Table 4).

Replication-defective adenovirus serotype 5 (Ad5)-based vectors like Merck's are the leading candidates in the pipeline (Table 3). Unfortunately, in some developing countries more than 80% of individuals have significant levels of antibodies to the naturally circulating Ad5 (which causes a severe form of the common cold), and this pre-existing immunity may impede the efficacy of Ad5-based vaccines. If the Merck

Table 2	HIV Vaccine Candidates in Phase I/IIa Trials	
Viral Vectors		
Adeno		
Adenovirus-5 (Clade B)	Merck	
Adenovirus-5 (Clades A,B,C) [DNA]	NIH-VRC	
Adenovirus-6 (Clade B)	Merck	
Viral Vectors—Pox		
Canarypox (Clade B/E), gp120 boost	Aventis	
MVA (Clade C) [DNA]	IAVI-ADARC	
MVA (Clade C)	IAVI-Therion-India	
MVA (Clade B) [fowlpox]	Therion	
MVA (Clade B) [DNA]	GeoVax	
MVA (Clade A/E) [DNA]	WRAIR	
Fowl pox (Clade B) [MVA]	Therion	
NYVAC (Clade C) [DNA]	EuroVac	
Vaccinia (Cocktail)	St. Jude’s Hospital	
Other		
VEE (Clade C)	AlphaVax	
AAV-2 (Clade C)	IAVI-CRI-TGEN-CHOP	
DNA Vectors		
Clade C, MVA boost	IAVI-ADARC	
Clade B—minigenes	Epimmune	
Clade B—nuclear anchor	FIT Biotech	
Clade B, MVA boost	GeoVax	
Multiclade—A,B,C, Ad5 boost	NIH-VRC	
Clade B—Micro particle, gp140 boost	Chiron	
Multiclade, gp120 boost	U. Mass	
Multiclade—ABC, MVA boost	Karolinska	
Clade C	Johns Hopkins	
Clade B/C, NYVAC boost	EuroVac	
Clade B—IL12, IL—15, peptide boost	Wyeth	
Subunit—Proteins		
gp120 [canarypox prime]	VaxGen	
gp120-multiple [DNA prime]	ABL	
Oliomeric gp140 [DNA prime]	Chiron	
P24 +fragment gp41	NCI-Ivanovsky-Russia	
Gag,nef-tat	GSK	
Subunit—Peptides		
Lipopeptides [ALVAC prime]	ANRS	
Multi-epitopes in GMCSF [DNA prime]	Wyeth	

Table 3	HIV Vaccines in/Soon to Be in Phase IIb and/or Phase III Clinical Trials	
Candidate	Scientific Question	Status
gp120 (VaxGen)	Protection against infection was observed in chimpanzees immunized with gp120, and the vaccine stimulated neutralizing antibodies against laboratory-adapted isolates of HIV.	Completed two efficacy trials of gp120. Both trials showed the vaccine had no effect in preventing HIV infection and no effect in suppressing viral load in those immunized subjects who subsequently became HIV infected.
Canarypox vector prime (Sanofi-Pasteur) + subunit gp120 boost (VaxGen)	gp120 alone failed to prevent HIV infection or suppress viral load in previous human efficacy trials. This clinical trial will assess whether priming with a canarypox vector and then subsequently boosting with gp120 provides additional benefit, e.g., prevents HIV infection or suppresses viral load.	Phase III. The trial is being conducted in Thailand and is fully enrolled with over 16,000 trial volunteers. Data from this trial are expected in 2008–09.
Replication-defective adeno-subtype 5 vector (Merck)	This trial is designed as a proof of concept to evaluate whether cell-mediated immune responses elicited by the Ad5 vectors containing three HIV genes (gag-pol-nef) confers any benefit. Phase I/II clinical trials with this candidate demonstrated that the vaccine is safe and that subjects not previously exposed to adeno-subtype 5 (i.e., no significant antivektor immunity) generated significant cell-mediated immune responses to the HIV antigens gag, pol, nef.	Phase IIb. This trial is enrolling 3,000 subjects, and initial data are expected in late 2007 or early 2008. This will be the first test of the vaccine, which should determine if any efficacy is conferred and provide the initial information on the potential impact of antivektor immunity. At the time of this writing, a second Phase IIb trial is being considered for this candidate, to be undertaken in South Africa, in order to assess the efficacy of this Clade B vaccine against Clade C isolates of HIV circulating in southern Africa.

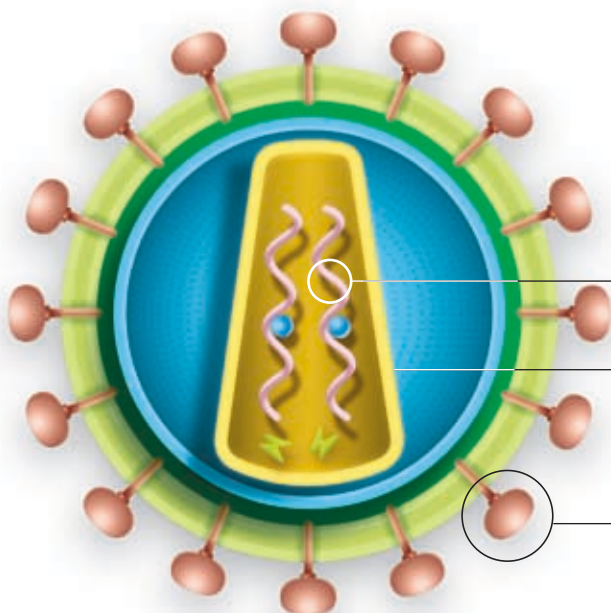


Table 4	
Potential Outcomes—Phase IIb Trial of Replication-Defective Ad5-HIV Vaccine	
Potential Outcome	Impact on the Field
Ad5-HIV vaccine suppresses viral load in significant numbers of subjects, irrespective of their pre-existing anti-Ad5 antibody titers.	This would be viewed as a very positive outcome, the first demonstration of benefit by an HIV vaccine in clinical trials, and would likely lead to additional Phase III trials of the Ad5-HIV vector in a move towards accelerating licensure. This would also enable validation of animal models, which would facilitate future candidate vaccine screening.
Ad5-HIV vaccine suppresses viral load in a subset of vaccinated subjects, but responses are ineffective or significantly impeded in subjects with high titers of pre-existing anti-Ad5 antibodies.	This would also be viewed as a very positive outcome, as the first demonstration of benefit by an HIV vaccine in clinical trials. If a clear mitigating effect of anti-Ad5 vector immunity is demonstrated, this likely would lead to accelerated testing of alternative adenovectors that offer the benefits of Ad5 without the concerns of antivector immunity.
Ad5-HIV vaccine has no effect on viral load, even in subjects where robust cellular immune responses against HIV are generated.	This would be viewed as important information for the field but would open a series of questions regarding the potential for CMI-based vaccines to provide benefit. Candidates which qualitatively or quantitatively provided benefits in Phase I/II trials and nonhuman primate challenge studies beyond those conferred by Ad5 would then be considered for potential efficacy trials.

VACCINES FROM HIV GENES

The vaccine uses HIV gene(s) as an immunogen. When taken up by human cells, these genes make HIV protein(s) that cannot cause disease but stimulate immune defenses.

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.

VACCINES FROM HIV PROTEINS

Proteins
The vaccine uses HIV proteins (e.g., gp120 on HIV's surface) as an immunogen.

Peptides
The vaccine uses small pieces of HIV protein(s) as an immunogen.

VACCINES FROM WHOLE HIV

Vaccines use whole HIV, as an immunogen, in its native structure but modified so it cannot cause disease.

Whole inactivated HIV
The vaccine contains killed HIV.

Live-attenuated HIV
The vaccine contains weakened HIV. While most licensed vaccines in use today for other diseases are live-attenuated, formidable safety concerns have limited research on live-attenuated HIV vaccines in humans.

COMBINATION

Combining different vaccine designs and/or different antigens could result in additive or synergistic effects capable of greater, broader, or more prolonged immune responses.

Figure 6 AIDS Vaccine Designs

Ad5-HIV vaccine candidate does suppress viral load in a subset of vaccinees but is less or not effective in those vaccinees with pre-existing immunity, there are a number of second-generation vaccine candidates in the pipeline. These candidates, which may enter clinical trials in the next 18–24 months, are not likely to be impeded by pre-existing immunity and include a variety of human (IAVI, NIH-Vaccine Research Center, Harvard), chimpanzee (IAVI-GSK partnership), and chimeric or hybrid (Harvard-Crucell) adenovirus-based vectors and cell lines (IAVI-Crucell) to support their production.

There is also a lack of candidates which can elicit HIV-specific mucosal immune responses, which will likely play an important role in preventing the establishment of persistent HIV infection. Vesicular stomatitis virus (Wyeth) and measles vectors (GSK), which could be administered intramuscularly or intranasally to induce systemic and mucosal immunity, are in development.

In conclusion, in the next two years only one other candidate will likely enter efficacy trials (DNA + Ad5, NIH-VRC). The emphasis on cellular immunity, which has been viewed as likely to be the most successful approach, has left the field with few alternative candidates and cultivated significant gaps in the breadth of the current clinical pipeline. To fill these gaps, efforts should focus on:

- Candidates that generate broadly neutralizing antibodies against HIV;
- Candidates that trigger mucosal immune responses against HIV;
- Replicating viral vectors or other candidates capable of generating persistent and long-lived immune responses against HIV;
- Candidates that elicit a comprehensive spectrum of anti-HIV immune responses, e.g., cellular immunity, mucosal immunity, neutralizing antibodies, durable immunity; and
- Candidates that improve upon the levels of protection conferred by adenovirus-based vectors in monkeys and/or protect against the establishment of persistent infection.

2.3 • A CHANGING POLICY LANDSCAPE TO SUPPORT AIDS VACCINE DEVELOPMENT[†]

Given the significant scientific challenges it is essential to ensure an optimally conducive policy environment. Recently there have been a number of positive develop-

ments towards ensuring adequate levels of well-targeted funding and the involvement of critical players in AIDS vaccine R&D.

Funding Vaccine R&D

Financial resources have grown significantly in recent years. In 2005 a total of US\$759 million was invested in AIDS vaccine R&D from all public, philanthropic, and commercial sources (Figure 7), more than double that invested in 2000.

Government funding consistently predominates. Of the 20 countries identified that invested public sector funds in AIDS vaccine R&D in 2005, the United States committed about 85% of the total, with European national governments and the European Commission collectively accounting for just over 10%. A comparison of investment in AIDS vaccine R&D as a percentage of GDP highlights the leading roles played by the United States, South Africa, and Canada (Figure 8).

The relative and absolute levels of contributions by sectors also fluctuate. In 2002 private sector investment represented 15% and philanthropic investment accounted for 17% of the total, reflecting a large contribution by the Bill & Melinda Gates Foundation (BMGF) and the ongoing Phase III VaxGen trial. It is anticipated that philanthropic support will rise in the coming years as BMGF increases its investments.

Private sector investment using internally generated funds has declined in recent years, from an estimated \$99 million in 2002 to \$75 million in 2005. This drop is largely due to the completion of VaxGen's Phase III

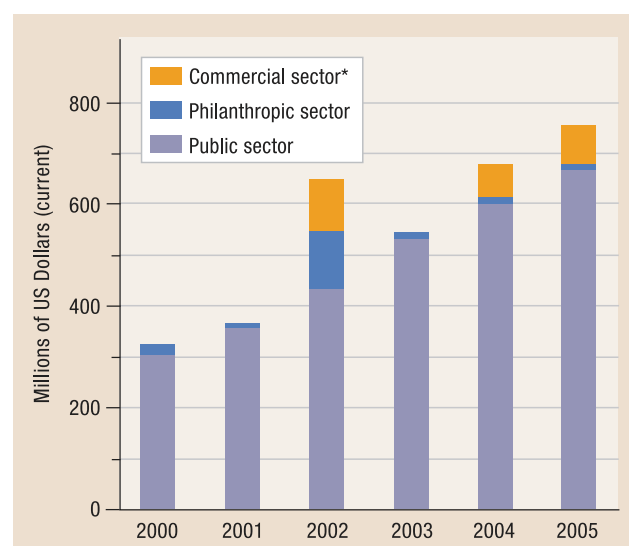


Figure 7 Funding Sources for Preventive HIV Vaccine R&D (2000–2005)

* Estimates of investment by the commercial sector (pharmaceutical and biotechnology companies) were made for selected years in the series.

Source: HIV Vaccines & Microbicides Resource Tracking Working Group (2006).
Adding It All Up: Funding for HIV Vaccine and Microbicide Development, 2000 to 2006.

% of GDP (x10 ⁻³)	Country
4.0–5.0	United States
2.0–3.0	Ireland
1.0–2.0	Canada, Netherlands, South Africa
0.5–1.0	Denmark, Norway, Sweden, United Kingdom
<0.5	Australia, Brazil, China, Finland, France, Germany, India, Italy, Japan, Russia, Thailand

Figure 8 Annual Average Public Sector Investments in Preventive HIV Vaccine R&D by Country Relative to National Wealth (2003–2005)

Note: This table is based on a 2006 study by the HIV Vaccines and Microbicides Resource Tracking Working Group; the full report is available at: www.hivresourcestracking.org. The study reviewed national, not subnational or provincial, public sector data. As no GDP data are available for Cuba, its investments are not captured in the table.

Source: HIV Vaccines & Microbicides Resource Tracking Working Group (2006). *Adding It All Up: Funding for HIV Vaccine and Microbicide Development, 2000 to 2006*.

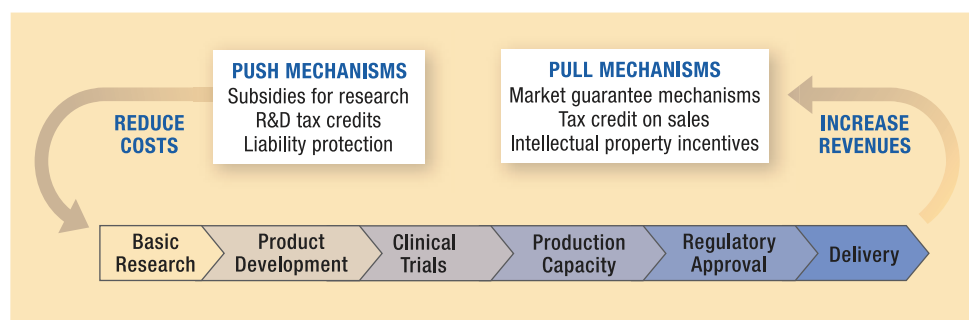
clinical trials and the company's subsequent exit from AIDS vaccines.

While the overall funding levels have risen, many in the field believe that inefficiencies exist and constrain R&D progress. Additionally, there is consensus that even greater resources will be required to support key areas that are currently under funded, particularly in Rational Vaccine Design, scientific empiricism for product development, and clinical trials capacity in developing countries. Resource needs will expand as multiple vaccine candidates enter costly later-stage clinical trials, especially if incidence rates drop due to counseling, treatment, and other interventions.

Developing an effective AIDS vaccine will be a long-term undertaking, so duration of funding and expectations need to be carefully managed to ensure sustained commitment. As the quantity of funding continues to grow, attention must be paid to improving the quality of financing by allocating new monies to the highest priorities and ensuring that they are managed efficiently.

Figure 9 “Push” and “Pull” Mechanisms to Incent AIDS Vaccine R&D

While “push” mechanisms remain the primary means to incent research and development, other mechanisms are complementary.



Harnessing Private Sector Resources and Expertise

The private sector holds much of the needed expertise to develop an AIDS vaccine, particularly in product development (bioprocess development, manufacturing of clinical lots, and vaccine trials) and commercialization. The corporate sector has been vital in the development of all recently licensed vaccines against other diseases, including the new rotavirus and HPV vaccines. Pharmaceutical and a small number of biotechnology companies are currently involved in AIDS vaccine R&D, often with external public sector financing. A far greater engagement of financial capital, intellectual capital, and product development expertise is needed.

In recent years policy discussions have focused on the use of push and pull incentive mechanisms to reduce the cost of R&D and to ensure viable markets for health technologies like AIDS vaccines (Figure 9). Push funding—specifically the direct subsidy of industry R&D—is by far the most important intervention to stimulate industry activity. Other push and pull mechanisms may be helpful complements to push funding.

Traditionally, most push funding goes directly to companies' research programs. Recently a number of government scientific research agencies and public-private partnerships (PPPs), including IAVI, have entered into agreements with companies in which R&D costs are shared and subsequent access is guaranteed to the developing world.

Other push mechanisms, such as tax credits and liability protection, are being investigated. In 2003, the UK government enacted the Vaccine Research Relief tax incentive for R&D related to AIDS, tuberculosis, and malaria; between 2003 and 2005 claims totaling £8 million were submitted, suggesting that companies are responding. Several other push mechanisms are also under discussion at global and national levels, particularly in the United States, where intellectual property incentives such as transferable patent extensions and fast-track regulatory approval have been suggested. These ideas are incorporated in legislative proposals but have not received strong political support to date.

On the pull side, an option under political and

financial consideration is advance market commitments (AMCs). An AMC would provide a legally binding promise by donors to vaccine manufacturers to subsidize the purchase of future vaccines at a fixed price, provided an appropriate vaccine is developed and it is demanded by developing countries. It could help to reduce market risks that discourage private sector investment in vaccine development and delivery while enhancing the availability and affordability of new vaccines for the countries that need them most. IAVI estimates that an AMC for an AIDS vaccine would require about \$3.3 billion.

Strengthening Developing Countries' R&D Capacity

Developing countries have been viewed as places where clinical trials are conducted rather than as sources of expertise, but increasingly the strong political, social, and practical reasons for ensuring that the AIDS vaccine R&D effort is truly global are being recognized and researchers are considering the contributions that can be made by training the next generation of developing-country scientists and strengthening health systems and infrastructure.

Extending the R&D effort to more countries builds capacity locally in scientific and clinical expertise and develops the scientific research infrastructure. Stronger ethical and regulatory institutions and processes help to maintain the quality of trials and to speed trial approvals, avoiding costly delays. Conducting trials can also bring important associated benefits to communities, including voluntary counseling and testing (VCT), healthcare services, prevention education, stigma reduction, and employment. Regulatory agencies in countries where vaccines have been tested may be more willing and able to approve successful vaccines.

The geography of AIDS vaccine R&D has evolved significantly in recent years, and the number of developing countries conducting vaccine trials continues to increase, with four additional countries—China, India, Rwanda, and Zambia—beginning trials since 2005. From a scientific perspective, testing vaccine candidates in populations with a high incidence of HIV infection equates to an accelerated timeline to results. The effectiveness of vaccine candidates needs to be tested in different populations and epidemiological and cultural settings, as well as against the different HIV subtypes that circulate globally.

Beyond clinical trials, innovative developing countries such as Brazil, China, and India can contribute to other aspects of the AIDS vaccine R&D process. With their growing technological capabilities in vaccine research, testing, and manufacturing, these countries are likely to increase their activity in the early discovery phases of R&D, as well as the later stages of production once a successful vaccine emerges.

2.4 • RECENT PROGRESS TOWARDS AN AIDS VACCINE

Since the XV International AIDS Conference in Bangkok, July 2004, steps have been taken towards the implementation of a more integrated vaccine design effort. Three of the founding members of the Enterprise have launched programs to design vaccines to elicit broadly neutralizing antibodies, elucidate the correlates of protective immunity, and address the scientific challenge of HIV variability:

- The Bill & Melinda Gates Foundation established the Collaboration for AIDS Vaccine Discovery (CAVD), a network of 11 vaccine-discovery consortia focused on designing AIDS vaccines that elicit durable and broad-spectrum cellular, neutralizing antibody, and mucosal immune responses, supported by five centralized facilities that provide standardized laboratory analysis and statistical support;
- The US National Institute of Allergy and Infectious Diseases (NIAID) established the Center for HIV/AIDS Vaccine Immunology (CHAVI) to study the virologic, genetic, and immunologic responses to acute HIV infection, elucidate correlates of human protection through a range of human and nonhuman primate studies, and translate this knowledge into the design of AIDS vaccines; and
- The International AIDS Vaccine Initiative (IAVI) expanded its Neutralizing Antibody Consortium (NAC) focused on solving the neutralizing antibody problem, established new consortia to elucidate the correlates of protective immunity, and established an industrial-style AIDS Vaccine Development Laboratory to provide enhanced capabilities for the field in process development, systematic optimization and prioritization of candidate vaccines, and new approaches to vaccine design.

New insights from HIV pathogenesis studies show the rapid seeding of HIV into gut-associated immune cell compartments very soon after infection, generating a renewed emphasis on mucosal immunity and the design of vaccine candidates capable of blunting HIV replication before the establishment of persistent infection. Advances in the structural analysis of the HIV envelope glycoprotein have opened new avenues of vaccine design to elicit neutralizing antibodies. And recent data suggest a prominent role for maintenance of CD4⁺ central memory cells in enhanced survival in preclinical SIV vaccine studies, highlighting a potential mechanism for protective immunity.

A number of countries are actively working to enhance the policy environment for AIDS vaccine R&D. For example, several developing countries have either promulgated national AIDS vaccine plans over the past two years (e.g., Kenya and Uganda) or worked to streamline their procedures for approval and monitoring of clinical trials (e.g., India and South Africa).

A movement of South-South collaboration has begun through specific political collaboration; India, Brazil, and South Africa announced a trilateral “IBSA” agreement known as the Rio Treaty to promote mutual technical assistance on AIDS vaccines and other disease programs.

Over the past decade the Group of Eight countries (the G8) has on numerous occasions recognized the imperative of developing a safe, effective, accessible

vaccine to prevent HIV infection. At the 2004 summit the G8 reaffirmed their commitment to expanded AIDS vaccine research and endorsed the concept of a Global HIV Vaccine Enterprise, “an alliance of independent agencies and research groups united by the moral commitment to accelerate HIV vaccine development and evaluation through participation in the implementation of a shared strategic scientific plan.” In both 2005 and 2006, these global leaders underscored their support for the Enterprise, increasing direct investment and moving ahead with groundbreaking work on market incentives. Within their messages the G8 focused specifically on public-private partnerships (PPPs), advance market commitments (AMCs), and building the research capacity of developing countries.

SECTION 3 Challenges Facing an AIDS Vaccine

Despite significant progress and over 30 candidates advancing to clinical trials, the goal of a safe, effective, and globally accessible preventive AIDS vaccine remains elusive. This is due primarily to the scientific challenges which HIV poses for vaccine development (Table 5).

3.1 • THE HIV HYPERVARIABILITY CHALLENGE

HIV is hypervariable, both within infected individuals and on a population basis, due to its rapid replication rate, high mutation rate, and capacity for recombination. Consequently the global picture of HIV variability (Figure 10) is classified into subtypes or clades, circulating recombinant forms, and unique recombinant forms. Putting this in context, the scale of HIV variability truly dwarfs that of another variable virus, influenza, for which a new vaccine formulation is developed each year (Figure 11).

The hypervariability challenge poses several problems for vaccine developers. First, it makes HIV a moving target, so selecting HIV antigens to include in a candidate vaccine is problematic: by the time the candidate has been designed, developed, and tested in Phase I/II safety and immunogenicity trials, the virus circulating in the population among whom efficacy trials will be undertaken may have evolved, complicating trial design. Second, no candidate in the current clinical pipeline has yet been demonstrated to be capable of neutralizing the wide spectrum of HIV isolates circulating worldwide. Third, vaccines targeted at conserved regions of the virus face the problem of “escape”—any CMI responses conferred by the vaccine mean that virus mutants that can evade those responses have an advantage and so quickly predominate. Fourth, the robust protection in

monkeys conferred by live-attenuated SIV is only effective against challenge with the homologous pathogenic SIV. If SIV in monkeys is predictive of HIV infection in humans, AIDS vaccines will need to be more effective than the live-attenuated SIV vaccines tested to date.

The global AIDS vaccine effort has yet to address this scientific challenge effectively. Current gaps include:

- Limited number of full-length HIV genomic sequences from isolates worldwide;
- Limited number of well-characterized SIV challenge virus stocks;
- Limited number of candidates in the clinical pipeline for which vaccine efficacy is being addressed and HIV antigens are modified to overcome variation issues;
- Lack of dedicated personnel committed to this scientific challenge; and
- Lack of high-throughput immunogen design and screening systems to address variability.

3.2 • THE NEUTRALIZING ANTIBODY CHALLENGE

Most vaccines work by neutralizing the infectious agent with antibodies and then eliminating the agent and/or infected cells. When natural infection induces an effective neutralizing antibody response, then mimicking infection should be an effective vaccine strategy, as is the case with the majority of killed (e.g., inactivated polio) or live-attenuated (e.g., measles) vaccines.

Table 5 Scientific Challenges in the Development of an AIDS Vaccine

Virus	<ul style="list-style-type: none"> • HIV isolates worldwide are hypervariable • HIV antigens required for protection remain undefined • HIV infects, suppresses, and destroys key cells of the immune system • there are limitations in the animal models for HIV/AIDS
Immune Response	<ul style="list-style-type: none"> • natural immune responses do not eradicate HIV • correlates of protective immunity remain undefined • the role of innate immunity remains poorly explored • superinfection with a second isolate of HIV is possible
HIV Transmission & Pathogenesis	<ul style="list-style-type: none"> • multiple forms: HIV is transmitted as cell-free and cell-associated virus • multiple routes: HIV is transmitted sexually, intravenously, and orally (breast-feeding) • 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 followed by amplification and seeding of other lymphoid organs • HIV incidence, time to set point, and required follow-up combine to make AIDS vaccine efficacy trials very complex and long (4–5 years)

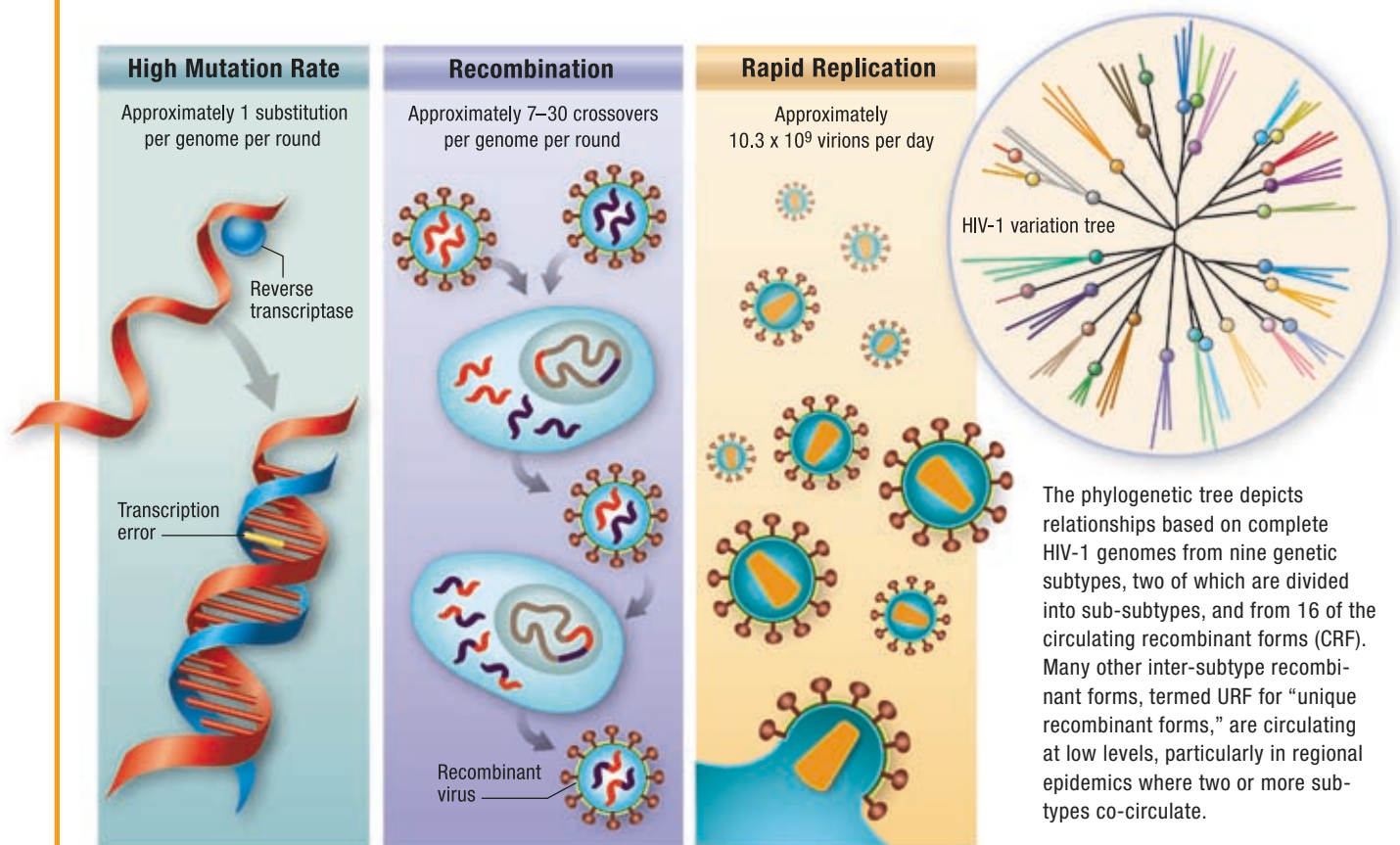


Figure 10 Causes of HIV Variability and Impact on the Circulating Virus

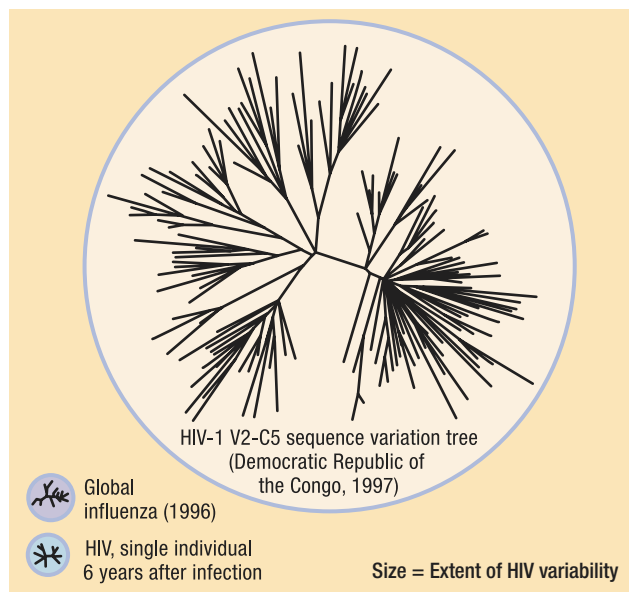


Figure 11 The Scale of HIV Variability

But HIV infection does not usually elicit broadly neutralizing antibodies due to the virus’s multitude of immune evasion strategies. These include the virus outer surface protein (Env or gp120) being decorated with a dense matrix of carbohydrates; the virus bind-

ing sites to its main host cell receptor (CD4) being normally shielded from neutralizing antibodies; and decoys to shift the immune response away from generating broadly neutralizing antibodies. HIV infection does sometimes induce broadly neutralizing antibodies and researchers have managed to isolate and purify these monoclonal antibodies and study their interaction with HIV to identify new approaches for vaccine design. Major global initiatives, including IAVI’s NAC, the Gates-sponsored CAVD and the NIAID-funded CHAVI, are providing increased resources to this field. Figure 12 outlines current strategies to address the neutralizing antibody challenge.

Key gaps that need to be addressed include:

- Lack of high-throughput screening assays to identify lead candidate immunogens that will elicit neutralizing antibodies;
- Lack of a systematic vaccine design effort comparable to drug discovery programs of the pharmaceutical industry;
- Reliance on part-time efforts of globally dispersed teams of academic investigators, rather than an industrial model with a full complement of resources devoted fully to the effort; and

- Lack of concentrated efforts to focus on new strategies to harness innate immunity, adjuvation, and immunogen delivery.

3.3 • THE RETROVIRUS CHALLENGE

HIV is a retrovirus which integrates its genetic material into the human genome and establishes a persistent and lifelong infection, and this has consequences for vaccine design. First, since HIV may be transmitted by free virus or virus-infected cells, multiple different immune responses might be required to provide complete protection. In particular, after integration into the host genome the HIV-infected cells appear no different from uninfected cells and so avoid immune defense mechanisms. Second, the establishment of persistence within the first 7–10 days after infection gives only a brief window of opportunity for vaccine-mediated immune responses to act, setting a steep challenge for the optimization of magnitude, durability, and localization of these responses. Once HIV has amplified and established infection in the lymphoid organs the best that can be expected from a vaccine is partial efficacy and slowing disease progression to AIDS, so the ultimate goal for an AIDS vaccine is to prevent the establishment of persistent infection. Licensed vaccines for another retrovirus, feline leukemia virus, have been successfully developed, suggesting that the problem is not intractable.

Key gaps that need to be addressed include:

- Lack of validated assays to assess mucosal immunity to HIV or SIV;
- Lack of vaccine candidates that elicit immune responses protecting the gut-associated lymphoid tissue where HIV is amplified early after infection; and
- Lack of vaccine candidates which elicit broadly

neutralizing antibodies, especially at the mucosal sites where initial HIV exposure occurs.

3.4 • THE ANIMAL MODEL CHALLENGE

HIV, like most pathogens, has highly restricted host specificity (tropism), so consequently there is no ideal animal model for HIV infection and disease. Nevertheless, vital tentative evidence of immunogenicity, safety, and efficacy may come from animal models that can parallel the human infection, immune response, and disease. Infection by HIV in nonhuman primates, such as chimpanzees, causes infection that does not progress to AIDS. Currently AIDS-vaccine designers rely on surrogate animal models, the most informative being the SIV-rhesus macaque model, but the pathogenesis of SIV infection in rhesus monkeys is more rapid than HIV in humans. The predictive value of this model will remain uncertain until protection of humans is demonstrated by an AIDS vaccine candidate in clinical trials. Rhesus macaques are also being utilized for preclinical immunogenicity and toxicology studies prior to the initiation of clinical trials. But, particularly for CMI-based vaccines, the identification of immunogenic regions of HIV in the rhesus macaque does not necessarily translate to immunogenic regions of HIV in humans since major histocompatibility antigens required for induction of CMI differ between the two species. However, many successful vaccines have been developed in the absence of an ideal animal model, including smallpox, measles, mumps, and pertussis.

Current gaps in the field regarding the animal model challenge include:

- A limited number of well-characterized SIV challenge virus stocks;
- Limited numbers of rhesus macaques available for SIV challenge studies;

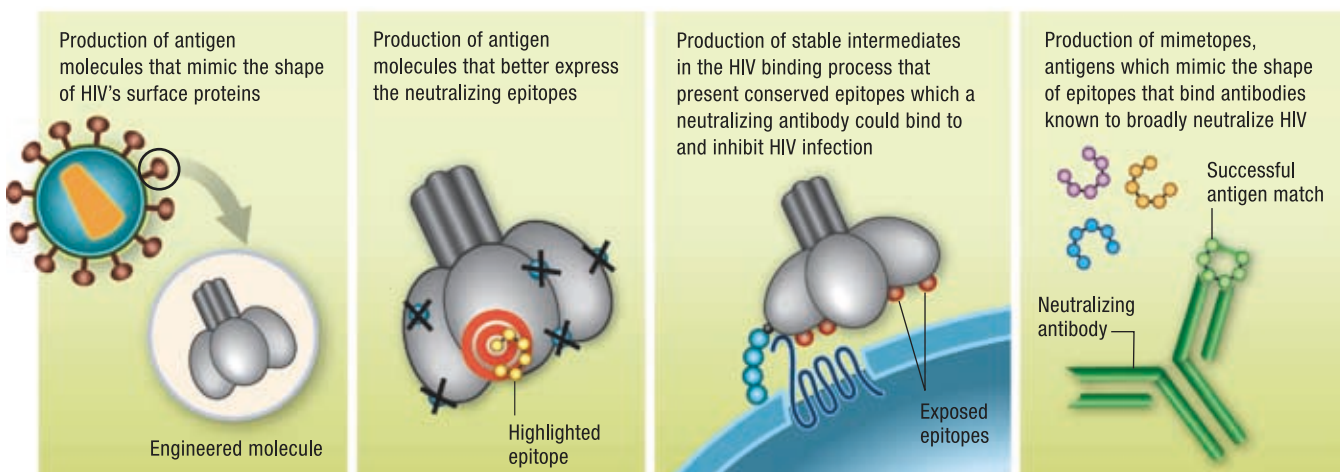


Figure 12 Current Strategies to Address the Neutralizing Antibody Problem

- Limited reagents to comprehensively assess immune responses in monkeys; and
- Lack of systematic planning. For example, preparations of comparative models (e.g., SIV- and SHIV-macaque studies with the analogous SIV inserts) should be preformed in anticipation of the results of the Merck Ad5 trials in 2008. If the Merck candidate is efficacious, there will be a unique opportunity to validate one or more of the monkey models.

3.5 • THE CORRELATES OF PROTECTIVE IMMUNITY CHALLENGE

In most infectious diseases persons can be identified who become infected with the pathogen, generate timely immune responses of the required magnitude and quality,

and clear the infection. Studying these individuals leads to identification of immune responses that correlate with protective immunity, which then facilitates vaccine development—for example, in the case of hepatitis B virus, antibodies to the virus surface antigen correlate with protection, providing a validated marker in vaccine trials. For HIV there is no documented case of “recovery” from infection so vaccine developers make hypotheses of the correlates of protection and then empirically test these in clinical trials. Figure 13 schematically depicts the potential correlates of protection against HIV. Effective vaccines against other diseases have been successfully developed in the absence of known correlates of protection—in fact, for most viruses there are no identified correlates of protection.

There are further practical considerations. Without a correlate of protection the field does not have a validated marker to determine whether one candidate

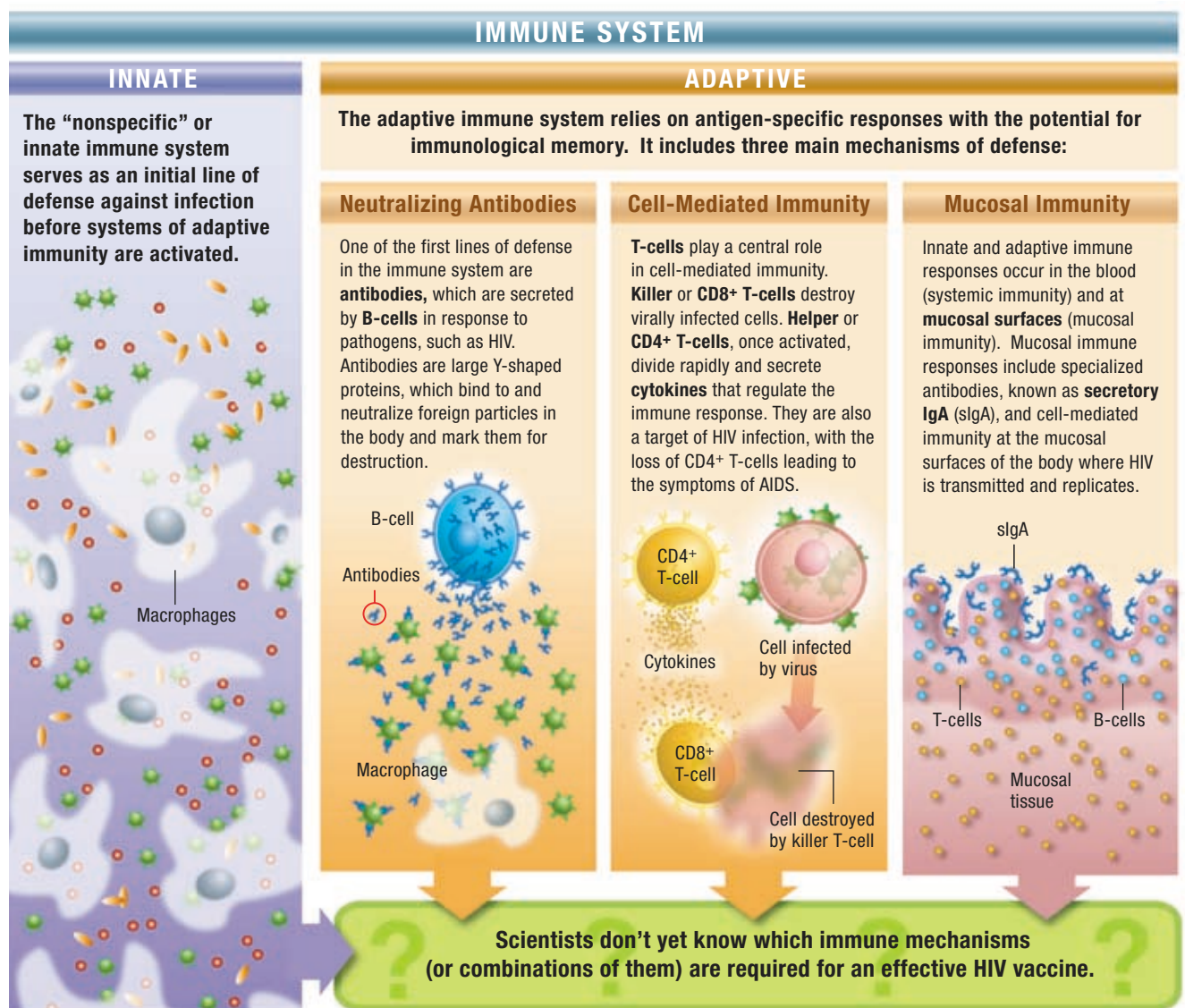


Figure 13 Potential Correlates of Protection Against HIV

is more effective than another. The current screening of CMI-based vaccines is focused on the ELISPOT assay, which tests whether a vaccine has stimulated cells of the immune system to react when they come into contact with specific HIV antigens. While this test can rank vaccines based on the magnitude and breadth of immune responses, it remains uncertain that those responses are biologically meaningful in the context of HIV infection.

A subset of HIV-infected humans termed “elite controllers” have, in the absence of antiretroviral therapy, controlled their infection for several years without progression to AIDS. Similarly, live-attenuated SIV vaccines have protected monkeys against challenge with homologous pathogenic SIV. Detailed study of these systems may reveal the correlates of protective immunity and so facilitate the design of new and improved vaccine candidates.

Current gaps in the field with regard to assessment of correlates of protection include:

- Lack of qualified and validated assays beyond the standard ELISPOT assay routinely used to assess cellular immunity;
- Lack of qualified and validated assays to assess mucosal immunity;
- Limited number of candidates in the pipeline that elicit immune responses other than cell-mediated immunity which have reached the stage of efficacy trials; and
- Lack of data demonstrating vaccine-induced protective immunity in humans.

3.6 • THE HIV ANTIGEN CHALLENGE

Candidate vaccines are being developed to test multiple HIV antigens in different combinations since it is not known which HIV antigens are needed for protection against infection. But this question has not been systematically addressed in either nonhuman primates studies or human efficacy trials that sequentially test different antigens in a specific vector that remains constant. Until some degree of efficacy is achieved in clinical trials and/or systematic studies are undertaken in nonhuman primates, this question will remain unanswered. Figure 14 schematically depicts the genome of HIV and highlights the major HIV antigens included in some of the leading candidate AIDS vaccines.

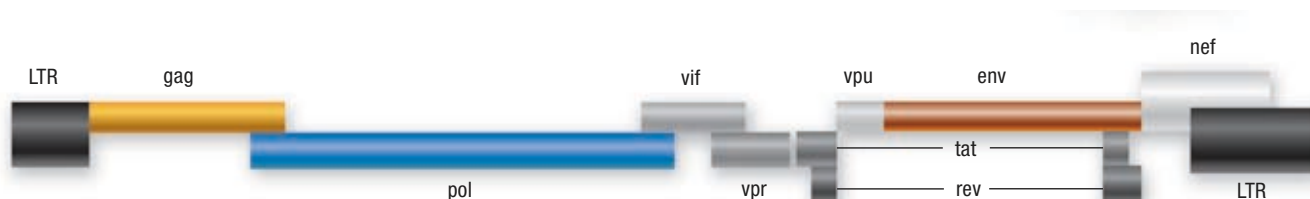


Figure 14 HIV Genome and Major Antigens

Current gaps include:

- No systematic assessment of the antigens required for protective immunity in vaccine studies in animal models;
- No comprehensive assessment of elite controllers to determine which HIV antigens are recognized by a human immune system that can maintain long-term control of HIV;
- No comprehensive assessment of the rare HIV exposed and uninfected individuals to determine which antigens are recognized; and
- Antigens required for protection by live-attenuated SIV vaccine have not been determined.

3.7 • THE CLINICAL TRIALS CHALLENGE

AIDS vaccine trials are conducted similarly to vaccine trials for other pathogens (Figure 5): Phase I trials focus on safety; Phase II on safety/immunogenicity; and Phase III on safety, immunogenicity, and efficacy. Phase IIb “proof of concept” trials are designed to obtain initial indications of the efficacy of vaccine candidates in a shorter time frame. While only one AIDS vaccine efficacy trial has so far been completed and took four to five years, the current ongoing Phase IIb trial is expected to yield significant data in three to four years. Given the urgency posed by thousands of people newly infected with HIV every day, strategies to accelerate clinical development of AIDS vaccines are imperative. Enhancing the capacity of regulatory and ethics review boards in developing countries could significantly shorten the time from protocol submission to initiation of a clinical study. Also, strategies to accelerate the testing of candidate AIDS vaccines in subjects at high risk for HIV infection, which to date has not occurred until Phase IIb or III trials, need to be considered.

Current gaps in efforts to accelerate clinical testing of AIDS vaccines include:

- Limited expertise in developing countries to conduct regulatory reviews of candidate vaccines, resulting in referral of regulatory review and risk-benefit analyses to developed countries, thereby stifling innovation;

- Unwillingness of trial sponsors to accelerate the testing of candidates in high-risk subjects, largely due to concerns that breakthrough infections will have negative repercussions;
- No comprehensive assessment of the roadblocks for accelerated clinical trials in developing countries, addressing issues such as infrastructure, training, liability, intellectual property, and costs; and
- Lack of experienced vaccine trials centers of excellence in developing countries capable of conducting multiple and parallel efficacy trials.

3.8 • THE FUNDING CHALLENGE

Much debate has focused on the financial resources available. More than \$700 million is devoted annually to AIDS vaccine research but it is widely agreed that there remain significant shortfalls in key areas, including:

- An overall shortfall estimated by IAVI of approximately \$300–400 million a year, even after spending increases flowing from the NIH's CHAVI and the new BMGF awards. This figure was confirmed by the Enterprise in costing its Scientific Strategic Plan;
- Additional funding for large-scale industrial-style consortia to support rational vaccine design and to increase clinical trials capacity. Resource demands will increase as more vaccine candidates continue through the clinical trial pipeline, particularly for larger, later-stage trials;
- Lack of an agreed burden-sharing plan that assigns a proportion of financing to all the major public (let alone philanthropic or private) organizations involved;
- Lack of consensus on which research areas are of relatively low or doubtful value and could therefore be terminated/curtailed to free up resources for other activities; and
- Lack of consensus on the organizational arrangements that will best expedite AIDS vaccine R&D and their financial implications. Expanded partnerships between research institutions, industry, and PPPs would have important financial repercussions.

3.9 • THE PRIVATE SECTOR ENGAGEMENT CHALLENGE

Greater engagement from pharmaceutical and biotech companies would undoubtedly expedite the success of the field. The private sector holds much of the needed expertise to develop an AIDS vaccine, including manufacturing, product development, and commercialization. Private investment represented only 10% of global totals in 2005, due in large part to the high scientific and commercial risks and uncertain returns on AIDS vaccine research.

Current gaps in the area of stimulating industry involvement include:

- Very few proposed incentive measures actually implemented or tested for effectiveness; and
- No existing forum for dialogue between private sector vaccine leaders and public sector and policy analysts to discuss constraints and possible incentive measures.

3.10 • THE DEVELOPING COUNTRY ENGAGEMENT CHALLENGE

There is a need to carry out R&D in a variety of epidemiological settings where populations are different and a variety of HIV isolates are circulating. It is also important to recognize the potential contributions of emerging biomedical research and manufacturing capabilities in innovative developing countries like Brazil, China, India, and South Africa. Recent years have seen significant progress in AIDS vaccine R&D capacity in developing countries but there are still some gaps, including:

- Ethical and regulatory systems which require further strengthening and streamlining;
- AIDS prevention and treatment services, including voluntary counseling and testing, are weak or absent in some existing or planned vaccine trial locales; and
- Community-awareness and mobilization structures need to be developed or reinforced at all vaccine trial locales to ensure their cultural appropriateness and continued acceptability.

SECTION 4 Addressing the Challenges

The theme of the XVI International AIDS Conference (Toronto, August 2006) is “Time to Deliver,” a call to the global community to achieve key milestones in the fight against HIV/AIDS. The urgency to accelerate progress in the search for an AIDS vaccine has never been greater and requires bold new initiatives to shorten the timeline for success.

The following set of recommendations address scientific and policy challenges outlined with five-year illustrative interim goals that could generate vital data, establish much-needed vaccine development infrastructure, and enhance the environment for R&D to bring us closer to developing a safe and effective AIDS vaccine.

4.1 • INTEGRATED PROGRAM FOR ACCELERATING AIDS VACCINE DEVELOPMENT

Scientific empiricism alone is unlikely to yield an effective vaccine. An integrated approach that incorporates rational vaccine design to address key scientific challenges to improve antigen development along with a more streamlined evaluation and testing procedure is required to accelerate AIDS vaccine development. In addition to the formidable scientific barriers to more rapid progress in AIDS vaccine R&D existing today, there are also major policy obstacles which must be overcome in order to speed scientific progress.

RECOMMENDATIONS:

Formalize a Comprehensive Rational AIDS Vaccine Design Effort

Despite more than \$700 million invested annually in AIDS vaccine R&D, HIV continues to outpace vaccine development efforts. In our assessment, this is due to four principal factors:

1. The scientific challenges posed by HIV are numerous and, in large part, are not being systematically addressed with adequate resources (see above);
2. The vast majority of the resources earmarked for the global AIDS vaccine effort go to university-based academic investigators who must fulfill the administrative, teaching, and other responsibilities inherent in the academic environment. This means that most investigators are only able to devote part of their time to AIDS vaccine research, which is inconsistent with the urgency and complexity of the problem;
3. The industrial model of vaccine development—which has formed the basis for all recently licensed vaccines, including but not limited to in-licensing of novel platform technologies, applied/translational research creating vaccine designs, process development, and rigorous milestone-driven product development—is currently not a major component of the global AIDS vaccine research and development endeavor; and
4. The AIDS vaccine effort is driven largely by scientific empiricism, which, while successful in the development of other vaccines, may not be adequate by itself to tackle HIV.

We believe that two complementary approaches are needed to accelerate AIDS vaccine development: a Rational AIDS Vaccine Design Effort and a next-generation Collaborative Scientific Empiricism Effort (see below). Although recent initiatives from individual stakeholders or collectively from the Enterprise are making positive steps towards establishing some of the required elements of a Rational AIDS Vaccine Design Effort, many factors—including the level of resources, time commitment of leading scientists, inadequate integration of research and development, lack of significant industrial involvement—have yet to attain a scale commensurate with the challenge. Resources must be made available to formalize a comprehensive Rational AIDS Vaccine Design Effort that focuses on solving the key scientific challenges and translating that new knowledge into novel vaccine designs. This should be closely integrated with a vaccine development infrastructure comparable to that found in industry, including process development and manufacturing capabilities, and closely linked to Vaccine Trial Networks of Excellence in the developing world (see below). The key elements for this effort would include:

- Closely linked multidisciplinary scientific teams, dedicating a majority of their time to solving the AIDS vaccine challenges;
- Implementation of rigorous, industrial project and portfolio management systems to monitor progress and shift resources accordingly;
- Core resources and enabling programs, including appropriate high-throughput tools and procedures adapted from drug discovery efforts;
- Dedicated nonhuman primate facilities

with adequate resources for comparison and prioritization of candidate vaccines; and

- Access to a dedicated vaccine development infrastructure, including process development and manufacturing capability for translating leads to the clinic.

Several models of organizational structure could be envisioned for the Rational AIDS Vaccine Design Effort, including: establishing dedicated AIDS vaccine R&D companies; building upon existing scientific consortia to include the requisite elements; building upon established biotechnology and pharmaceutical industry activities; and linking these to established scientific consortia with elements described above. In the absence of such an entity, the current system will continue to suffer from significant inefficiencies, duplication of effort, and, perhaps most importantly, the lack of linkage to industrial skills, management techniques, and accountability critical for successful vaccine development.

The following represent illustrative interim goals:

1. Identify one or more immunogens capable of neutralizing at least 50% of a standard reference panel of moderately resistant and globally diverse HIV isolates;
2. Solve the mechanism of protection observed with live-attenuated SIV vaccine in monkeys, including which antigens are required;
3. Solve the mechanism of protection in HIV elite controllers and/or exposed/seronegative persons;
4. Establish and validate assays to assess mucosal immune responses associated with HIV infection in preparation for clinical trials of vaccine candidates that elicit mucosal immunity; and
5. Systematically prioritize novel vector vaccine candidates based on standardized SIV protection studies and advance at least one new promising candidate to clinical trials that shows greater protection against SIV than the leading adenovirus vector-based candidates.

Develop an Enhanced Collaborative Scientific Empiricism Effort

An enhanced Collaborative Scientific Empiricism Effort should focus on the design and clinical efficacy testing of AIDS vaccine candidates that improve qualitatively or quantitatively upon the immune responses elicited by the current adenovirus vector-based candidates, which are likely to provide the next set of human efficacy data and, hopefully, become the interim “gold standard.” In

addition, the field will gain important scientific insights if a set of small trials (about 500 subjects at high risk for HIV infection per trial) were conducted in parallel to provide preliminary assessments of efficacy.

The vast majority of AIDS vaccine candidates currently in the clinical pipeline focus on generating CMI responses against HIV. The Collaborative Scientific Empiricism Effort would link closely to the recommended Rational AIDS Vaccine Design Effort (see above), with the collective goal of expanding, qualitatively and quantitatively, the clinical pipeline of candidate vaccines within the next five years (Figure 15).

The following represent illustrative interim goals:

1. Create new assays, better able to predict efficacy of candidate vaccines in preclinical and clinical trials;
2. Develop candidates to address the gaps noted within the current pipeline and at least one should advance to Phase IIb clinical trials (dependent on safety in Phase I trials) when any of the following benchmarks are reached:

Neutralizing antibody: Candidate elicits neutralizing antibodies in at least 60% of subjects in Phase I trials and the antibodies neutralize at least 50% of moderately resistant, globally diverse isolates from standardized panels;

Cellular immunity: Candidate induces cellular responses in at least 60% of subjects in Phase I trials, and is either qualitatively different from (and so tests a new scientific hypothesis) or quantitatively better than the existing cellular standard currently set by the Merck Ad5 and NIH-VRC DNA + Ad5 regimen;

Mucosal immunity: Candidate elicits HIV-specific mucosal immunity in at least 60% of subjects in Phase I trials;

Protection by analogous SIV vaccine candidate from pathogenic SIV challenge: HIV vaccine candidates have generated anti-HIV immune responses in 60% of subjects in a validated potency assay in Phase I trials and the analogous SIV vaccine candidate has suppressed viral load greater than 2.0 logs at set point.

3. Evaluate and develop novel adjuvants that enhance immune responses to candidate vaccines and advance the best of these into clinical trials.

Establish a New Model for Accelerating AIDS Vaccine Trials

AIDS vaccine clinical trials currently follow the standard

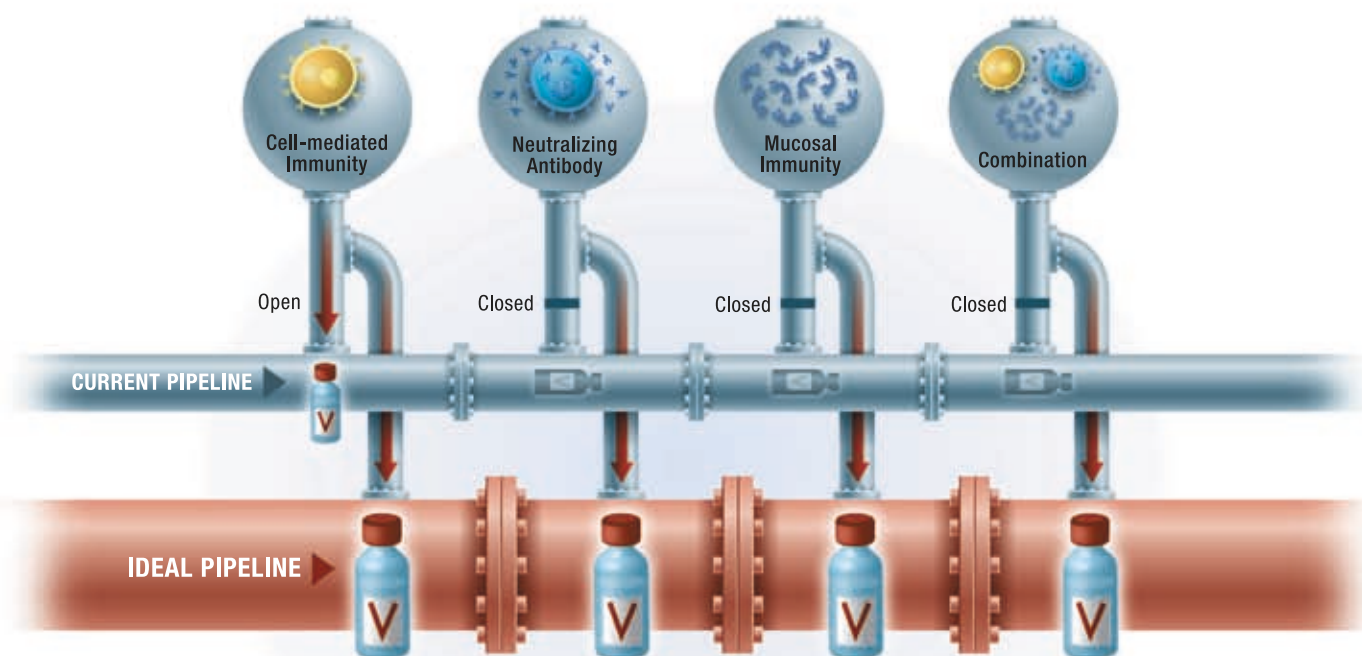


Figure 15 The AIDS Vaccine Pipeline

clinical trial paradigm that does not allow for the accelerated testing and prioritization of promising candidates. The weaknesses of the current paradigm include:

- Markers/HIV immunogenicity studies—the immunological markers being assessed may not correlate with protection;
- Monkeys/SIV challenge studies—it remains unclear how predictive the SIV/macaque models are until human efficacy data are demonstrated and can be compared; and
- Time/Current Phase IIb designs—current designs of Phase IIb trials of 3,000 persons take a minimum of three years to obtain an interim analysis; six trials of 500 persons each comparing different vaccine candidates could be accomplished with the same resources.

Given the urgency of HIV/AIDS, a novel paradigm is needed. We propose that candidates which fulfill the criteria above should be rapidly advanced into Phase II trials in subjects at high risk of HIV infection to allow preliminary efficacy assessments. Utilizing the Vaccine Trial Networks of Excellence (see below) in locations of high incidence, the following new paradigm should be established:

Candidates to enter Phase I trials: those based on novel scientific hypotheses that are qualitatively or quantitatively superior in preclinical studies to the current leading adenovirus vector-based candidates. These safety trials should be conducted in a small number (<50) of subjects at sites where Phase II trials would be conducted.

Candidates to enter Phase II preliminary efficacy trials: those that fulfill the criteria above should be advanced immediately to Phase II trials of approximately 500 subjects at high risk for HIV infection, such as serodiscordant couples in populations where HIV incidence rates exceed 4–5% per year. While these data would not provide a statistically significant evaluation of efficacy, the expected 20–25 new infections per year would provide important new information for the field, including: a) an expansion of the database of safety and immunogenicity on leading candidates; and b) an ability to assess, in the context of acute HIV infection, anti-HIV immune responses, viral load at peak and set point, and host genetics. This would also provide the initial preliminary efficacy data on candidates that, when considered with the safety and immunogenicity data and other factors, would allow for improved prioritization of the most promising candidates.

Based on preliminary efficacy data from these accelerated Phase II efficacy trials, an algorithm would be established for either terminating, modifying/improving, or advancing the candidate to Phase III trials, taking into account additional process development and manufacturing activities likely required for Phase III trials to commence.

The following represents an illustrative interim goal:

To test the value of this new paradigm, a series of 500-person Phase II trials using subjects at high risk for HIV infection could be conducted on representative DNA-, adenovirus-, and poxvirus-based candidates, plus prime-boost combinations of same.

Finance a Dynamic Global R&D Program

Further evaluation of resource allocation is required to establish the Rational AIDS Vaccine Design and Scientific Empiricism Efforts described above. Funding must remain flexible in order to respond to changing R&D priorities, while at the same time donors must be prepared to commit long-term, probably for a decade or more, before one or several new generations of more effective vaccines emerge.

As the Enterprise monitors and updates its Scientific Strategic Plan in the coming years, it will provide the field with greater clarity and transparency regarding the highest-priority scientific questions, avoiding unwarranted duplication of effort and enabling the efficient reduction/termination of lines of investigation when resources are better spent elsewhere.

Recent modeling of the AIDS vaccine R&D pipeline and the effects of various spending decisions suggests that the probability of successfully developing a vaccine in the coming years is possible with a combination of targeted measures to expand the number of candidate vaccines being tested, raise the diversity and overall quality of those vaccines, and reduce average “time in phase” for trials and licensure.

To achieve this, the major scientific institutions, government funders, companies, and others must:

- Analyze the funding gaps and the composition of spending, taking into account the potential for reallocation of existing resources;
- Agree to clear targets for required spending;
- Develop an equitable financial-burden-sharing formula to be applied to all developed- and developing-country governments. This formula should recognize that developing countries may be better placed to contribute by building capacity for vaccine R&D;
- Monitor actual financial commitments and spending levels; and
- Explore other innovative mechanisms to encourage broader participation by foundations and the wider (non-healthcare) private sector.

The following represent illustrative interim goals:

1. Resource gaps are identified and evaluated; an appropriate formula for public sector financing of AIDS vaccine R&D is developed and applied;
2. A system for monitoring resource needs is in place;
3. The resource gap is filled by greater (and more balanced) public sector contributions

that are matched in scale and scope to R&D efforts; and

4. Philanthropic and private contributions increase substantially.

Increase the Engagement of the Private Sector

Recent policy discussions on the use of push and pull incentive mechanisms to engage pharmaceutical and biotech companies in AIDS vaccine R&D have been wholly theoretical; these mechanisms now need to be implemented and evaluated. They could be usefully tried in developed countries and also where private sector capabilities in pharmaceutical and biotech R&D are nascent but promising, for example in China, India, or Russia.

For large pharmaceutical companies, a variety of push and pull mechanisms could be deployed. Expanding push funding through public sector research grants and through support to public development partnerships (PDPs) are proven options, but others to be explored include market guarantees through AMCs, liability protection, enhanced intellectual property protection, and fast-track regulatory approvals. Earlier efforts to influence industry R&D decisions—including orphan drug rules in the United States, EU, and Japan, along with patent extension and market exclusivity for pediatric formulations in the United States and EU—have had noticeable impacts and similar mechanisms could be developed for AIDS vaccines.

Pharmaceutical companies can also contribute to AIDS vaccine R&D through indirect and in-kind means like providing staff and equipment to PDPs and to developing countries. Vaccine companies could also make available their expertise in areas such as structural chemistry and bioprocess development.

Biotechnology companies typically have narrower pipelines, limited or nonexistent revenue streams from existing commercialized products, and access to shorter-term capital, so will likely require incentives that can be converted to cash more rapidly (within five years or less). They might be engaged through the design and test of interim pull measures that reward the successful completion of specified scientific milestones, such as a proof of concept trial with clearly specified and appropriate end points.

To meet this challenge of a private sector gap, governments and industry need to work together to:

- Monitor the expected AMC pilot program and agree with its major donors on how it might be extended to an AIDS vaccine after success in a proof of concept trial;
- Develop a plan to test additional incentive measures for the private sector; and

- Explore new approaches tailored to the needs of smaller biotech firms.

The following represent illustrative interim goals:

1. Lessons drawn from the AMC pilot program are used to reconsider and launch an AMC for AIDS vaccines;
2. Additional incentive mechanisms are in place in several countries (OECD and non-OECD); and
3. A review of interim pull measures suitable for smaller biotech firms is completed and recommended measures are implemented.

4.2 • CAPACITY BUILDING TO PAVE THE WAY FOR FUTURE AIDS VACCINE DEVELOPMENT

In order to effectively capitalize on the recommendations above, the capacity to allow for rapid advancement of clinical trials and the political environment to support research and access must be carefully established and fostered in the next few years.

RECOMMENDATIONS:

Establish Vaccine Trial Networks of Excellence

Despite significant investment over the past two decades there are still only a limited number of clinical trials centers in the developing world capable of conducting multiple and parallel AIDS vaccine trials, and none in areas of the world like India, China, and Russia, where epidemics are burgeoning. The proposed Networks of Excellence (NOE) should have the capacity to conduct trials of candidate vaccines against diseases of the developing world other than HIV, particularly malaria and tuberculosis (TB). They should also have the capacity to conduct clinical HIV research that will inform subsequent vaccine design and prepare for vaccine efficacy trials, including incidence studies, molecular epidemiology of the transmitted virus, and population-based host immune response studies of HIV infection.

Regional NOE should be considered in East, West, and South Africa; India; China; Russia/Eastern Europe; Southeast Asia; and Latin America/the Caribbean, where circulating HIV isolates vary, to conduct multi-center trials. Clinical trial designs conducted at these NOE should plan for success and be able to transition adaptively from Phase I (safety) to Phase II (preliminary efficacy) to Phase III (efficacy/licensure) trials, shortening time delays associated with clinical development and enabling faster and more effective screening of candidates.

It is critical that these NOE provide career paths for young researchers, long-term financial stability, adequate

remuneration, a culture of excellence, and reliability in data collection and implementation of research. Key elements for these NOE would include: strong leadership; academic links; clinical trials capacity; laboratory capacity, including accredited and validated labs; data management; epidemiology; training facilities; community links; and national and international support.

The following represent illustrative interim goals:

1. Establish regional Vaccine Trial Networks of Excellence in the areas of the world noted above;
2. Conduct clinical research and Phase I trials at each of the new NOE within five years; and
3. Develop capacity to conduct at least five Phase II trials of 500 volunteers at high risk for HIV infection within five years.

Train the Next Generation of Scientists for AIDS Vaccine R&D

The development and deployment of a safe and effective AIDS vaccine is a marathon, not a sprint. Attracting and maintaining the best and brightest scientists to the AIDS vaccine field is critical to maintain momentum. We propose that new training initiatives be established in association with the Rational Vaccine Design Effort and new Vaccine Trial Networks of Excellence.

The following represent illustrative interim goals:

1. Establish new postdoctoral fellowships for assay development, data management, molecular virology, structural biology, HIV immunology, mucosal immunity, HIV clinical trials, and other related disciplines;
2. Set a predetermined quota of new scientists to be trained each year in these disciplines;
3. Establish training programs for laboratory technicians, veterinary scientists, and other support teams to ensure adequate infrastructure;
4. Establish career pathways for talented young scientists in developing countries that include adequate remuneration and incentives to stay in-country; and
5. Create new funding paradigms for the Rational Vaccine Design Effort to enable scientists to focus on the research rather than grant writing, administration, and other activities.

Improve the Environment for AIDS Vaccine Research in Developing Countries

It is vitally important to test vaccines in those populations and countries hardest hit by the epidemic. Engagement

in vaccine research by a country also enhances the chances that the government and civil society groups will embrace rapid uptake of the vaccine once it has been proven effective. At national and local levels, a comprehensive approach is required to successfully conduct trials and reduce risks of delays.

To encourage expanded engagement of developing countries in vaccine R&D, research sponsors, donors, and developing-country governments should:

- Undertake social science research to elucidate barriers to trial participation;
- Ensure far-reaching voluntary HIV counseling and testing in and around trial sites;
- Provide technical assistance to national regulatory agencies; and
- Train trial staff on social harm, gender, and ethics.

Steps must also be taken to develop a favorable global policy environment for clinical trials. Development of open trial sites, agreement on guidelines for inclusion of adolescent populations in vaccine trials, and setting standards of care in evolving treatment and prevention environments would facilitate the conduct of trials. Regulatory support for trials in resource-poor countries may be sought from national regulatory agencies in other countries, the WHO's Developing Countries Regulatory Network, and the UNAIDS Vaccine Steering Committee. To meet these global policy challenges, the field must reach agreement on:

- Common standards for running clinical trials to assure that valid and comparable data are obtained using laboratory infrastructure that meets international best practice;
- Application of good clinical practice standards created by the International Conference on Harmonisation (ICH-GCP); and

- Definition of consensus equipment, validation of techniques, and development of standard operating procedures, along with quality control of all assays and laboratories.

The following represent illustrative interim goals:

1. National AIDS vaccine plans are completed and receive high-level government endorsement in key developing countries;
2. A comprehensive review of national ethical and regulatory systems is completed and proposals are developed and implemented in developing countries; and
3. AIDS vaccine trials (enrollment, community advisory boards, local leadership, communications activities) are conducted and best practices published.

Prepare for Rapid Vaccine Approval and Uptake

In the past, as new vaccines have been launched there have been significant delays in availability, especially in resource-poor countries. Given the global patterns of HIV prevalence and the impact of the disease on the poorest countries, it would be unconscionable not to make an effective AIDS vaccine widely available as soon as possible after its development.

Many key characteristics of an effective vaccine remain unknown, but a plan for its global introduction should be developed and include the following recommendations:

- Taking forward AIDS vaccine demand scenario-building; modeling of the epidemiological, health, and economic impact of a vaccine; assessing financing options; and performing cost-effectiveness and cost-benefit analyses of AIDS vaccines; and

- Validating these analyses by a group of global stakeholders representing public and private sectors.

The following represent illustrative interim goals:

1. Analytical work on demand scenarios, impact modeling, financing, and cost-effectiveness/ costs-benefits is completed;
2. At least one regional mechanism for vaccine registration and licensing is in place;
3. Lessons from introduction of HPV and rotavirus vaccines are compiled and consultations are held to disseminate their implications for AIDS vaccines; and
4. AIDS vaccine introduction scenarios are formulated for developing countries with significant HIV epidemics.

4.3 • CRITICAL ACTIONS TO BUILD AND SUSTAIN LONG-TERM POLITICAL SUPPORT AND COMMITMENT

Implementing these recommendations will require enormous commitment from many groups that will have to be sustained until vaccines are accessible to all those who need them. This will require support on many levels, from the grassroots to the global. The future of AIDS vaccines, however, is dependent not only on the excitement that the research engenders but on the general perceptions of the importance of HIV.

While some key political documents make reference to AIDS vaccines and other new preventive technologies, there are still a number of underutilized opportunities to build support for vaccines. For example, while attention is closely focused on the global commitment to universal access to AIDS prevention, treatment, and care, few champion better prevention

tools as critical to containing the ever-growing costs of treatment. Similarly, while the global debate is recognizing the feminization of the pandemic—linked to women’s biologic, social, and economic vulnerabilities—there is a tendency to promote microbicides rather than call for a range of options to give women and girls choices appropriate to their lives. Startlingly, campaigns calling for a generation without AIDS do not even mention vaccines.

Other voices can galvanize greater government engagement. Leaders from the South can call for attention and ensure that their domestic policies and programs foster research and build systems for delivery. They can also play important roles in sharing good practices, for example through regional and other (e.g., IBSA) collaborations. Civil society groups—particularly those advocating for women’s health and reproductive rights, for HIV treatment and prevention, for programs targeting marginalized and vulnerable populations, and for youth—should include AIDS vaccines among their priorities.

While most will recognize that AIDS vaccine R&D is a long-term challenge, political and financial realities often have much shorter time horizons. Continued political support, from leaders of high-, middle-, and low-income countries, is required. Recent G8 statements reflect the awareness and priority these countries assign to AIDS vaccines, but more needs to be done to turn these declarations into real resources and tangible results.

AIDS vaccine advocacy activities aimed at mobilizing broad and sustained political and financial support should continue, and the following represent illustrative interim goals:

1. Continued focus on AIDS vaccines in key fora, notably the African Union, the G8 summits, and United Nations General Assembly; and
2. Implementation by UNAIDS and co-sponsors of the policy and programmatic priority action recommendations contained in the UNAIDS Prevention Policy Position Paper.

SECTION 5 Conclusion

With 40 million infections worldwide, AIDS is the pandemic that will define our generation. History will judge governments, institutions, and organizations by their response. The world's best hope to end this pandemic is a preventive vaccine. However, it will take a significant shift in the way R&D is funded, organized, and conducted and the way policy is implemented to successfully galvanize the resources, talents, and sense of urgency necessary to expedite progress towards a vaccine.

An AIDS vaccine is possible. As President Bill Clinton said in his Morgan State University commencement

address in 1997, "It is no longer a question of whether we can develop an AIDS vaccine, it is simply a question of when. And it cannot come a day too soon." This Blueprint outlines a series of initiatives—improving the pipeline through rational vaccine design and enhanced scientific empiricism efforts; accelerating product testing by creating a new paradigm for AIDS vaccine clinical trials; and building capacity, particularly in developing countries—that will speed the development of an AIDS vaccine for the world. Given the 14,000 new HIV infections that occur every single day, these recommendations could save millions of lives.

APPENDIX 1 The AIDS Vaccine Field—Major Players

Though the list is not comprehensive, the following are the most widely known players in the AIDS vaccine R&D field.

PUBLIC SECTOR

United States

The United States, through the President's Emergency Plan for AIDS Relief, has made the largest commitment ever by any nation for an international health initiative dedicated to single disease — a five-year, \$15 billion, multifaceted approach to combating the disease in more than 120 countries around the world. The US National Institutes of Health (NIH; www.nih.gov) is the largest public sector source of funding for AIDS vaccine research and development and supports basic and applied research and conducts clinical trials. The lead agency for NIH in AIDS vaccine R&D is the National Institute of Allergy and Infectious Diseases (NIAID). Basic research is driven by investigator-initiated grants. Vaccine design and product development are conducted via collaborative agreements and contracts. NIH supports the HIV Vaccine Trials Network (HVTN; www.hvtm.org), an international network of clinical trials units, with laboratory, administrative, and statistical support units. In addition to its extramural efforts, the NIH Dale and Betty Bumpers Vaccine Research Center (www.vrc.nih.gov) is focusing on DNA and adenovector approaches. NIH has established the Partnership for AIDS Vaccine Evaluation (PAVE), a volunteer consortium of US government agencies and key US government-funded organizations. The US Military HIV Research Program (USMHRP; www.hivresearch.org), a member of PAVE, focuses on vaccine development in Thailand and East Africa. With the Thai government and Aventis, USMHRP is conducting a Phase III trial of a canarypox vector prime plus gp120 boost. USMHRP has an MVA vector program and is developing trial sites and conducting clinical trials in East Africa. The US Centers for Disease Control and Prevention (www.cdc.gov) is building clinical and laboratory infrastructure at international sites, including a site in Kenya. The US Agency for International Development (USAID) also supports AIDS vaccine research internationally by funding vaccine development partnerships, clinical trial and laboratory infrastructures and policy analysis.

European Union

The EU (www.europa.eu.int) is funding HIV/AIDS research on new drug treatments, microbicides, and vaccines through new collaborative efforts within Europe and with developing countries. The EU finances more than 300 academic and industrial research groups in Europe, including Eastern countries and sub-Saharan Africa. The European Union is funding new innovative approaches to develop an HIV/AIDS vaccine—the AIDS

Vaccine Integrated Project (AVIP; www.avip-eu.org) and Mucosal Vaccines for Poverty-Related Diseases (MUVAPRED; www.mucosalimmunity.org/muvapred). The EU also supports expanded efforts in clinical trial site capacity building, through the European and Developing Countries Clinical Trials Partnership (EDCTP; www.edctp.org). The EDCTP continues to link European and African researchers, providing research capacity in developing countries.

WHO-UNAIDS

The World Health Organization (WHO; www.who.int) United Nations Joint Program on HIV/AIDS (UNAIDS; www.unaids.org) provides technical support to developing countries in order to conduct vaccine research and development and address ethical, training, and capacity-building issues related to evaluation of candidate AIDS vaccines in the developing world. The WHO-UNAIDS program manages an international network of scientists and laboratories participating in the isolation and characterization of globally diverse strains of HIV. The WHO-UNAIDS HIV Vaccine Initiative plays a critical role in serving as a neutral focus for discussion of issues relevant to AIDS vaccine clinical trials. WHO-UNAIDS houses the African AIDS Vaccine Program, a network of researchers based in Africa.

Australia

The Australian government (www.health.gov.au) provides funding support to the National Centre in HIV Social Research, the National Centre in HIV Epidemiology and Clinical Research, the Australian Centre for HIV and Hepatitis Virology Research (ACH2) (formerly the National Centre for HIV Virology Research), and the Australian Research Centre in Sex, Health and Society (ARCHS) as well as providing several other research grants.

Canada

The Government of Canada (www.acdi-cida.gc.ca) continues to support AIDS vaccine research both at home and internationally. The “Canadian HIV Vaccines Plan,” the first comprehensive strategy for AIDS vaccine research, advocacy, and funding to be created in a developed country, is now in the final stages of development.

China

The Government of China, through the China Center for Disease Control and Prevention (www.chinacdc.net.cn), is sponsoring and conducting the design and manufacturing of new AIDS vaccine candidates. China is currently conducting the first Phase I clinical trial in Nanning, Guangxi Province, with a vaccine candidate developed at Johns Hopkins University Bloomberg School of Public Health and domestically manufactured in Changchun, Jilin Province.

France

The French government (www.sante.gouv.fr) provides support for AIDS vaccine programs, including preclinical research and clinical trials. In an innovative public-private partnership, the Agence Nationale de Recherches sur le SIDA (ANRS; www.anrs.fr) supported a significant proportion of AIDS vaccine efforts at sanofi-aventis. ANRS is involved in the development of mucosal immunity assays, as part of work to conduct clinical trials of lipopeptides administered via the mucosal route.

India

The Indian government, through the Indian Council of Medical Research (ICMR; www.icmr.nic.in) and the National AIDS Control Organization (NACO; www.naco.nic.in), is committed to develop and conduct clinical trials of AIDS vaccine candidates. The Department of Biotechnology (DBT) and the Council of Scientific and Industrial Research (CSIR), Ministry of Science and Technology, are exploring areas of upstream research that can accelerate vaccine development in India and globally, including HIV genotyping and sequencing, design and optimization of new vectors, design of immunogens capable of inducing neutralizing antibodies against primary isolates, and identification of new broadly neutralizing monoclonal antibodies.

Italy

The Italian government, through the Italian Istituto Superiore di Sanità (ISS; www.iss.it), carries out work in AIDS vaccine research as well as developing-country work in research into the prevention and treatment of HIV/AIDS. Commencing in March 2005, the ISS funds clinical trials of candidate AIDS vaccines.

Japan

The Japanese government's (www.nih.go.jp) current research activities include basic HIV retrovirology, pathogenesis of AIDS, development of HIV animal models, development of HIV vaccines and therapeutic agents, and the evaluation of HIV laboratory diagnosis and current antiretroviral therapy. In addition, they are involved in collaborative studies on HIV-AIDS with researchers from other Asian and HIV endemic countries.

South Africa

South Africa has established the South African AIDS Vaccine Initiative (SAAVI; www.saaavi.org.za), which supports vaccine design programs for DNA, viral vector, and bacterial vector approaches. SAAVI is also supporting a plant-based virus-like particle approach. SAAVI has established clinical trials infrastructure in the country.

Sweden

The Swedish government (www.fhi.se) supports activities focused on DNA vaccine development and primate models for AIDS through the work of the Karolinska Institute. The Swedish International Development Cooperation Agency (SIDA/SAREC) and the Swedish Ministry of Foreign Affairs also support AIDS vaccine research and development.

Thailand

Thailand has led the developing world in the establishment of infrastructure for conducting AIDS vaccine efficacy trials. The Ministry of Public Health (www.eng.moph.go.th) conducted the first Phase III clinical trial in a developing country, testing VaxGen's gp120 AIDSVAX candidate.

United Kingdom

The UK government is a strong supporter of AIDS vaccine research and development through the Department for International Development (DFID; www.dfid.gov.uk). The Medical Research Council (MRC; www.mrc.ac.uk) provides support through competitive grants for basic and applied research, and has long-standing collaborations in developing countries, which provide potential infrastructure for AIDS vaccine clinical trials.

In addition, Ireland, the Netherlands, Norway, and Denmark are strong supporters of AIDS vaccine research and development.

PHARMACEUTICAL COMPANIES

GlaxoSmithKline

GlaxoSmithKline (www.gsk.com) has focused its AIDS vaccine development efforts on recombinant protein vaccine candidates and has conducted trials of a gp120 plus NefTat fusion protein. In addition, GSK has an active program in the development of adjuvants for recombinant protein vaccines. GSK has recently diversified its portfolio to include nonhuman primate adenovirus and measles vectors as vaccine candidates.

Merck

The Merck (www.merck.com) AIDS vaccine research program is focusing on replication-defective recombinant adenovirus vectors. In collaboration with HVTN, its lead candidate has begun a collaborative Phase IIb study at both Merck and HVTN clinical trial sites in North and South America, the Caribbean, and Australia. Merck has also tested a series of DNA candidates in trials, evaluating copolymer and alum adjuvants aimed

at enhancing the immunogenicity of DNA vaccines in humans. Finally, Merck has teamed with sanofi-aventis to evaluate a vaccination strategy of adenovirus vectors to prime and canarypox vectors to boost.

sanofi-aventis

Sanofi-aventis (<http://en.sanofi-aventis.com>) has focused its AIDS vaccine design efforts on optimizing candidate vaccines based on its proprietary position in recombinant viral vectors, specifically canarypox vectors, the most advanced of which are in Phase III clinical trials.

Wyeth

Wyeth (www.wyeth.com) has focused its AIDS vaccine research on DNA technology adjuvanted with IL-12, DNA followed by synthetic peptide boost, and vesicular stomatitis virus (VSV) as a live vaccine delivery vehicle. The VSV research program is in collaboration with Yale University. Wyeth has conducted clinical trials of DNA and peptide candidates.

BIOTECHNOLOGY COMPANIES

Advanced BioScience Laboratories (www.ablinc.com) is a biotechnology company that specializes in biomedical research with a focus on virology. ABL has entered into a multi year agreement with the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, to perform preclinical development of promising HIV-1 vaccines and microbicides.

AlphaVax (www.alphavax.com) is developing new vaccine technology with broad applications against infectious disease, cancer, and biodefense threats which have the potential to redefine vaccines and the role they play in medicine. AlphaVax uses a specialized viral vector system to make alphavirus replicon vaccines called alphavaccines, which have shown excellent protection in multiple models for infectious disease.

Crucell (www.crucell.com) is a biotechnology company focused on research, development, production, and worldwide marketing of vaccines and antibodies that combat infectious diseases. The AdVac vectors, adenovirus serotypes 11 and 35, have shown promising results as vectors for AIDS vaccines in a series of studies by Crucell in collaboration with Harvard Medical School. Crucell has entered into an exclusive license agreement with IAVI to develop this technology and a cell line for the production of adenovector-based vaccines.

GeoVax (www.geovax.com) is a biotechnology company developing vaccines for HIV-1 and other infectious

agents. Successful Phase I clinical trials of a DNA vaccine have demonstrated the safety of this vaccine. Phase Ia/Ib trials to test various combinations of DNA and MVA AIDS vaccines in volunteers for safety and immunogenicity are planned for 2006.

FIT Biotech (www.fitbiotech.com) is an innovative medical biotechnology company engaged in the development and commercialization of its proprietary Gene Transport Unit (GTU) technology and GTU product applications in DNA vaccination as well as in immuno- and gene therapies. FIT Biotech's HIV DNA therapeutic vaccine candidate has advanced to a Phase II trial in collaboration with Chris Hani Baragwanath Hospital, Pediatric Research Centre, Soweto, South Africa.

Maxygen (www.maxygen.com) is developing a preventive HIV vaccine. Its "MolecularBreeding" directed evolution platform generates novel HIV-1 antigens potentially capable of inducing broad antibody responses to multiple strains of the HIV-1 virus. An SBIR award funds investigations into the effect on immunogenicity of secondary modifications to a specific HIV-1 envelope protein. A grant from the Department of Defense funds work to develop a high-throughput HIV vaccine screening platform.

Mymetics (www.mymetics.com) is developing vaccines and therapies to combat AIDS. Its lead vaccine candidate combines the company's HIV-1 gp41-

derived peptide antigen grafted onto virosomes. Previous research has demonstrated that virosome-based vaccine technology is able to elicit protective antibodies in various anatomical compartments, which may prevent HIV translocation across mucosal tissues.

Targeted Genetics (www.targetedgenetics.com) is a biotechnology company focused on the development of innovative targeted molecular therapies. Targeted Genetics, in collaboration with IAVI, Columbus Children's Research Institute, and Children's Hospital of Philadelphia, is pursuing development of an AIDS vaccine, tgAAC09, a recombinant vaccine candidate that delivers select genes from HIV packaged within the capsid of an adeno-associated virus (AAV).

Therion Biologics (www.therionbio.com) is engaged in the development of therapeutic vaccines

for cancer and preventive vaccines for AIDS. Therion is developing a preventive AIDS vaccine based on the MVA pox virus vector for IAVI.

Vical (www.vical.com) researches and develops biopharmaceutical products based on DNA delivery technologies. In 2003, Vical entered into a subcontract agreement to manufacture bulk DNA vaccines for the VRC.

Virax (www.virax.com.au) is an early-stage-development biopharmaceutical company focusing on the development of immunotherapeutics for the treatment of autoimmune disorders, HIV/AIDS, cancers, and infectious diseases. Virax's preventive HIV program is focused on a recombinant fowl pox virus designed to co-express genes for immunogenic but highly conserved parts of the HIV-1 virus in conjunction with a human cytokine (interferon gamma).

PHILANTHROPIC SECTOR

Bill & Melinda Gates Foundation

The Bill & Melinda Gates Foundation (BMGF; www.gatesfoundation.org) is the largest private foundation supporting AIDS vaccine research and development. It also serves as the secretariat for the Global HIV Vaccine Enterprise.

amfAR

The American Foundation for AIDS Research (www.amfar.org) recently awarded a series of small basic and applied research grants aimed at supporting new and innovative concepts in AIDS vaccine development.

Until There's A Cure Foundation

Until There's A Cure (www.utac.org) has been providing ongoing support for the global AIDS vaccine effort through its funding of IAVI since 1996.

Wellcome Trust

The Wellcome Trust (www.wellcome.ac.uk) fosters and promotes research with the aim of improving human and animal health. This includes basic epidemiological, clinical, and field studies of pathogens, host responses, vector biology, and early-stage vaccine and drug development. Wellcome also develops capacity and infrastructure in developing countries to support vaccine trials related to tropical diseases.

IAVI

The International AIDS Vaccine Initiative (IAVI; www.iavi.org) is a global not-for-profit organization whose mission is to ensure the development of a safe, effective, and accessible vaccine to prevent HIV infection and AIDS for use throughout the world. IAVI's efforts are focused on four primary strategies: sustaining and securing global commitment; engaging developing countries where the epidemic is most severe; advocating for supportive policy initiatives to enhance research and development and eventual vaccine access; and accelerating research and development.

A

adjuvant: a substance sometimes included in a vaccine formulation to enhance or modify the immune-stimulating properties of a vaccine.

AIDS (acquired immunodeficiency syndrome): the late stage of HIV disease, characterized by a deterioration of the immune system and a susceptibility to a range of opportunistic infections and cancers.

ALVAC-HIV: a genetically engineered HIV vaccine composed of a live, weakened canarypox virus (ALVAC™) into which parts of genes for noninfectious components of HIV have been inserted. When ALVAC™ infects a human cell, the inserted HIV genes direct the cell to make HIV proteins. These proteins are packaged into HIV-like particles that bud from the cell membrane. These particles are not infectious but fool the immune system into mounting an immune response to HIV. ALVAC™ can infect but not grow in human cells, an important safety feature. (See also canarypox.)

antibody: an infection-fighting protein molecule in blood or secretory fluids that tags, neutralizes, and helps destroy pathogenic microorganisms (e.g., bacteria, viruses) or toxins. Antibodies, known generally as immunoglobulins, are made and secreted by B lymphocytes in response to stimulation by antigens. Each specific antibody binds only to the specific antigen that stimulated its production. (See also neutralizing antibody.)

antigen: any substance that stimulates the immune system to produce antibodies. Antigens are often foreign substances such as invading bacteria or viruses. (See also immunogen.)

attenuated: weakened. Attenuated viruses are often used as vaccines because they can no longer produce disease but still stimulate a strong immune response, like that to the natural virus. Examples of attenuated virus vaccines include oral polio, measles, mumps, and rubella vaccines.

C

canarypox: a virus that infects birds and is used as a live vector for HIV vaccines. It can carry a large quantity of foreign genes. Canarypox virus cannot grow in human cells, an important safety feature. (See also ALVAC-HIV™; vector.)

CD4+ T lymphocyte: immune cell that carries a marker on its surface known as “cluster of differentiation 4” (CD4). These cells are the primary targets of HIV. Also known as helper T-cells, CD4+ T-cells help orchestrate the immune response, including antibody responses as well as killer T-cell responses. (See also T-cell.)

cellular immunity: the immune response coordinated by helper T-cells and CTLs. This branch of the immune system targets cells infected with microorganisms such as viruses, fungi, and certain bacteria.

challenge: in vaccine experiments, the deliberate exposure of an immunized animal to the infectious agent. Challenge experiments are never done in human HIV vaccine research.

clade: also called a subtype. A group of related HIV isolates classified according to their degree of genetic similarity (such as of their envelope proteins). There are currently two groups of HIV-1 isolates, M and O. M consists of at least nine clades, A through I. Group O may consist of a similar number of clades. (See also isolate.)

clinical trial: any precisely controlled test of an experimental drug, vaccine, or other intervention, performed on human volunteers.

correlates of protection: the immune responses that must be present to protect an individual from a certain infection. The precise correlates of immunity in HIV transmission are unknown.

cytokine: a soluble, hormone-like protein produced by white blood cells that acts as a messenger between cells. Cytokines can stimulate or inhibit the growth and activity of various immune cells. Cytokines are essential for a coordinated immune response and can also be used as immunologic adjuvants. HIV replication is regulated by a delicate balance among cytokines.

D

DNA (deoxyribonucleic acid): the double-stranded, helical molecular chain found within the nucleus of each cell. DNA carries the genetic information that encodes proteins and enables cells to reproduce and perform their functions.

DNA vaccine: direct injection of a gene(s) coding for a specific antigenic protein(s), resulting in direct production of such antigen(s) within the vaccine recipient in order to trigger an appropriate immune response.

E

efficacy: in vaccine research, the ability of a vaccine to produce a desired clinical effect, such as protection against a specific infection, at the optimal dosage and schedule in a given population. A vaccine may be tested for efficacy in Phase III trials if it appears to be safe and shows some promise in smaller Phase I and II trials.

empirical: based on experience or observational information and not necessarily on proven scientific data. In the past, vaccine trials have been performed based exclusively on empirical data and without a full understanding of the disease processes or correlates of immunity.

envelope: outer surface of a virus, also called the coat. Not all viruses have an envelope. (See also virus.)

epitope: a specific site on an antigen that stimulates specific immune responses, such as the production of antibodies or activation of immune cells.

G

genome: the complete set of genes present in a cell or virus.

gp: abbreviation for glycoprotein. A protein molecule that is glycosylated, that is, coated with a carbohydrate, or sugar. The outer coat proteins of HIV are glycoproteins. The number after the gp (e.g., 160, 120, 41) is the molecular weight of the glycoprotein.

gp41: glycoprotein 41. A protein imbedded in the outer envelope of HIV that anchors gp120. gp41 plays a key role in HIV's infection of CD4+ T-cells by facilitating the fusion of the viral and cell membranes. Antibodies to gp41 can be detected on a screening HIV ELISA.

gp120: glycoprotein 120. One of the proteins that forms the envelope of HIV. gp120 projects from the surface of HIV and binds to the CD4 molecule on helper T-cells. gp120 has been a logical experimental HIV vaccine because the outer envelope is the first part of the virus that encounters an antibody.

H

homologous: similar in appearance, structure, and usually function. For HIV, the same strain of the virus.

host: a plant or animal harboring another organism.

hypothesis: a tentative statement or supposition, which may then be tested through research.

I

immunity: natural or acquired resistance provided by the immune system to a specific disease. Immunity may be partial or complete, specific or nonspecific, long-lasting or temporary.

immunogen: a substance capable of provoking an immune response.

immunogenicity: the ability of an antigen or vaccine to stimulate immune responses.

incidence: the rate of occurrence of some event, such as the number of individuals who get a disease divided by a total given population per unit of time. (Contrast with prevalence.)

informed consent: an agreement signed by prospective volunteers for a clinical research trial that indicates their understanding of (1) why the research is being done, (2) what researchers want to accomplish, (3) what will be done during the trial and for how long, (4) what risks are involved, (5) what, if any, benefits can be expected from the trial, (6) what other interventions are available, and (7) the participant's right to leave the trial at any time.

intervention: a vaccine (or drug or behavioral therapy) used in a clinical trial to improve health or alter the course of disease.

isolate: a particular strain of HIV-1 taken from a person.

L

lymphoid tissue: tonsils, adenoids, lymph nodes, spleen, and other tissues that act as the body's filtering system, trapping invading microorganisms and presenting them to squadrons of immune cells that congregate there.

M

memory cell: memory cells are a subset of T-cells and B-cells that have been exposed to specific antigens and can then proliferate (recognize the antigen and divide) more readily when the immune system re-encounters the same antigens.

mucosal immunity: resistance to infection across the mucous membranes. Mucosal immunity depends on immune cells and antibodies present in the linings of the reproductive tract, gastrointestinal tract and other moist surfaces of the body exposed to the outside world.

N

neutralizing antibody: an antibody that keeps a virus from infecting a cell, usually by blocking receptors on the cells or the virus.

P

pathogen: any disease-causing organism.

pathogenesis: the origin and development of a disease. More specifically, it's the way a microbe (bacteria, virus, etc.) causes disease in its host.

peptide: a short compound formed by linking two or more amino acids. Proteins are made of multiple peptides.

Phase I vaccine trial: a closely monitored clinical trial of a vaccine conducted in a small number of healthy volunteers. A Phase I is designed to determine the vaccine's safety in humans, its metabolism and pharmacologic actions, and side effects associated with increasing doses.

Phase II vaccine trial: controlled clinical study of a vaccine to identify common short-term side effects and risks associated with the vaccine and to collect information on its immunogenicity. Phase II trials enroll some volunteers who have the same characteristics as persons who would be enrolled in an efficacy (Phase III) trial of a vaccine. Phase II trials enroll up to several hundred participants and have more than one arm.

Phase III vaccine trial: large controlled study to determine the ability of a vaccine to produce a desired clinical effect on the risk of a given infection, disease, or other clinical condition at an optimally selected dose and schedule. These trials also gather additional information about safety needed to evaluate the overall benefit-risk relationship of the vaccine and to provide adequate basis for labeling. Phase III trials usually include several hundred to several thousand volunteers.

placebo: an inactive substance administered to some study participants while others receive the agent under evaluation, to provide a basis for comparison of effects.

prevalence: the number of people in a given population affected with a particular disease or condition at a given time. Prevalence can be thought of as a snapshot of all existing cases at a specified time. (Contrast with incidence.)

preventive HIV vaccine: a vaccine designed to prevent HIV infection.

prime-boost: in HIV vaccine research, administration of one type of vaccine, such as a live-vector vaccine, followed by or together with a second type of vaccine, such as a recombinant subunit vaccine. The intent of this combination regimen is to induce different types of immune responses and enhance the overall immune response, a result that may not occur if only one type of vaccine were to be given for all doses.

priming: giving one vaccine dose(s) first to induce certain immune responses, followed by or together with a second type of vaccine. The intent of priming is to induce certain immune responses that will be enhanced by the booster dose(s).

protocol: the detailed plan for a clinical trial that states the trial's rationale, purpose, vaccine dosages, routes of administration, length of study, eligibility criteria, and other aspects of trial design.

R

reagent: any chemical used in a laboratory test or experiment.

receptor: a molecule on the surface of a cell that serves as a recognition or binding site for antigens, antibodies, or other cellular or immunologic components.

retroviruses: HIV and other viruses that carry their genetic material in the form of RNA rather than DNA and have the enzyme reverse transcriptase that can transcribe it into DNA. In most animals and plants, DNA is usually made into RNA, hence “retro” is used to indicate the opposite direction.

S

SHIV: genetically engineered hybrid virus having an HIV envelope and an SIV core.

SIV (simian immunodeficiency virus): an HIV-like virus that infects and causes an AIDS-like disease in some species of monkeys.

strain: one type of HIV. HIV is so heterogeneous that no two isolates are exactly the same. When HIV is isolated from an individual and worked on in the lab, it is given its own unique identifier, or strain name (i.e., MN, LAI).

subtype: also called a clade. With respect to HIV isolates, a classification scheme based on genetic differences.

T

therapeutic HIV vaccine: a vaccine designed to boost the immune response to HIV in a person already infected with the virus. Also referred to as an immunotherapeutic vaccine.

V

vaccine: a preparation that stimulates an immune response that can prevent an infection or create resistance to an infection.

vaccinia: a cowpox virus, formerly used in human smallpox vaccines. Employed as a vector in HIV vaccines to transport HIV genes into the body.

vector: in vaccine research, a bacterium or virus that does not cause disease in humans and is used in genetically engineered vaccines to transport genes coding for antigens into the body to induce an immune response. (See also vaccinia and canarypox.)

virus: a microorganism composed of a piece of genetic material—RNA or DNA—surrounded by a protein coat. To replicate, a virus must infect a cell and direct its cellular machinery to produce new viruses.

This Glossary is adapted from the Office of Communications and Public Liaison. National Institutes of Health. HIV Vaccine Glossary. www.niaid.nih.gov/factsheets/GLOSSARY.htm (accessed June 28, 2006).

Notes

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Die Welt
braucht einen
AIDS-
Impfstoff

世界需要
艾滋病
疫苗

วัคซีนเอดส์
สิ่งจำเป็นของ
มวลมนุษย์

Мировое
сообщество
нуждается в
вакцине против
СПИДа

El mundo
necesita
una vacuna
contra el SIDA

Le monde
a besoin
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contre le SIDA

The world
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समय की माँग -
एड्स का टीका