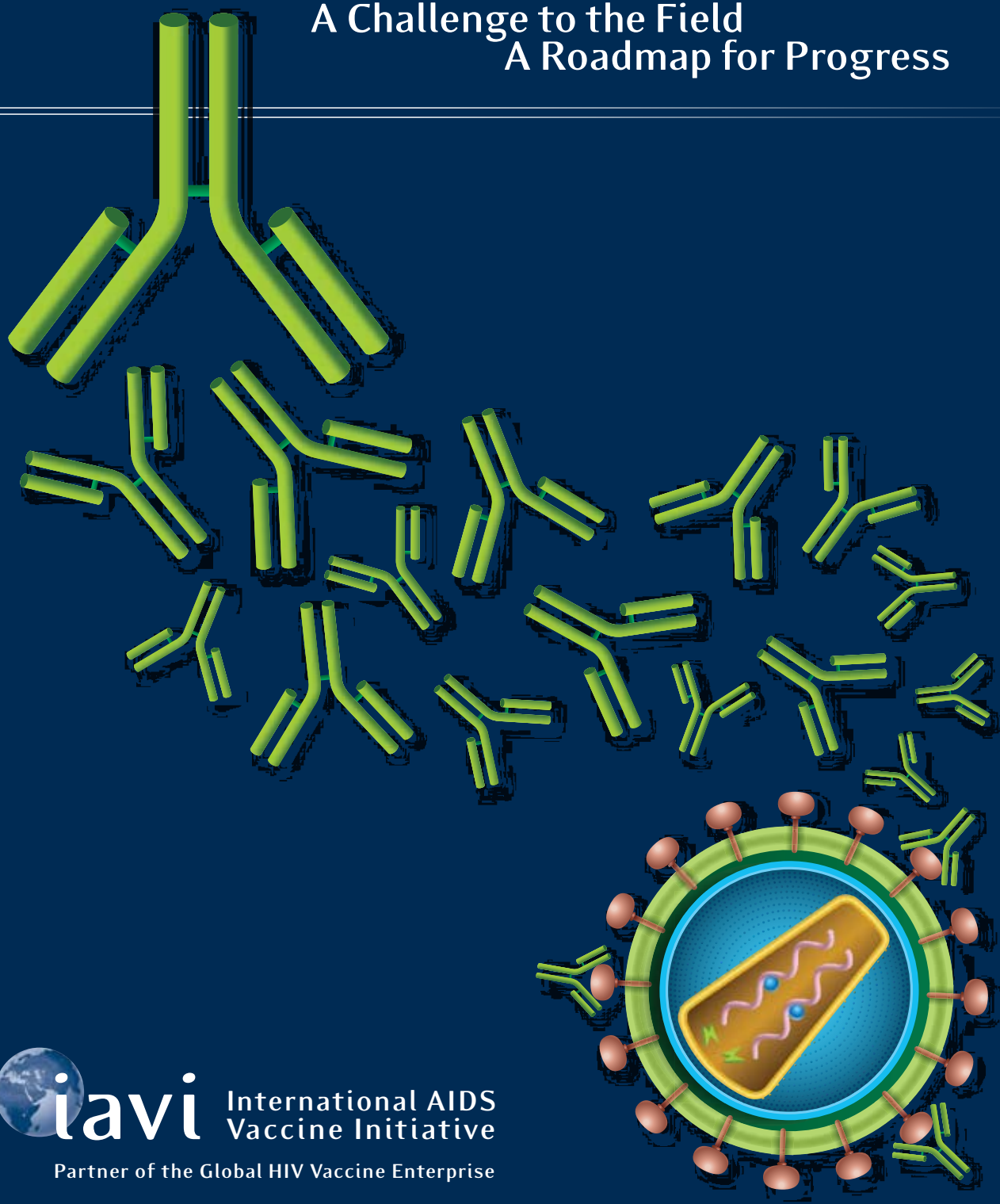


# AIDS VACCINE BLUEPRINT 2008

A Challenge to the Field  
A Roadmap for Progress



**iavi** International AIDS  
Vaccine Initiative

Partner of the Global HIV Vaccine Enterprise

---

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

## **Imagine a World Without AIDS**

*AIDS Vaccine Blueprint 2008: A Challenge to the Field, A Roadmap for Progress*  
ISBN # 0-9792432-8-9

Copyright © 2008 International AIDS Vaccine Initiative.  
The IAVI logo is a trademark of the International AIDS Vaccine Initiative.

All rights reserved. This material may be quoted or reproduced without charge for noncommercial purposes only; however, please acknowledge source and send a copy of reproduced materials to IAVI.

The full text of this report is also available online at the IAVI website at <http://www.iavi.org/blueprint2008>.

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

Design and layout by Melissa Thomas Design.  
Illustrations by Samuel Velasco / SW Infographic, Melissa Thomas and Lucy Reading-Ikkanda.

### **IAVI OFFICES:**

**New York Office/  
Headquarters**  
110 William Street, Floor 27  
New York, NY 10038-3901  
USA  
Tel: +1 212 847 1111  
Fax: + 1 212 847 1112

**East Africa Office**  
Postal address:  
PO Box 340 KNH  
Nairobi, Kenya 00202  
Tel: +254 20 445 3596/7/8  
Fax: + 254 20 445 3598

**Europe Office**  
Herengracht 208  
1016 BS Amsterdam  
The Netherlands  
Tel: +31 20 521 0030  
Fax: +31 20 521 0039

**India Office**  
193, Floor 1, Jorbagh  
New Delhi, 110003, India  
Tel: +91 11 24652668  
Fax: +91 11 246464464

**Southern Africa Office**  
Ground Floor, Block 6,  
Albury Park  
Corner Albury Rd. &  
Jan Smuts Ave.  
Dunkeld West 2196  
Johannesburg, South Africa  
Tel: +27 11 325 4737

**WEBSITE:** [www.iavi.org](http://www.iavi.org)

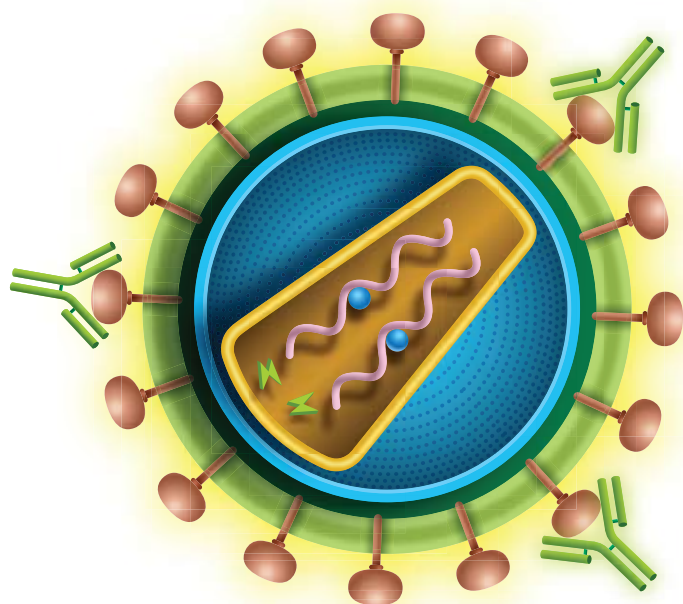
**E-MAIL:** [pubs@iavi.org](mailto:pubs@iavi.org)



Printed on recycled paper.

# AIDS VACCINE BLUEPRINT 2008

A Challenge to the Field, A Roadmap for Progress



**International AIDS Vaccine Initiative**  
Partner of the Global HIV Vaccine Enterprise

---

---

# TABLE OF CONTENTS

---

---

LIST OF FIGURES .....	ii
LIST OF TABLES .....	ii
<b>1.0 INTRODUCTION</b> .....	1
<b>2.0 WHY AN AIDS VACCINE</b> .....	3
<b>3.0 THE AIDS VACCINE LANDSCAPE: 1983-2008</b> .....	6
The First Wave: 1983-1994.....	6
The Second Wave: 1995-2007.....	7
The Third Wave: 2008 Onwards.....	12
<b>4.0 KEY ASSUMPTIONS</b> .....	14
4.1 Basic Research Assumptions.....	14
4.2 Vaccine Discovery and Development Assumptions.....	15
4.3 Resource Assumptions.....	18
<b>5.0 RECOMMENDATIONS</b> .....	20
5.1 Vaccine Discovery and Development Recommendations.....	20
5.1.1 Solve the HIV Neutralizing Antibody Problem.....	20
5.1.2 Solve the HIV Cell-Mediated Immunity Problem.....	22
5.1.3 Improve the Pipeline.....	23
5.2 Recommendations for Sustaining the Effort.....	24
<b>6.0 CONCLUSION</b> .....	27
<b>APPENDIX 1:</b> Major Players in AIDS Vaccine R&D.....	32
<b>APPENDIX 2:</b> AIDS Vaccine Glossary.....	38
<b>APPENDIX 3:</b> List of Abbreviations.....	42
<b>REFERENCES</b> .....	43



---

## LIST OF FIGURES

---

<b>Figure 1:</b> Immune Responses after Vaccination.....	2
<b>Figure 2:</b> How HIV Establishes Lifelong Infection Within Days.....	5
<b>Figure 3:</b> The Hypervariability of HIV.....	8
<b>Figure 4:</b> Cell-Mediated Immunity (CMI) in HIV Infection.....	9
<b>Figure 5:</b> Structure of an Antibody.....	11
<b>Figure 6:</b> Contributions and Allocations in 2007.....	11
<b>Figure 7:</b> A Steady Growth in Investment.....	12
<b>Figure 8:</b> A Novel Approach to Antibodies.....	13
<b>Figure 9:</b> Approaches to Designing Immunogens that Neutralize a Broad Spectrum of Circulating HIV Strains.....	15
<b>Figure 10:</b> The Platforms used to Design Vaccines.....	16
<b>Figure 11:</b> The Benefits of Replication.....	17
<b>Figure 12:</b> Steps Toward the Ultimate Goal.....	21
<b>Figure 13:</b> Milestones for the Development of Replicating Viral Vectors.....	28

---

## LIST OF TABLES

---

<b>Table 1:</b> To Create a Vaccine: Always Years, Sometimes Decades.....	3
<b>Table 2:</b> Scientific Challenges in AIDS Vaccine Development.....	4
<b>Table 3:</b> Key Findings in AIDS Vaccine Design and Development.....	6
<b>Table 4:</b> AIDS Vaccine Candidates in Clinical Trials.....	10
<b>Table 5:</b> Interim Goals and Milestones for Monitoring Progress in AIDS Vaccine Development.....	29



# 1 INTRODUCTION

The quest to develop an AIDS vaccine is at a pivotal moment. Scientific evidence supports the idea that an AIDS vaccine is feasible. However, the high-profile failure in September 2007 of a vaccine candidate in an advanced trial has helped generate a broad consensus within the field that it is time to carefully evaluate where and how best to utilize the finite available resources. The International AIDS Vaccine Initiative (IAVI) has, through its biennial *Blueprints* begun in 1998, monitored the state of the global AIDS vaccine effort. In this latest installment, *AIDS Vaccine Blueprint 2008*, we challenge the field to reset both expectations and focus.

The ultimate goal remains the development of a safe, effective, preventive AIDS vaccine that can be licensed and made accessible to all throughout the world. We must acknowledge, however, that while AIDS vaccine research to date has yielded enormous advances in knowledge, it has also provided many lessons in humility. Achieving the ultimate goal will take more time and ingenuity than anyone originally imagined.

Although we have evidence of feasibility in animal models, studies have yet to demonstrate that an AIDS vaccine candidate benefits humans. While it may appear obvious, then, the next major advance on the way to the ultimate goal of an effective, licensed AIDS vaccine will be **the first demonstration that a candidate AIDS vaccine provides benefit in humans**. Achieving this intermediate goal would provide very strong evidence that an AIDS vaccine is indeed feasible, help answer key research questions impeding advances, give researchers a platform on which to improve, validate our animal models, and attract new investment and creative energy to the field. IAVI endeavors in this *Blueprint* to offer a roadmap of tangible proposals on how to reach this intermediate goal.

To give context to the current landscape of AIDS vaccine development, the *Blueprint* provides a historical review of the first 25 years of work in the field. It sets the stage for a “Third Wave” of AIDS vaccine research and development (R&D) that is just beginning and lays out a series of Key Assumptions in the areas of science, policy, and operations that we consider to form the base from which the field can progress.

In **Recommendations**, the *Blueprint* provides a comprehensive vision of the directions that IAVI considers

AIDS vaccine development should pursue. We propose that those of us engaged in the quest for an AIDS vaccine divide our mission into components that are more readily attainable than our ultimate prize—a finished vaccine—or even the intermediate goal of proof of benefit in humans. This process of subdividing the task before us could help stakeholders refocus their work, create more reasonable expectations for the field and devise a means of monitoring incremental progress.

We consider two of the recommendations particularly noteworthy. The first is practical: to **shift resources away from the majority of vaccine candidates currently in the clinical pipeline on the basis of their probability** of success, and steer freed resources into preclinical and clinical vaccine discovery, with the aim of generating a much improved and more diverse product development pipeline. The second is strategic: to **focus significantly increased resources on immunogen design to provide a foundation for a much improved pipeline**. In addition to increasing efforts to discover how to induce broadly neutralizing antibodies to HIV, the field needs to strengthen the effort to effectively induce cell-mediated immune (CMI) responses to control HIV. This would entail greater exploration of potentially more effective viral vectors for the delivery of HIV antigens, including replicating vectors, and ramping up efforts to determine what HIV antigens should be included in such vectors to provide control of HIV infection. Until now, the field has focused more on how to deliver antigens and less on the antigens themselves.

As a founding partner of the Global HIV Vaccine Enterprise, IAVI offers these recommendations hoping to stimulate discussion among all stakeholders in AIDS vaccine development about the way forward and to promote a resetting of priorities. Stakeholders could then tackle the goals and milestones that most closely align with their core capabilities. There is an urgent need to foster closer collaboration and teamwork, in the spirit of the Enterprise, to ensure that critical activities are addressed and that redundancy and duplication of effort are minimized. This does not mean convergence of the effort; healthy competition is necessary to the discovery and research process; it is only unnecessary redundancy and duplication that we are trying to minimize. We hope our fellow stakeholders—our colleagues, partners, and collaborators—will embrace this *Blueprint* in the spirit in which it is intended.

## HOW AN AIDS VACCINE WOULD WORK

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

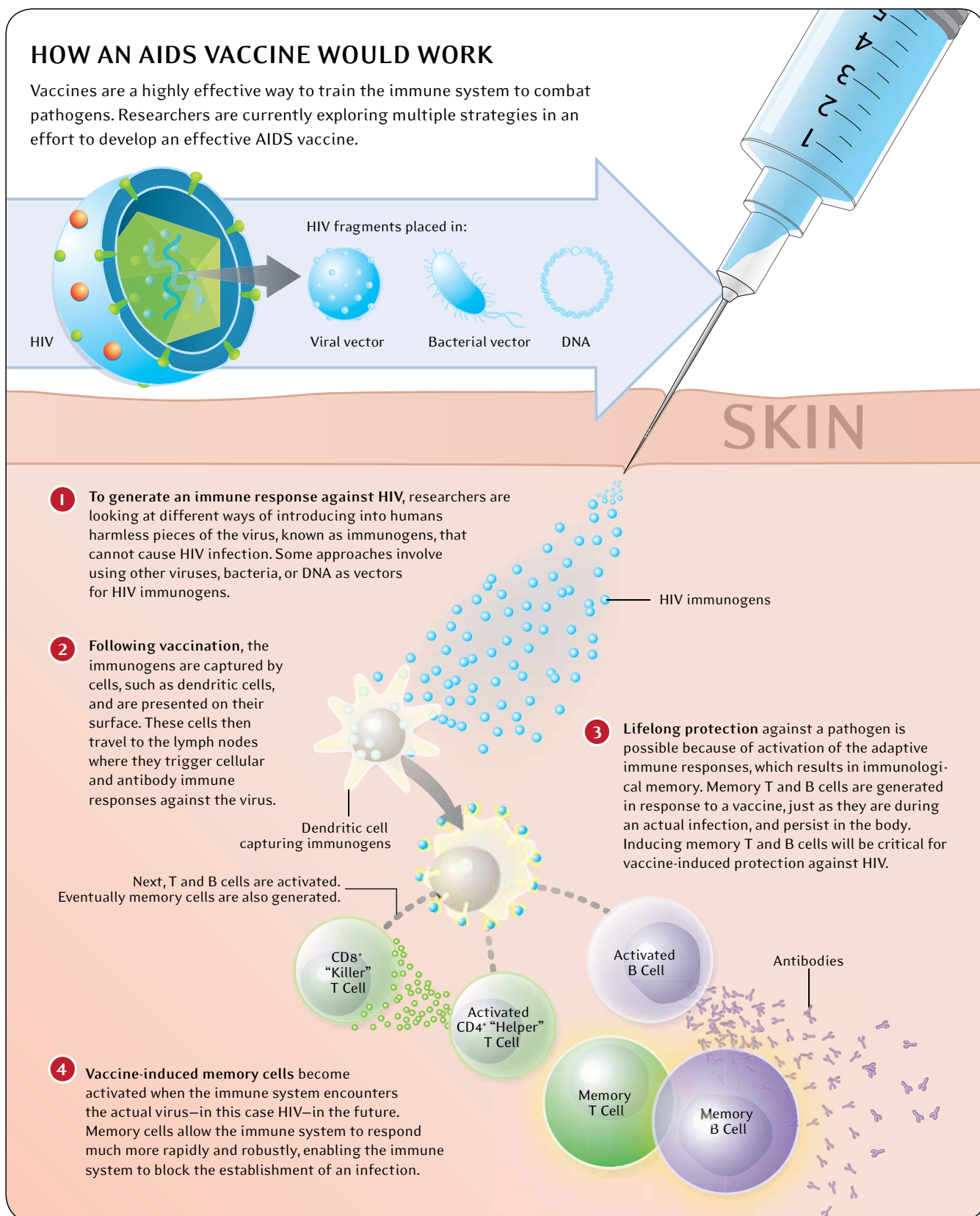


Figure 1 Immune responses after vaccination

# 2 WHY AN AIDS VACCINE

An AIDS vaccine is needed now more than ever. The AIDS pandemic is one of the greatest global health crises of our time. In the 25 years since HIV was identified as the cause of AIDS, an estimated 23 million people have already died of the disease and 33 million more are living with HIV (Joint United Nations Programme on HIV/AIDS 2007). In 2007, 2 million died from AIDS and an additional 2.7 million people became infected with HIV, which translates to some 7,500 new infections every day. Despite advances in HIV education, the development of antiretroviral drugs, and expanded access to the drugs in some parts of the developing world, the pandemic continues to outpace global efforts at prevention and control.

The world's response to HIV and AIDS must be comprehensive, encompassing education, prevention, treatment, and care, and should include strategies to further increase access to life-prolonging treatment to all who need it. With the same urgency there must be investment in development of better technologies for the

future: improved diagnostics and new drugs for treatment, microbicides and other methods for prevention, and, in particular, vaccines that can control or, better yet, prevent HIV infection.

Without doubt, vaccines are the most effective public health technology we have for controlling epidemic infectious disease. Vaccines have eradicated smallpox and facilitated progress towards the elimination of polio and measles. Millions around the world owe their lives to vaccines.

A vaccine remains the best hope of ending the AIDS pandemic. The ultimate goal is the development of a safe, effective, licensed, accessible vaccine for use throughout the world (Figure 1). The ideal vaccine would **prevent establishment of persistent HIV infection**, be effective against the huge diversity of HIV isolates worldwide, provide durable immunity, work against all forms of transmission, and be applicable for use in the developing world, where the need is greatest.

**TABLE 1 To Create a Vaccine: Always Years, Sometimes Decades**

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

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

\* Although BCG vaccine is effective and widely used in children, no highly effective licensed vaccine against adult tuberculosis is currently available.

The September 2007 high-profile failure of the Merck adenovirus serotype 5 (AD5) candidate in a large Phase IIb trial coupled with unrealistic expectations have many questioning why we don't have an AIDS vaccine after 25 years. However, 25 years is not a long time when viewed in the context of vaccine development for other pathogens. It can take decades to develop a vaccine (Table 1). Technical and scientific challenges inherent in vaccine development lead to significant attrition of candidates along the path to licensure. In a survey of more than 200 vaccine development projects, on average only 20 percent advanced from preclinical to Phase I trials. Momentous advances in molecular biology, immunology, and virology in the decades since HIV was discovered have ushered in a new era of biotechnology and have become the primary engine for vaccine discovery. Yet despite these advances there are still no effective vaccines for many viruses apart from HIV, including hepatitis C

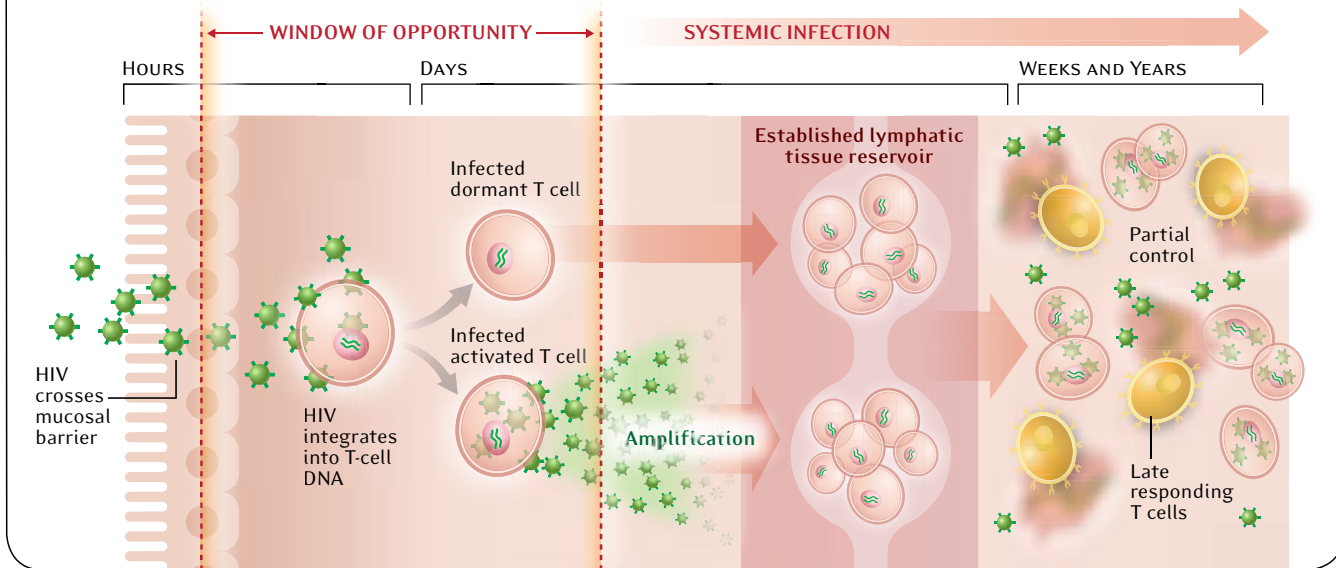
virus, cytomegalovirus, and parainfluenza virus, which cause significant morbidity and occasional mortality. And none of these viruses come close to presenting the daunting challenges to vaccine development that HIV presents. In addition, the AIDS vaccine effort has only become a robustly funded enterprise in recent years. Today, estimated annual global funding for AIDS vaccine research and development (R&D) amounts to US\$ 961 million, but as recently as the mid-1990s the figure amounted to less than US\$ 200 million.

But the main reason there is no AIDS vaccine is that the scientific challenges inherent in AIDS vaccine development dwarf those for any other viral pathogen for which vaccine development has been attempted (Table 2). HIV is a retrovirus that persistently infects and integrates its genetic material into host cell chromosomes, where it resides for the life of the host. Within the first week following infection, HIV

TABLE 2 Scientific Challenges in AIDS Vaccine Development	
HIV is a retrovirus	<ul style="list-style-type: none"> <li>• HIV integrates its genetic material into human chromosomes inside the cells it infects.</li> <li>• HIV establishes a persistent and lifelong infection within the first 7 to 10 days after infection.</li> <li>• This gives only a brief window of opportunity for vaccine-mediated immune responses to act.</li> </ul>
HIV does not induce protective immunity	<ul style="list-style-type: none"> <li>• There is no documented case of recovery from HIV infection.</li> <li>• The correlates of protection in HIV infection remain unknown.</li> <li>• Without a correlate of protection, the field does not have a validated marker to determine whether one candidate is more effective than another.</li> </ul>
HIV is hypervariable	<ul style="list-style-type: none"> <li>• HIV has an error-prone reverse transcriptase that, combined with a rapid replication rate, leads to a high mutation rate.</li> <li>• HIV has a high capacity for recombination.</li> <li>• HIV hypervariability enables "immune escape".</li> <li>• Hypervariability renders HIV a moving target—by the time a vaccine candidate has been designed and tested, the virus might well have mutated significantly.</li> </ul>
HIV has immune evasion mechanisms	<ul style="list-style-type: none"> <li>• The virus outer surface protein and neutralizing antibody target, gp120, is especially well adapted to avoid the immune system: <ul style="list-style-type: none"> <li>◊ it is decorated with a dense matrix of carbohydrates that shield it from neutralizing antibodies;</li> <li>◊ its binding sites to the main host cell receptor (CD4) are normally concealed from neutralizing antibodies;</li> <li>◊ it has decoys to shift the immune response away from generating broadly neutralizing antibodies.</li> </ul> </li> <li>• HIV targets the very immune cells that are needed to keep infection at bay.</li> </ul>
HIV infects humans	<ul style="list-style-type: none"> <li>• There are no ideal animal models for HIV infection and AIDS.</li> <li>• The best surrogate animal model is the SIV/rhesus macaque model, but SIV is not HIV and macaques are not humans.</li> </ul>
HIV is a sexually-transmitted infection	<ul style="list-style-type: none"> <li>• HIV infects by multiple routes (genital tract, rectal, oral, intravenous) and forms (cell-free and cell-associated virus), so robust mucosal immunity may be required.</li> <li>• Sexually-active adolescents through to the elderly can be infected, so an effective vaccine will have to induce durable, long-term protective immunity.</li> </ul>

## WINDOW OF OPPORTUNITY TO PREVENT HIV INFECTION

With HIV, it is only a matter of days before systemic lifelong infection occurs. HIV integrates into T-cell DNA, is amplified and then establishes a reservoir in lymphatic tissue. The natural adaptive immune response to HIV occurs after systemic infection occurs. These immune responses will hold viral load at bay for a number of years until they are eventually overwhelmed.



**Figure 2** How HIV establishes lifelong infection within days

rapidly amplifies in gut-associated lymphoid tissue (GALT) and seeds the cells of the lymphoid organs. This means that the window of opportunity to prevent establishment of persistent HIV infection is very brief (Figure 2).

Still, many scientists believe that an AIDS vaccine is possible based on preclinical proof of principle vaccine studies in nonhuman primates (NHPs), together with clinical observations of long-term control of HIV infection.

In NHPs:

- When passively administered to NHPs, broadly neutralizing antibodies identified from HIV-infected persons can completely protect from infection with an HIV-like virus (simian/human immunodeficiency virus, or SHIV); and
- NHPs immunized with weakened forms of simian immunodeficiency virus (SIV)—called live-attenuated SIV vaccines—are completely protected from disease caused by matching strains of SIV, which normally causes AIDS in some NHP species.

In humans:

- In the normal course of HIV infection, cellular immune responses suppress the HIV viral load for a substantial period of time, often a decade or more, delaying the progression to AIDS; and
- A small number of individuals, termed elite controllers, suppress their HIV viral load to undetectable levels for long periods of time; moreover, some individuals remain uninfected despite good evidence of repeated exposure to HIV.

In light of these data, we believe that, though challenging, the development of an AIDS vaccine is possible and remains the best hope of ending the AIDS pandemic.



# 3 THE AIDS VACCINE LANDSCAPE: 1983-2008

Progress towards an AIDS vaccine has been incremental and built on a foundation of research from many scientific disciplines. **Table 3** provides a list of some key findings in AIDS vaccine development that underscore the importance of combining basic, applied, and clinical research. In 25 years we have learned more about the basic biology of HIV than about any other pathogen, and the spin-offs from AIDS vaccine and HIV research have led to noteworthy advances in related fields, such as adjuvant development, deoxyribonucleic acid (DNA) vaccine development, viral vector-based vaccine development, and antiviral drug development. Even our fundamental understanding of human immunology has progressed immensely due to research driven by the problem of HIV.

The history of AIDS vaccine development may be viewed as two overlapping waves (Esparza 2003) with a third wave now just beginning.

## The First Wave, 1983-1994: Follow the Hepatitis B Road

Immediately after HIV was identified as the etiologic agent causing AIDS, the search for a safe and effective AIDS vaccine began. Some thought it would be simple, some even suggesting that a vaccine would be discovered within two years (Silverman, 1985). At that time, advances and successes were emanating from the hepatitis B vaccine field, and researchers from biotechnology companies planned to follow a similar strategy for HIV: first identify the antigen on the virus that elicits neutralizing antibodies, then purify the antigen and formulate it with an adjuvant to create an immunogen capable of eliciting similar antibodies in animals. This would then lead into process development and preclinical and clinical testing.

Public sector agencies ramped up infrastructure during this period to facilitate AIDS vaccine research

**TABLE 3** Key Findings in AIDS Vaccine Design and Development

First Wave 1983-1994	<ul style="list-style-type: none"> <li>Human immunodeficiency virus (HIV) identified as the cause of AIDS</li> <li>First demonstration of antibody and cell-mediated immune (CMI) responses against HIV</li> <li>HIV Env (gp120) protein identified as the primary target for antibodies</li> <li>CD4 identified as the primary host cell receptor for HIV</li> <li>Diagnostic assays developed that measure antibody and CMI responses to HIV</li> <li>First clinical trial of an AIDS vaccine candidate</li> <li>First viral vector-based AIDS vaccine candidate designed</li> <li>HIV genetic hypervariability first described</li> <li>Simian immunodeficiency virus (SIV) discovered</li> <li>Prime-boost vaccination strategy for HIV proposed</li> <li>First-generation Env-based vaccines elicit antibodies that neutralize laboratory-adapted HIV strains but not circulating primary isolates</li> <li>Clinical centers established in the developing world provide HIV incidence and genetic sequence diversity data</li> <li>Live-attenuated SIV protects against disease after challenge with pathogenic SIV</li> <li>First AIDS vaccine trials in the developing world conducted</li> </ul>
Second Wave 1995-2007	<ul style="list-style-type: none"> <li>Broadly neutralizing monoclonal antibodies (bnMAbs) against HIV identified</li> <li>CCR5 identified as co-receptor for HIV</li> <li>Refined and validated assays developed to measure viral load and CMI responses against HIV</li> <li>HIV-specific CMI responses correlated with viral control</li> <li>BnMAbs against HIV protect against challenge with chimeric simian/human immunodeficiency virus (SHIV)</li> <li>Scientific consortia established to focus on HIV neutralizing antibody problem and other specific research problems</li> <li>First efficacy trial of Env-based vaccine fails to protect against HIV infection or suppress viral load</li> <li>Structures of bnMAbs bound to Env determined</li> <li>HIV shown to deplete CD4<sup>+</sup> T cells and amplify in gut-associated lymphoid tissue (GALT) very early after infection</li> <li>Efficacy trial of leading vaccine candidate designed to elicit CMI responses shows no evidence of effectiveness</li> </ul>



and development. The US National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases (NIAID) supplemented its clinical trial Vaccine Evaluation Units so that they could assess AIDS vaccine candidates. The first Food and Drug Administration (FDA)-approved AIDS vaccine trial began in 1987 at the NIH, followed shortly by trials at the Vaccine Evaluation Units. To attract scientists to the new field of AIDS vaccine R&D, NIAID launched the National Cooperative Vaccine Development Groups for AIDS (NCVDG) in 1988, linking academic, government, and industrial scientists into consortia focused on designing new vaccine concepts and advancing them to clinical trials. A Central Immunology Laboratory was set up to compare immunologic responses to the vaccine candidates, together with a Data Management support contract for data analysis and statistical support. Cohorts of HIV-infected individuals were established to monitor progression from infection to AIDS, with the aim of understanding correlates of control of HIV infection applicable to vaccine discovery. On the preclinical front, national primate centers were enlisted as SIV Vaccine Evaluation Units for preclinical assessment of SIV vaccines analogous to HIV vaccines in clinical development. A reagent repository was established by NIAID to develop core reagents applicable to AIDS vaccine research, and a database was set up at Los Alamos National Laboratory to collate and analyze HIV genetic sequence variation and was subsequently expanded to address immunologic epitope analyses.

Other public-sector agencies refocused to launch AIDS vaccine discovery and development programs. France's Agence nationale de recherche sur le sida et les hépatites virales (ANRS) was among the initial groups to establish partnerships in the developing world to determine pathogenesis of HIV infection. The UK Medical Research Council's AIDS Directed Programme launched a complementary repository of reagents for European investigators and began developing whole inactivated SIV vaccines. The World Health Organization (WHO) launched its Global AIDS Program, which included establishment of the HIV Virus Isolation & Characterization Network to identify HIV isolates from all over the world and to begin to grasp the breadth of the virus's genetic variability. The US Department of Defense set up an international screening program on the molecular epidemiology of HIV.

Annual meetings of the NCVDG provided one of many forums to bring the world's AIDS vaccine researchers together, to review annual advances in the field, and to foster new partnerships and initiatives in AIDS vaccine discovery. Unfortunately, the hepatitis B vaccine model

did not prove instructive for AIDS vaccine development; when scientists learned at the NCVDG meeting in 1991 that sera from HIV Env-based candidate vaccines had no effect on primary isolates of HIV, it marked the beginning of the end of the First Wave. By 1993, first-generation Env-based protein and peptide vaccines had entered clinical trials, two had advanced to Phase II trials, and the first AIDS vaccine trials in the developing world were ongoing. In 1994, NIAID decided not to advance the leading first-generation AIDS vaccines (Genentech's and Chiron's gp120 candidates) to efficacy trials, deeming that the vaccines had a low probability of success.

In hindsight, the 1994 decision was scientifically correct, and it was validated nearly a decade later when VaxGen, which licensed the Genentech gp120 vaccine, conducted two efficacy trials that showed that the candidate was ineffective (VaxGen 2003). However, the 1994 decision had a chilling effect on industrial AIDS vaccine development programs since industry was disillusioned by what it considered to be a rapidly changing playing field where criteria for advanced clinical development remained vague. Private sector investment in AIDS vaccine development decreased, and the First Wave ended with the field grappling with key scientific obstacles on the path to an AIDS vaccine:

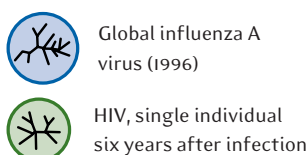
- How to elicit broadly neutralizing antibodies against HIV;
- How to mimic the protection conferred by live-attenuated SIV;
- Which HIV antigens are required for protection; and
- Which immune responses are required for protection.

### The Second Wave, 1995-2007: Harnessing the Power of Cell-Mediated Immunity and Public-Private Partnerships

The Second Wave of AIDS vaccine development began with a round of reflection. The Levine Committee was commissioned by the NIH to review its AIDS vaccine portfolio and recommended greater focus on basic research to address the fundamental scientific problems impeding AIDS vaccine development. The landscape of global AIDS vaccine development was much different from that of today: the resources dedicated to developing an AIDS vaccine applicable to the developing world were negligible; there were no public-sector-supported laboratories capable

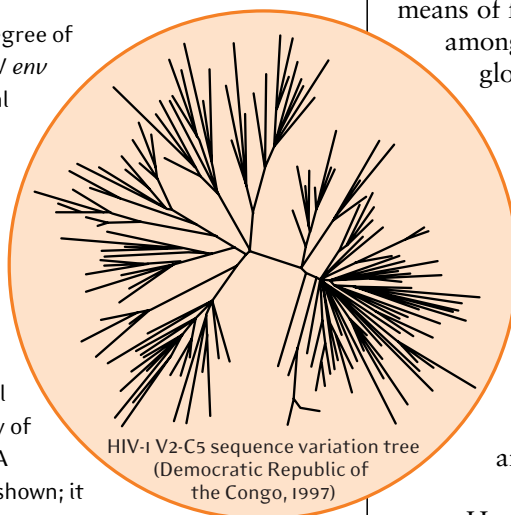
## WHY HIV IS A MOVING TARGET

This figure shows the degree of genetic variability of HIV *env* gene in one geographical region, the Democratic Republic of Congo, and within a single HIV-infected individual. The lengths of the branches represent the genetic divergence of different virus isolates. For comparison, the total global genetic variability of the influenza A virus (HA gene) in a whole year is shown; it is similar to the genetic variability seen in a single HIV-infected individual. HIV's hypervariability renders it a moving target for vaccine intervention.



Weiss, R.A 2003

Size = Extent of HIV variability



of the Global HIV Vaccine Enterprise as an alliance of independent entities was first put forward in 2003 as a means of further increasing coordination of global efforts among the different stakeholders and developing a global scientific strategic plan (Klausner 2003).

When data emerging during the First Wave began to suggest that live-attenuated SIV protected monkeys from disease caused by pathogenic SIV challenge and that induction of broadly neutralizing antibodies against HIV would be a formidable challenge (Figure 3), scientists began exploring ways of harnessing the CMI arm of the immune system, with the eventual goal of designing vaccines that elicited both broadly neutralizing antibodies and CMI responses.

Human epidemiological data and preclinical studies with candidate vaccines together provided an impressive case for the importance of CMI responses in controlling HIV infection (Figure 4) (Betts 2006). Technologies that were developed to assess CMI responses—such as tetramer staining, flow cytometry-based intracellular cytokine staining, and viral suppression assays—provided researchers with more sophisticated tools (Tobery 2006, Allen 2001). Moreover, proteomics and genomics had advanced to the stage that they were of value in addressing questions in AIDS vaccine discovery (Telenti 2006, Yan 2008).

**Figure 3** The hypervariability of HIV

of conducting validated assays of HIV-specific immune responses; there were no concentrated research programs dedicated solely to solving the major scientific challenges impeding AIDS vaccine development; there were no laboratories focused on systematically evaluating and prioritizing AIDS vaccine concepts at the preclinical level; and there was reticence towards conducting clinical trials of AIDS vaccines in the developing world.

Against this backdrop, the International AIDS Vaccine Initiative (IAVI) was formed in 1996 as a global, not-for-profit, public-private partnership, with the mission of ensuring the development of a safe, effective, preventive AIDS vaccine, applicable for use in the developing world where the pandemic is most severe. In addition to IAVI, during the Second Wave a number of other initiatives emerged, including EuroVacc, the Collaboration for AIDS Vaccine Discovery (CAVD), the Center for HIV/AIDS Vaccine Immunology (CHAVI), and the South African AIDS Vaccine Initiative (SAAVI). The concept

Initially, however, the pendulum swung too far in the direction of developing candidate vaccines focused exclusively on eliciting CMI responses, so that of the more than 30 candidates that entered the clinical pipeline during this wave, virtually all were intended to elicit CMI responses (Table 4). Moreover, there was significant duplication of effort among the stakeholders and no concerted effort to trim the pipeline to advance only the most promising candidates. For example, from an initial DNA and modified vaccinia ankara (MVA) concept that entered clinical trials in 2000 (Hanke 2000), more than 20 candidates based on some combination of DNA and/or poxvirus vector eventually entered the clinic. Prioritization could occur only by comparative Phase 1 clinical trials done in validated laboratories or NHP studies, but many vaccine researchers were reluctant to have their vaccines tested head-to-head against other candidates, and stakeholders could not agree on criteria to force the issue, making comparisons initially difficult.

Two NHP models for AIDS were proposed for assessment of CMI-based vaccines, one utilizing SIV and

the other using SHIV. However, the models gave conflicting results. Virtually all candidates assessed in the SHIV model demonstrated efficacy in terms of lowering viral load; in contrast, with the notable exception of the live-attenuated SIV vaccine, virtually none of the candidate vaccines provided benefit against SIV, as measured by control of viral load.

Based on Phase I clinical trial data, the Merck Ad5 candidate began to emerge as the leading CMI-based vaccine and was advanced to efficacy trials. Studies over the past few years have suggested that SIV is more HIV-like in many respects than SHIV (Feinberg 2002), and this has been further supported by the Phase IIb clinical trial results of the Merck Ad5 candidate (STEP trial); the trial results confirmed the negative results seen in the SIV model but not the positive results seen in the SHIV model. Even though it is imperfect, most scientists now prefer the SIV model of AIDS for preclinical evaluation of vaccines. But this SIV-rhesus macaque model will not be validated as a true predictor of human efficacy until an HIV vaccine has demonstrated protection in humans and the analogous SIV vaccine has demonstrated protection against SIV in rhesus macaques.

In 2001 IAVI conducted a comprehensive assessment of the global response towards solving the scientific challenges impeding AIDS vaccine development, with the goal of improving the product development pipeline of candidate vaccines. This assessment revealed that the overwhelming majority of resources focused on these scientific problems was being distributed in small amounts to large numbers of independent investigator-initiated projects. Unlike the large-scale, industrial-style, milestone-based efforts required for the successful development of virtually all licensed vaccines, the global effort to address the key scientific challenges in AIDS vaccine research consisted primarily of loosely linked consortia of academic investigators with no track record of vaccine development. New and innovative approaches to vaccine discovery were needed to overcome the scientific obstacles in AIDS vaccine development.

This assessment led IAVI to establish its Neutralizing Antibody Consortium (NAC), the first scientific consortium in the AIDS vaccine field focused entirely on the design of immunogens to elicit broadly neutralizing antibodies. Subsequently other consortia have been

## HOW AN EFFECTIVE CMI VACCINE WOULD PROVIDE BENEFIT

A CMI vaccine could potentially affect the natural course of HIV infection and provide benefit. The red line depicts the number of HIV RNA copies (or viral load) over time in natural infection. The green line indicates a theoretical scenario of viral load after vaccination with an AIDS vaccine candidate that elicits effective CMI responses. After vaccination, a rapid CMI response could potentially lower peak viral load and maintain a much lower level of HIV over time. This could lead to reduced transmission of HIV and delayed onset of AIDS.

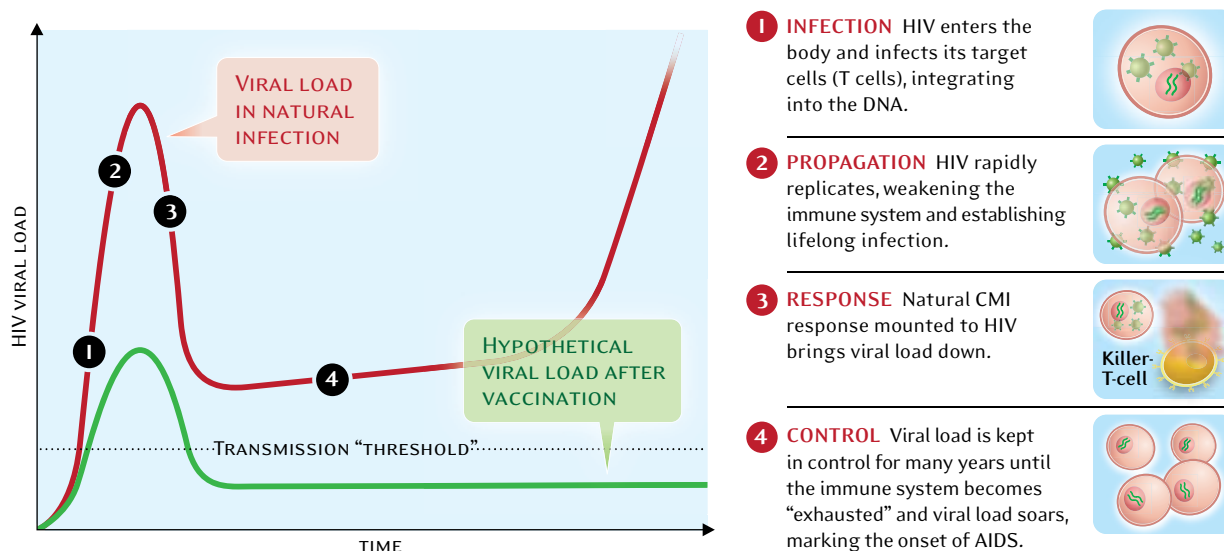
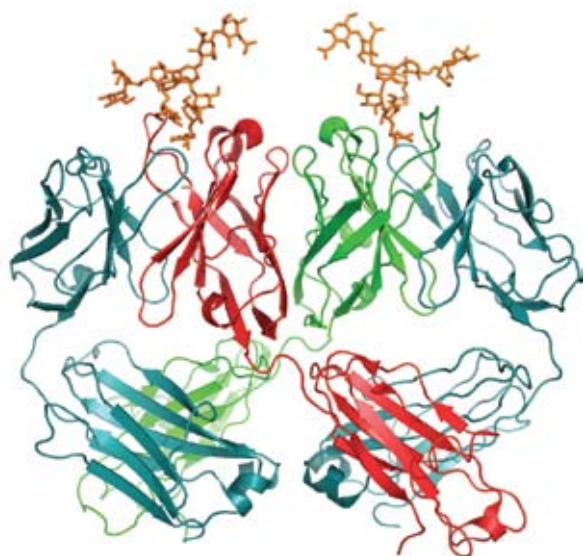


Figure 4 Cell-mediated immunity (CMI) in HIV infection

TABLE 4 AIDS Vaccine Candidates in Clinical Trials	
Protein Prime + Vector Boost	Phase III
Canarypox Clades B, E, gp120 prime	US Department of Defense, Ministry of Public Health Thailand, National Institute of Allergy and Infectious Diseases, Thai AIDS Vaccine Evaluation Group, sanofi pasteur, VaxGen
DNA Vectors +/- Vector Boost	Phase I/II
Clade B'C + Electroporation	International AIDS Vaccine Initiative, Ichor, Aaron Diamond AIDS Research Center
DNA polyepitopic, MVA boost	Epimmune Pharmexa, Bavarian Nordic
Clade B, MVA boost	GeoVax, US Military HIV Research Program
Multiclade A, B, C, Ad-5 boost	National Institute of Allergy and Infectious Diseases
Multiclade A, B, C, MVA boost	Karolinska Institute
Clade B'C, MVA boost	Johns Hopkins University, Guangxi, Changchun Baike
Clade C, NYVAC boost	EuroVacc, Agence national de recherches sur le sida et les hépatites virales
Clade B + IL-12, IL-15, peptide boost	Wyeth
DNA Clade C, MVA boost	South African AIDS Vaccine Initiative
DNA Clade A, E, FPV boost	The HIV Netherlands Australia Thailand Research Collaboration
Pennvax-B	University of Pennsylvania, VGX Pharmaceuticals
Viral Vectors	Phase I/II
Adenovirus	
Ad-6 Clade B	Merck
Ad-35 Clade A, +/- Ad-5 (prime or boost)	National Institute of Allergy and Infectious Diseases, Vaccine Research Center
Ad-26 Clade A	National Institute of Allergy and Infectious Diseases, Harvard University
Poxvirus	
ALVAC-HIV	National Institute of Allergy and Infectious Diseases, sanofi pasteur
MVA Clade A, E	Walter Reed Army Institute of Research
MVA multiantigen	Bavarian Nordic
MVA Clade C	International AIDS Vaccine Initiative
Vaccinia multiclade (DNA & protein cocktail)	St. Jude Children's Research Hospital
Proteins	Phase I/II
Gp140 Clade C <i>mucosal</i>	St. George's, University of London
C-terminal p17, full p24, fragment of gp41 with polyoxidonium adjuvant	Institute of Immunology, Moscow
Adjuvanted Gag, Pol and Nef	GlaxoSmithKline

## THE GOAL OF IMMUNOGEN DESIGN

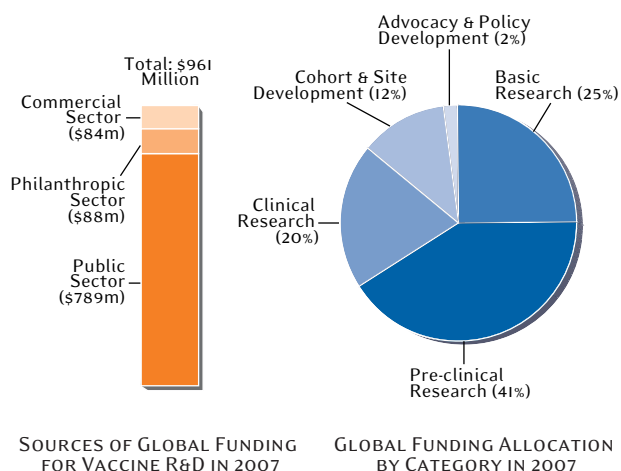


Crystal structure of human broadly neutralizing antibody 2G12. These three-dimensional structures give scientists clues on how to design immunogens that will induce broadly neutralizing antibodies.

Calarese DA, 2003

**Figure 5** Structure of an antibody

## AIDS VACCINE WORK: FUNDING AND SPENDING



**Figure 6** Contributions and Allocations in 2007

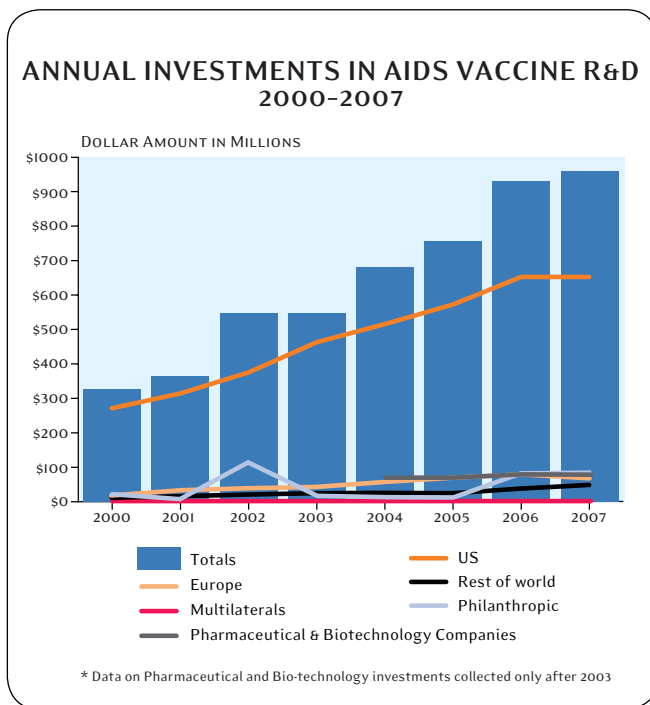
established, including NIAID's CHAVI, the Bill & Melinda Gates Foundation's (BMGF) Collaboration for AIDS Vaccine Discovery (CAVD), and IAVI's Control of HIV/ Live Attenuated and Vectors Consortia. Collectively these consortia have provided new and important scientific insights that open new avenues for vaccine discovery.

The field has seen some significant advances during the Second Wave. Scientists associated with the NIAID's CHAVI are gaining important insights on the nature of the virus that is transmitted from an infected person and establishes infection in a new host. This growing knowledge of the transmitted virus and the very early events in HIV infection have refocused efforts on the design of new candidate vaccines, including vaccines based on persistent and replicating vectors aimed at eliciting both systemic and mucosal immunity, in research sponsored by the BMGF's CAVD. Scientists connected to the IAVI NAC have determined the molecular-level structures of the most bnMAbs and identified their binding sites on HIV. Now, for the first time, these findings are enabling establishment of an industrial-scale vaccine discovery effort to design candidate vaccines that elicit similar broadly neutralizing antibodies (Figure 5).

Funding for AIDS vaccines R&D increased substantially during this period, reaching an estimated US\$ 961 million in 2007. Much of the total AIDS vaccine R&D funding (68 percent) was allocated to basic research and pre-clinical activities, which include applied science, candidate discovery, and animal testing. Clinical trials accounted for 20 percent of spending. The public sector provided the great majority (82 percent) of these resources, and the US government alone contributed US\$ 659 million, or 69 percent of total global investment in AIDS vaccine R&D. Philanthropic foundations, notably the BMGF, accounted for an additional nine percent of total funding (Figure 6). Together, public sector and philanthropic funding for AIDS vaccines nearly tripled between 2000 and 2007. In contrast, commercial investment has stagnated in recent years, accounting for only nine percent of total investment in 2007 (Figure 7).

The Second Wave included disappointments and discord surrounding product development: the VaxGen gp120 candidate showed no evidence of efficacy, and there was controversy regarding the more than US\$ 100 million spent on an ongoing prime-boost efficacy trial in Thailand testing a sanofi pasteur canarypox vector prime and the VaxGen gp120 boost, with data expected in 2009. Additionally Merck's Ad5 AIDS vaccine candidate, tested for efficacy in the STEP trial by NIAID's HIV Vaccine





**Figure 7 A steady growth in investment**

Trials Network (HVTN), neither prevented HIV infection nor reduced viral load in vaccinees who subsequently became infected with HIV. Moreover, there was a higher number of HIV infections in vaccine recipients compared with those given placebo, primarily among uncircumcised male volunteers who had pre-existing Ad5 immunity from prior exposure to this virus. The mechanism of this seemingly enhanced susceptibility to HIV infection is not yet understood and is the subject of intensive research. This may well have bearing on the design and development of future vaccine candidates.

The VaxGen and Merck candidate failures came after a number of similar failures in the microbicide and new prevention technology field, leading scientists to call for greater efforts in fundamental vaccine discovery and innovation. In an effort to bring new ideas and scientists into the field, IAVI and BMGF launched complementary programs focused on bringing greater innovation to AIDS vaccine discovery, and NIAID enhanced its ongoing innovations program with greater resources.

The Second Wave of AIDS vaccine development ended as it began—with a bout of reflection and a lack of solutions to the key scientific obstacles identified at the end of the First Wave. Data from the trial of the Merck Candidate suggested that inducing effective CMI responses may be as challenging as solving the HIV neutralizing antibody

problem. The results told us that new strategies, new ways of doing business, greater innovation, and a long-term commitment will be required for success.

### The Third Wave, 2008 Onwards: Harnessing Innovation and Accelerating AIDS Vaccine Discovery

The Third Wave, which is just beginning in 2008, will harness innovation to accelerate AIDS vaccine development. Rather than follow a standard product development plan towards eventual licensure, clinical development will likely be iterative, adaptive, and with emphasis on clinical research that informs vaccine discovery. Large-scale efficacy/licensure trials, like the ongoing 16,000-person sanofi pasteur canarypox + gp120 trial in Thailand, will probably be replaced by multiple and smaller preliminary efficacy trials, with only those candidates that show some evidence of efficacy advancing to large-scale trials. Greater integration of preclinical and clinical research, utilizing standard protocols and predetermined criteria to advance candidates, will become the norm (Bernstein 2008).

Several pieces of positive data in 2008 have fortified efforts in AIDS vaccine discovery. Sera collected from cohorts of individuals infected with HIV show that broadly neutralizing antibodies are more prevalent than originally thought, with approximately 10 percent of these individuals having neutralizing sera. Preclinical studies show that some neutralizing antibodies “punch above their weight,” requiring significantly less antibody than originally thought necessary to provide protection in vivo to neutralize HIV isolates and passive immunity studies using vector-mediated gene transfer to express bnMAbs have shown protection in NHP models (Figure 8).

The field now has several years’ experience with the strengths and weaknesses of scientific consortia in tackling the major scientific obstacles impeding AIDS vaccine development, and we expect that the recently created full-time Global HIV Vaccine Enterprise management team will become fully engaged as a resource in bringing together the independent entities in the field. Harnessing high-throughput tools from drug discovery, implementing industrial-style screening processes, and ensuring maximum time commitment of leading investigators to focus on research rather than administrative and grant-writing activities will all be keys to success, as will continuing efforts towards accelerated product development and testing. Additionally, investment in people rather than specific projects should be considered an adjunct to current funding strategies by

stakeholders, together with training of and investment in the next generation of scientists who will continue the AIDS vaccine development effort in both developed and developing countries.

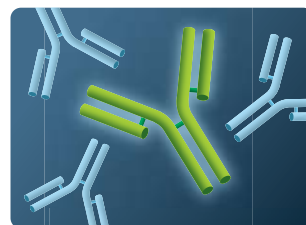
This *Blueprint* proposes a roadmap for accomplishing our intermediate goal of demonstration that a candidate AIDS vaccine provides benefit in humans in this Third Wave of AIDS Vaccine Development. IAVI challenges the field to debate the recommendations laid out in Section 4 and, as we progress in the Third Wave, encourages stakeholders to tackle those goals and milestones that most closely align with their capabilities.

## LOOKING FOR CLUES THROUGH GENE THERAPY

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

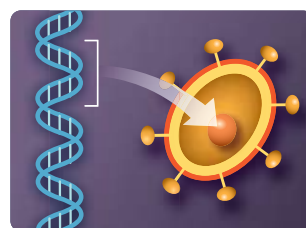
### 1 IDENTIFICATION

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



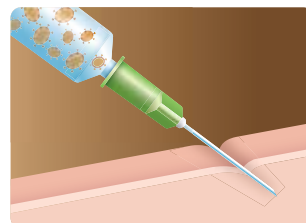
### 2 INSERTION

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



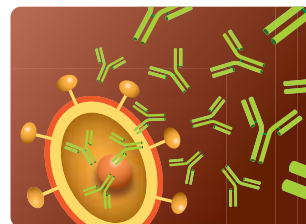
### 3 INJECTION

After injection, the vector establishes itself in the body.



### 4 PROTECTION

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



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

SAMUEL VELASCO / 5W INFOGRAPHIC

Figure 8 A novel approach to antibodies

# 4 KEY ASSUMPTIONS

During the development of this *Blueprint*, IAVI conducted an assessment of the state of the field in order to develop a roadmap of tangible goals and milestones for advancing AIDS vaccine development. The recommendations, goals, and interim milestones outlined in Section 5 are built on a number of Key Assumptions.

## 4.1 BASIC RESEARCH ASSUMPTIONS

The fundamental principles gleaned from basic research are the essential underpinning of any successful scientific endeavor. A good consensus is now emerging within the AIDS vaccine field that, in the balance between R&D, there should be a return to first principles and stronger emphasis on basic research to improve understanding of the underlying principles fundamental to HIV and its interaction with the human immune system. At the same time, at the clinical end of the spectrum, rather than focusing only on long-term and large-scale product development, a true clinical research agenda should be launched that tests new vaccine concepts very early in their development in humans.

Vaccinology has moved from an almost entirely empirical science—tinkering with vaccine candidates until they protect, with relatively little comprehension of how they work—towards a more mechanistic scientific discipline that seeks to elucidate the biology that defines the immune response. Delineating exactly how the human immune system works and precisely how HIV compromises it are huge challenges that will require application of novel scientific disciplines now emerging, such as systems biology, computational biology, and genomics and microarray technology.

We list here some of the basic science areas in which more knowledge is required. Some of these areas are already being tackled in existing programs, others will be addressed during the investigation of the recommendations in Section 5, and still others will require devoted programs and/or principal investigator-led projects to provide further insight that can then be exploited in translational research towards practical application. As the traditional powerhouses of fundamental research, national research agencies such as the NIH are the obvious choice for addressing many of these fundamental areas of basic research.

### Pathogenesis and early events in HIV infection, including mucosal immunity

Because HIV integrates into human chromosomes and thereby becomes a persistent lifelong infection, a vaccine will probably have to prepare the immune system to respond very

early, possibly within a week or so of initial exposure to HIV. Studying the very early events of HIV infection has been an area of intense activity in recent years, but we still need to know more about the cells that HIV first infects, how long it remains a localized infection before it is broadcast systemically, and how vulnerable to immunological intervention these early events are. We also need to know more about the nature of the infective virus—is it free virus or cell-associated virus? Only one, or a few, viruses initially infect; what is the mechanism, and can this be exploited? And do the early founder viruses have common characteristics that might be an Achilles' heel that a vaccine can target?

While it is clear that HIV inflicts huge immunological damage very early in infection at the GALT, it is not known whether a vaccine will need to elicit immune responses at this site, or indeed any other mucosal site. New insights are needed on mucosal immunity and its importance for an AIDS vaccine.

### Basic mechanisms of B-cell biology, including B-cell memory

Improved understanding of B-cell biology will be critical in order to better manipulate the antibody response. In general, we need to better define the role that helper T cells and regulatory T cells play in B-cell responses, as well as the role of B cells in antigen processing and presentation. Improved strategies for targeting dendritic cells and other antigen-presenting cells to better support increased antibody responses will also be important. The identification of functional Toll-like receptors on B cells suggests that innate immune stimulators might affect antigen-responsive B cells, and this might pave the way to improved immune modulators and adjuvants. Critical to any vaccine modality is the maintenance and reactivation of protective B-cell immunological memory. Mechanisms of achieving this must be defined in the context of HIV specific antigens.

### Greater understanding of innate responses, including adjuvants to elicit them

It is becoming increasingly clear that innate immunity can significantly shape adaptive immune responses. Just as innate immunity may be important in natural protection from HIV infection, this arm of the immune system could have a critical role to play in an effective AIDS vaccine. The role of natural killer cells in HIV infection has recently received closer attention, and important areas that still need to be defined include the precise roles of macrophages and



dendritic cells. How all of these cell types interact with other cells of the immune system may provide clues to harnessing innate immune responses to enhance adaptive immunity.

It will be important to elucidate the relative contribution of various molecules, such as Toll-like receptors and chemokines, to HIV pathogenesis and protection. It is likely that innate immune mechanisms will be especially valuable in developing new adjuvants to bolster vaccine responses.

Intrinsic immunity is an emerging field that describes intracellular antiretroviral defense, a part of innate immunity. It remains to be determined whether important molecules like TRIM5 $\alpha$  and APOBEC3G can be manipulated to provide protection from HIV infection.

### Immunological assay development

New immunological assays will be vital to many avenues of vaccine discovery, and as the immune correlates of protection become clearer these will have to be adapted. The current screening of CMI-based vaccines is focused on the ELISPOT assay, which uses a cytokine marker (usually interferon- $\gamma$ ) to indicate stimulation of T cells when they come into contact with specific HIV antigens. While this test can rank vaccines based on the magnitude and breadth of immune responses, in the STEP trial, positive ELISPOT did not correlate with protection. It has long been acknowledged that a new generation of assays that better reflect T- and B-cell biology are needed. Often termed functional assays, these are under development and will measure such aspects

as how well T cells from a vaccinee suppress HIV replication and how well they produce perforin, a molecule important in killing infected cells.

## 4.2 VACCINE DISCOVERY AND DEVELOPMENT ASSUMPTIONS

### An AIDS vaccine is unlikely before the HIV neutralizing antibody problem is solved

The HIV neutralizing antibody problem is one of the major obstacles impeding AIDS vaccine development. Simply put, scientists have not yet succeeded in designing an immunogen to elicit antibodies that neutralize the broad spectrum of isolates of HIV being transmitted. Most viral vaccines work by neutralizing the virus with antibodies and then eliminating the virus and/or virus-infected cells. In diseases in which natural infection induces an effective neutralizing antibody response, mimicking infection is often an effective vaccine strategy; this is the case with the majority of killed vaccines (e.g., inactivated polio) or live-attenuated vaccines (e.g., measles). But HIV infection does not usually elicit broadly neutralizing antibodies due to the virus's multitude of immune evasion strategies. However, over the years a handful of bnMAbs against HIV have been isolated from HIV-infected individuals. These antibodies and their interaction with HIV are the subject of intensive research to identify new approaches to vaccine design (Figure 9).

Although significant progress has been made, given the scale of the AIDS pandemic and the urgency for successful

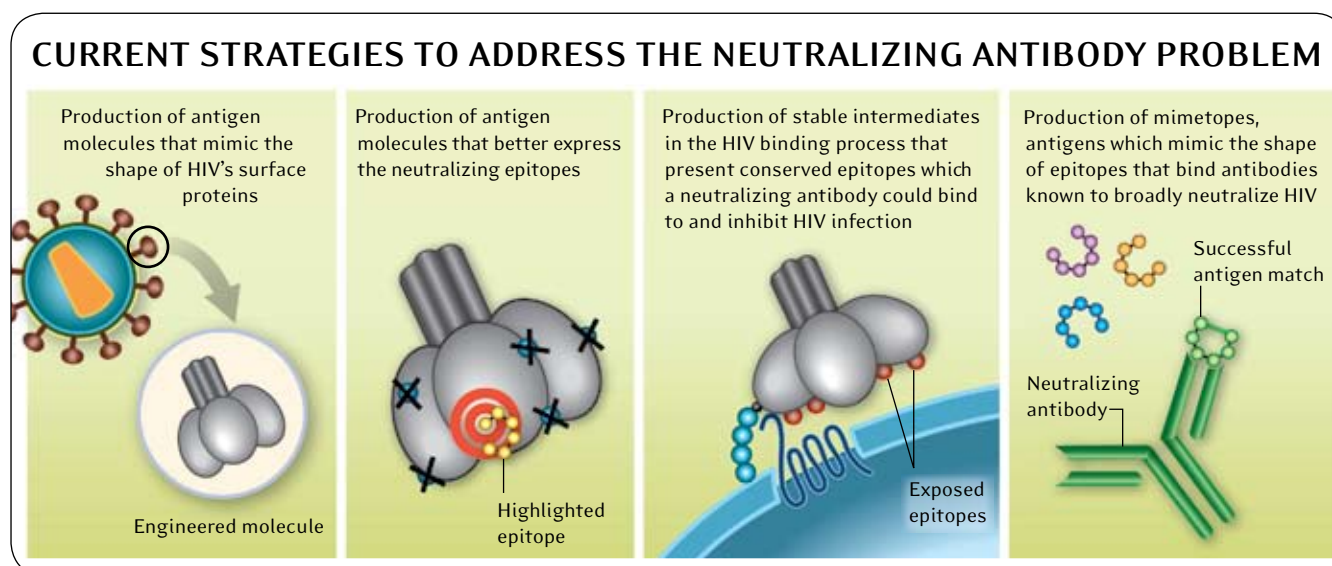
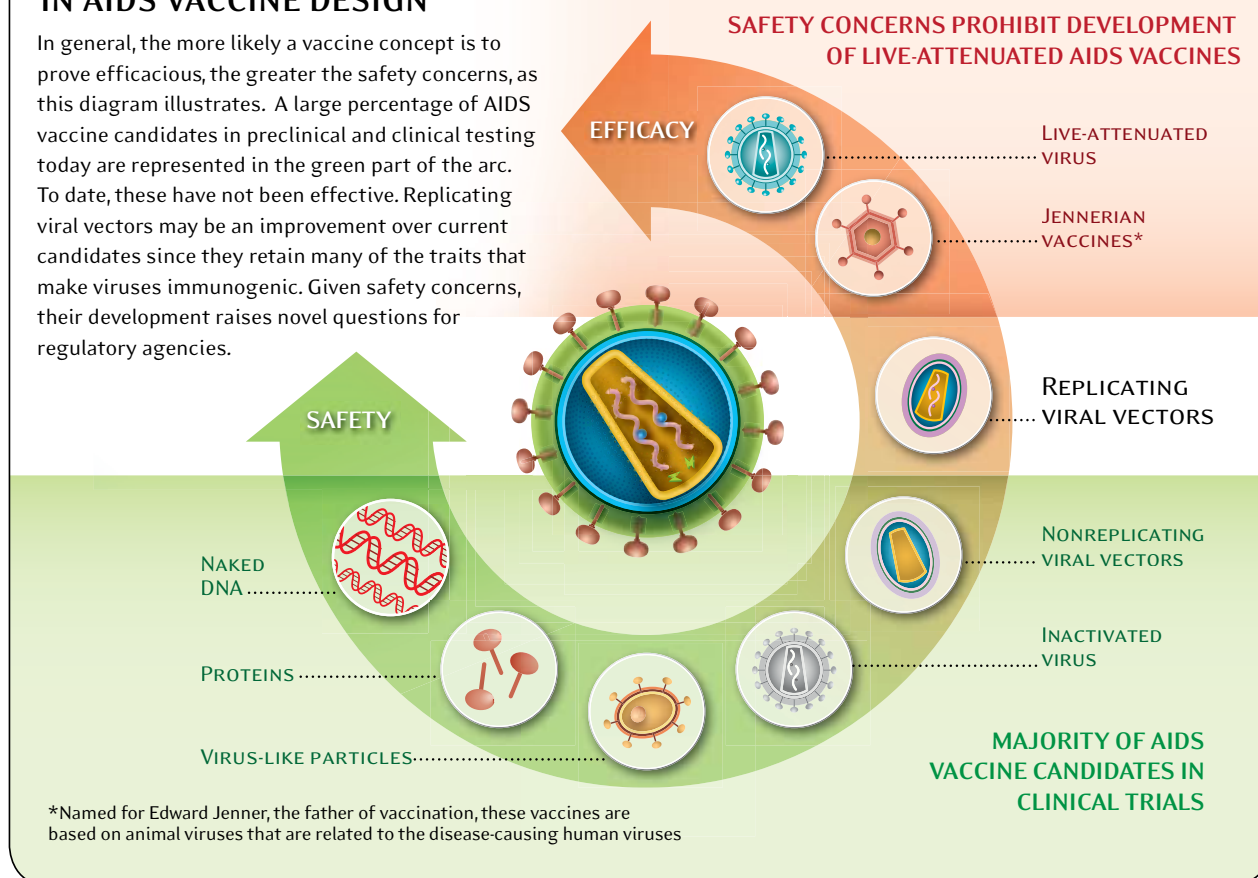


Figure 9 Approaches to designing immunogens that neutralize a broad spectrum of circulating HIV strains

## SAFETY VERSUS EFFICACY IN AIDS VACCINE DESIGN

In general, the more likely a vaccine concept is to prove efficacious, the greater the safety concerns, as this diagram illustrates. A large percentage of AIDS vaccine candidates in preclinical and clinical testing today are represented in the green part of the arc. To date, these have not been effective. Replicating viral vectors may be an improvement over current candidates since they retain many of the traits that make viruses immunogenic. Given safety concerns, their development raises novel questions for regulatory agencies.



**Figure 10** The platforms used to design vaccines

development of an effective vaccine, we believe that the pace of discovery is too slow and that current efforts are insufficient. While collaborative consortia such as IAVI's NAC, the BMGF-funded CAVD, and the NIAID-funded CHAVI offer major advances over individual investigator-initiated research, none of these consortia fully maximize progress on complex, multidisciplinary scientific problems. Most importantly, due to funding constraints and administrative obligations, the investigators connected to these consortia spend only a fraction of their time focused on research. Further, investigators are often isolated from other colleagues due to the challenges of effectively working across geographically separated institutions and disciplinary barriers. Implementation of new mechanisms for addressing these constraints, combining significant long-term commitments from funders with significant long-term commitments from leading scientists across multidisciplinary areas, would enhance the potential for the innovation and new ideas that are required to solve the neutralizing antibody problem.

## An effective AIDS vaccine will have to elicit more than broadly neutralizing antibodies

Solution of the HIV neutralizing antibody problem will be a necessary advance towards an effective AIDS vaccine but will probably not be sufficient alone. Studies with other retroviruses in which prevention and control have been achieved indicate that both neutralizing antibodies and robust cellular immune responses are required for protection. Interestingly, significantly less research has focused on the identification and prioritization of the HIV antigens required for control of HIV infection than has been conducted on vectors and formulations to deliver such antigens. A clinical research program for systematically assessing the required antigens has yet to be implemented; neither the HIV antigens recognized by the human immune system in elite controllers nor the SIV antigens required for protection of NHPs by live-attenuated SIV vaccine have been identified. Understanding which antigens are required to elicit beneficial responses would significantly advance the field.

### An effective AIDS vaccine will have to control HIV as well as or better than live-attenuated SIV protects against pathogenic SIV challenge

Live-attenuated viral vaccines—including those against measles, mumps, rubella, oral polio, yellow fever, and varicella—are among the most effective vaccines. Their efficacy probably derives from their induction of a comprehensive and long-lived antibody and CMI response to the pathogen. Live-attenuated SIV is the only vaccine approach that consistently provides a thousandfold reduction of viral load against a matched SIV challenge: if there were an HIV vaccine candidate that elicited broadly neutralizing antibodies against HIV and controlled SIV infection in macaques to an extent similar to live-attenuated SIV vaccine, there would be a groundswell of support for accelerating the candidate to efficacy trials.

No serious consideration is being given to developing a live-attenuated HIV vaccine because of concerns that the attenuated vaccine might revert to its virulent form and cause infection and disease. The amount of safety data required to convince the scientific community, regulatory agencies, vaccine manufacturer executives, activists, and the general public that a live-attenuated HIV vaccine could be administered safely to humans would be prohibitive. Live-attenuated SIV is used in vaccine discovery programs as a model system for understanding the mechanisms of protective immunity and translating this information into the design of improved AIDS vaccine candidates that mimic its efficacy. However, even live-attenuated SIV is not as effective when the challenge virus is not an exact match to that in the vaccine. HIV is different all over the world; the viruses circulating today in North America are different from those ravaging different parts of sub-Saharan Africa, which are different again from those in Asia, and so on. As a result, AIDS vaccines will probably have to improve upon the efficacy conferred by live-attenuated SIV vaccines against heterologous challenge.

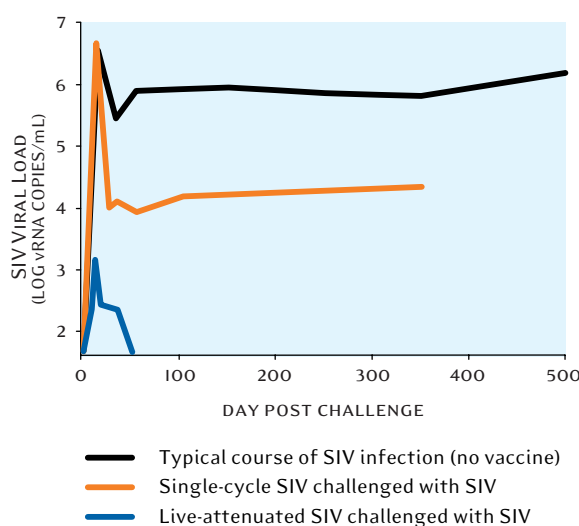
### Live replicating viral vectors are likely to provide improvements over candidates currently in the pipeline

A number of technological platforms may be explored for AIDS vaccine candidates. The vast majority of resources are devoted to development and testing of non-replicating vector and subunit vaccines (Figure 10). But so far, clinical trial results have failed to validate any non-replicating viral vector, DNA vaccine, or subunit antigen as a standout platform of choice to aggressively develop as an AIDS vaccine.

The control of SIV infection afforded by live-attenuated SIV in macaques sets a standard for AIDS vaccines to attain or exceed. It is likely that this impressive level of control is at least partly due to the replicative nature of live-attenuated SIV, since SIV that has been genetically engineered so that it is limited to a single cycle of infection is not nearly as beneficial in macaques (Figure 11). And even though HIV presents multiple obstacles in the path of vaccine development, many of these obstacles have been overcome in other diseases with the use of replicating vaccines: Variola virus, the cause of smallpox, encodes proteins that modulate specific host pathways required to engage innate antiviral defenses or mount an effective immune response, yet ridding the world of smallpox through immunization is one of public health's greatest achievements; measles virus, like HIV, causes considerable T-cell depletion and an acute state of immune suppression; varicella zoster virus persists

#### LEARNING FROM THE LIVE-ATTENUATED MODEL

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



Evans DT, et al. *J. Virol.* 79, 7707, 2005

MELISSA THOMAS

Figure 11 The benefits of replication

for the life of its host; and a number of viral pathogens, notably influenza virus, contain mutable genomes that result in extensive genetic diversity. In addition, experimental vaccines for other pathogens (Ebola, Marburg, and avian influenza viruses) that use replicating vectors have recently shown promise in NHP studies (Koff 2008, Jones 2005).

Taken together, this evidence indicates the promise of replicating viral vectors as vaccine strategies. It is likely that they will be an improvement on current candidates since they retain many of the traits that make viruses immunogenic: efficient delivery through natural virus receptor-mediated pathways; immunogen expression within infected cells that provides the natural context for antigen presentation to the immune system; and, perhaps most important, replication resulting in abundant, disseminated, and sustained expression of antigens.

Because of the novel and unprecedented regulatory issues raised by the development and testing of replicating viral vectors for AIDS vaccines, partnerships will be required among vaccine developers, regulatory agency scientists, scientists in developing countries, public health officials, institutional review boards, and communities in which the clinical trials will take place.

### **Innovation will be key to solving the major scientific challenges impeding AIDS vaccine development**

Albert Einstein once defined insanity as “doing the same thing over and over again and expecting different results.” There is virtually universal agreement that to tackle the daunting scientific problems on the road to an AIDS vaccine, innovation will be vital to success. The challenge comes in identifying innovation applicable to AIDS vaccine discovery, nurturing it, and ensuring that mechanisms are in place to rapidly translate the periodic breakthrough innovations into substantive vaccine development. The three innovation programs launched by IAVI, NIAID, and BMGF are the most recent attempts to foster innovation. Through its program jointly supported by the BMGF, IAVI is attempting to engage the biotech sector in identifying novel technology platforms applicable to AIDS vaccine development. One of these—an attempt to develop an in vitro artificial immune system that predicts observations in human clinical trials—would, if successful, accelerate the screening of immunogens and decrease the need for some preclinical screening. The BMGF Grand Challenges Exploration program targets academic investigators and the private sector around the world for novel ideas with small seed grants that could lead to larger grants for a small number of successful projects.

Innovation may also be fostered by investing in people. Important ways to ensure a flow of new ideas include attracting promising new investigators and establishing dedicated teams to develop and assess novel approaches to AIDS vaccine discovery. Cross-fertilization with fields like general viral immunology, drug discovery, structural genomics, and glycobiology will also help identify applicable new technology platforms. The AIDS vaccine field should also guard against groupthink, which can encourage conservatism and quash innovation. Healthy competition and diversity are crucial.

### **Clinical research is an integral component of vaccine discovery**

The fundamental building blocks from basic science will be critical to advancing towards an AIDS vaccine, but that alone will not be enough. Conducting clinical research in a variety of epidemiological settings in diverse populations and in environments in which a broad spectrum of HIV isolates circulate will also be vital. Crucial clinical questions include: What is the nature of the transmitted virus? Which immune responses are required for the control of HIV infection in elite controllers? What role does host genetics play in the control of HIV infection? And how best can this information be applied to vaccine discovery?

Although the field has made significant progress in its understanding of HIV, the major questions in AIDS vaccine development in 1994 (see “First Wave”) remain largely unanswered in 2008. The field needs to develop new and improved ways of focusing on these questions. Closer integration between clinical researchers and basic scientists will lead to improved clinical research protocols for tackling the specific questions relevant to AIDS vaccine discovery. To foster advances in clinical research, particularly in the developing world, ethical and regulatory systems must be strengthened and streamlined and training initiatives are required to ensure appropriate capacity of well-trained clinical research teams.

## **4.3 RESOURCE ASSUMPTIONS**

### **Product development capabilities and clinical trials in the developing world are required in order to accelerate AIDS vaccine development**

Integration of product development capabilities with preclinical and clinical vaccine discovery efforts is a prerequisite to accelerating AIDS vaccine development. Moreover, innovation in clinical trials design will enable



scientific questions to be answered more rapidly. Questions regarding potential immunodominance by one or more HIV antigens, strategies for eliciting responses to multiple epitopes on HIV antigens, how best to address the genetic variability of HIV, and how to account for host genetics and environmental conditions will all require a nimble and flexible clinical-trial infrastructure in the developing world where preliminary efficacy trials will probably be undertaken.

Since similar DNA platforms, vectors, adjuvants, and other delivery systems are in development for vaccines for Tuberculosis (TB) and malaria, among other diseases, assessment of such vaccines in safety/immunogenicity trials at clinical research centers predominantly used for AIDS vaccine trials may offer opportunities to address some related scientific questions while maintaining capacity at the centers. Similarly, conducting clinical research—towards understanding, for example, the nature of the transmitted virus, HIV incidence rates, and co-factors such as parasitic infections—in communities from which AIDS vaccine trial volunteers will be recruited is important in preparation for such trials.

Developing countries, especially emerging economies like Brazil, China, India, and South Africa, can contribute much more than trial capacity to the search for an AIDS vaccine. These countries boast substantial scientific capacity and burgeoning biotechnology industries, and will play an increasing role in basic science, vaccine discovery, and eventual manufacture of AIDS vaccines. National commitments to AIDS vaccine R&D, coupled to policies supportive of innovation and international collaboration in biomedical R&D, can strengthen these countries' contribution to the global vaccine effort.

Engagement, capacity, and commitment to AIDS vaccine research in many developing countries are strong and likely to remain that way; these countries are the hardest hit by the pandemic and can better envisage the impact of an effective AIDS vaccine. Developing countries will continue to be invaluable partners that inform and contribute to the vaccine research agenda, including through efforts to develop improved candidates. It is important to sustain the capacity in the global South for clinical research and to harness opportunities for expanding the cadre of scientists in developing countries to work towards meeting key scientific challenges.

Further, civil society groups, policymakers, and other key stakeholders in the developing world should also continue to ensure that AIDS vaccine research remains a global priority and that accurate advocacy messages about the state of

research are disseminated regularly. Reduced emphasis on large-scale trials should not imply reduced focus on the crucial role scientists, leaders, and communities in developing countries must continue to play. At the same time, the battles against TB and malaria are increasingly recognized along with the fight against AIDS as global priorities, and the AIDS vaccine field should look for opportunities to collaborate with TB and malaria vaccine researchers and advocates on policy, financing, and advocacy.

### Training the next generation of AIDS vaccine scientists is essential

AIDS vaccine development will require that the best and brightest young scientists enter the field, bringing renewed energy, ideas, and enthusiasm. The field should also engage and train scientists from low- and middle-income countries who can provide meaningful research contributions and build scientific capacity in their home countries, as well as act as champions there to influence policymakers, civil society, and the wider communities in support of AIDS vaccine research.

### The stability, flexibility, and appropriate allocation of AIDS vaccine financing are as important as the total quantity of resources

The AIDS vaccine field has enjoyed substantial and growing funding for several years. However, much of the current funding is relatively short-term, taking the form of one- to three- or five-year grants, with no guarantee of subsequent funding. Since vaccine development is a long-term endeavor and the ambitious new AIDS vaccine discovery initiatives will take several years to bear fruit, the security and stability of funding will be critical to planning and sustaining the next phase of AIDS vaccine R&D. At the same time, funding will have to be sufficiently flexible to permit reallocation as priorities shift in response to new data and new ideas. Although traditional grants from government agencies and foundations to investigators, consortia, and organizations will continue to be the mainstay of AIDS vaccine funding, new financing mechanisms, perhaps modeled on recent innovations in other areas of health and development financing, could help provide the greater stability and flexibility required. Innovative funding approaches could bring other benefits as well, reaching across national boundaries to support the best researchers wherever they work, involving the private sector, and extending beyond the AIDS vaccine field to support development of other urgently needed vaccines or HIV prevention technologies.

# 5 RECOMMENDATIONS

As we enter the Third Wave of AIDS vaccine development, we must acknowledge that our ultimate goal of a safe, effective, preventive AIDS vaccine that can be licensed and made accessible to all, throughout the world, will take more time and ingenuity than any of us originally imagined.

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

How, then, to get to this intermediate goal? This *Blueprint* proposes that those of us engaged in the search for an AIDS vaccine divide our mission into components that are more readily attainable than the ultimate goal of an effective vaccine or even the intermediate goal of proof of benefit in humans. In recommending interim goals and milestones to both guide and measure advances in the field for future years (Table 5), IAVI, as a founding partner of the Global HIV Vaccine Enterprise, hopes to stimulate discussion among all the stakeholders in AIDS vaccine development about the way ahead. The outcome of this debate could promote a resetting of priorities and facilitate the Enterprise in updating its Strategic Scientific Plan. In turn, stakeholders could undertake those goals and milestones that most closely align with their core capabilities (Figure 13).

Some of these recommendations are already being addressed in one form or another by various stakeholders, and there will be diversity of opinion as to which will be the crucial approaches and how precisely to proceed; that is one of the strengths of having parallel initiatives tackling the major obstacles. But only by proposing and discussing the big picture can a broad consensus be reached to ensure that all pertinent research directions are pursued, with sufficient overlap to guarantee diverse approaches without slipping into redundancy.

## 5.1 VACCINE DISCOVERY AND DEVELOPMENT RECOMMENDATIONS

IAVI believes that an effective AIDS vaccine will probably require solution of the neutralizing antibody problem as well as the problem of how to control HIV infection. While these ideas are not unique, IAVI believes that the field must realign resources appropriately towards these problems to make advances.

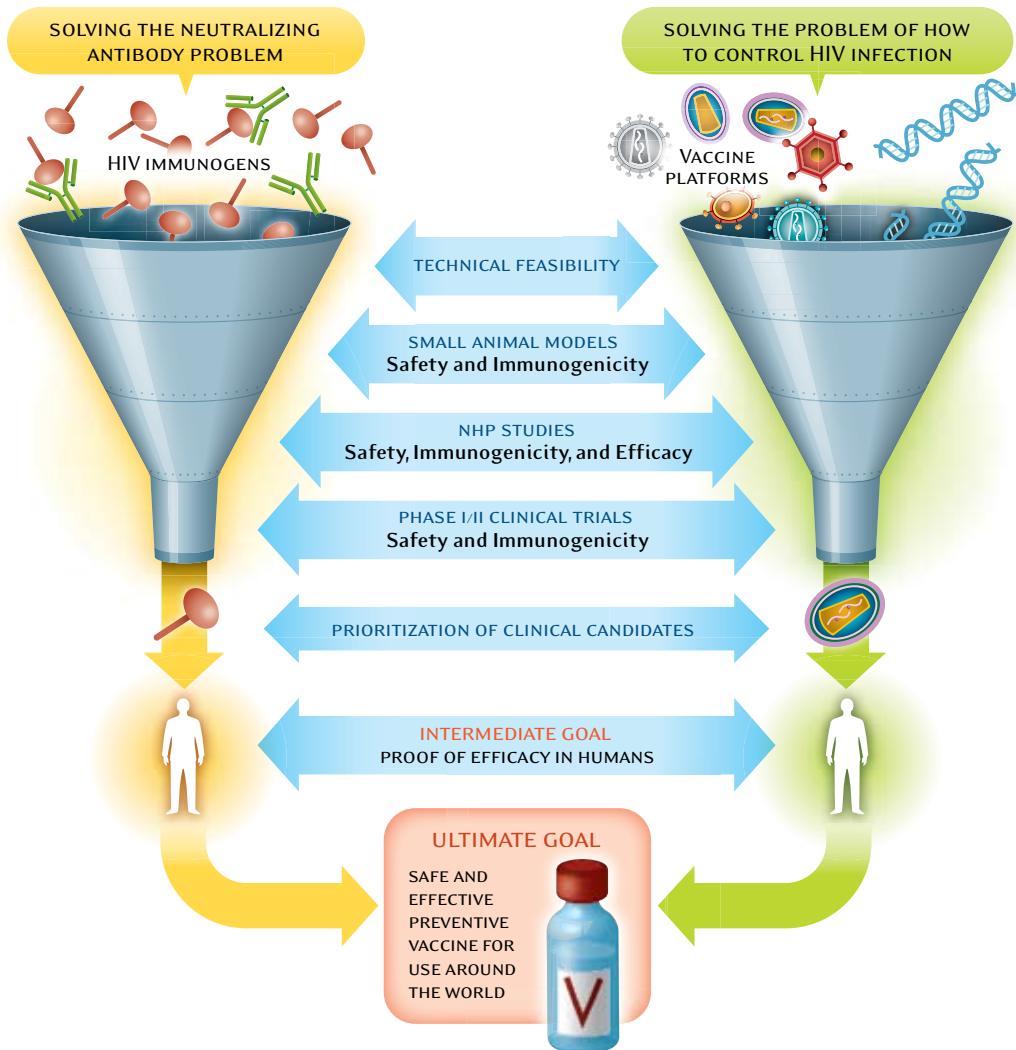
### 5.1.1 Solve the HIV neutralizing antibody problem

We believe that solving the neutralizing antibody problem is central to developing a preventive AIDS vaccine and that, while significant progress has been made in the last few years, the pace of discovery is not commensurate with the scale of the AIDS pandemic.

There have been major advances in understanding the relevant molecular biology and pathogenesis of HIV; the structures of the most bnMAbs against HIV and their binding sites on gp120 have been solved, and preclinical proof of principle that sufficiently high titers of neutralizing antibodies can prevent SHIV infection in NHPs has been demonstrated. However, the complexity of the HIV neutralizing antibody problem is such that it has resisted all attempts to solve it, and, although we now have far better tools at our disposal, to be frank, we are still far from solving it. A paradigm shift is required in terms of the scale of resources, time commitment of leading researchers, new ideas, and innovation from within and outside the field, and long-term commitment of funding to increase the potential for success.

We propose the scaling up of dedicated programs, in the form of consortia, laboratories, or discovery centers, that focus on the HIV neutralizing antibody problem and that they be provided with long-term funding commitments to develop high-throughput immunogen design and screening technologies to accelerate immunogen design and screening. This should include identifying and characterizing new bnMAbs against HIV from infected individuals and determining their gp120 binding sites and their structure. Major efforts at turning structural knowledge into immunogens must follow, and to that end, the field could adapt tools from high-throughput, small-molecule drug development to biologics development. Information from these efforts would be even more valuable once the structure of the native trimer of Env is determined, a longstanding

## ROADMAP FOR AIDS VACCINE DISCOVERY AND DEVELOPMENT



The next major advance on the way to the ultimate goal of an effective, licensed AIDS vaccine will be the first demonstration that a candidate AIDS vaccine provides benefit in humans. To achieve this intermediate goal, IAVI believes the field must achieve a series of tangible milestones that will solve both the neutralizing antibody problem and the question of how to control HIV infection.

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

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

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

Figure 12 Steps toward the ultimate goal

goal of the field that should be addressed with renewed vigor.

*Interim Goal: Identify and advance to clinical trials an immunogen that neutralizes a substantial proportion of circulating HIV strains, a suggested initial benchmark being at least 50 percent of moderately resistant HIV isolates*

### 5.1.2 Solve the HIV CMI problem

We believe that robust cellular immune responses will also be required for an effective AIDS vaccine. One of the lessons of the Merck trial is that inducing effective CMI responses will be more challenging than originally envisioned and perhaps as challenging as solving the neutralizing antibody problem. Existing programs should be scaled up and new tacks pursued:

#### Determine the antigens and immunologic mechanisms responsible for control of HIV infection by elite controllers

In the late 18th century, Edward Jenner's breakthrough observation that milkmaids exposed to cowpox were spared from the scourge of smallpox led to his eventual discovery of the smallpox vaccine. For AIDS vaccine discovery, the "milkmaids" are likely to be elite controllers—individuals who, for prolonged periods, control their HIV infection to below detectable levels without antiretrovirals—and potentially highly exposed seronegatives—individuals, such as some commercial sex workers, who are multiply exposed to HIV through infected sex partners yet remain uninfected. Studies in highly exposed seronegatives have been under way for some years and could be refocused with novel immunologic assays to examine the mechanisms of protection. We believe a higher priority is to address the major shortfall in resources and attention devoted to studying elite controllers. Since no licensed vaccine against other diseases completely protects against infection, understanding mechanisms of control of HIV infection by elite controllers and the HIV antigenic targets that confer this control would provide knowledge important to AIDS vaccine development.

As with the HIV neutralizing antibody problem, we propose building on established dedicated programs that focus on studying the control of HIV infection and ensuring that they have long-term support. An important first step would be to build additional cohorts of elite controllers to identify significant immune correlates of control. These programs should have the technological capacity for high-

throughput screening and genomics and close linkage with capacity to evaluate novel leads towards immunogen development in a clinical research program. The study of elite controllers should also take into account the possible role of innate immunity in control of HIV infection and how this can be applied to AIDS vaccine discovery.

*Interim Goal: Define the immune targets (HIV antigens and epitopes) of CD4+ and CD8+ T cells in elite controllers*

#### Determine the antigens and immunologic mechanisms responsible for control of SIV infection by live-attenuated SIV

Rhesus macaques protected against pathogenic SIV challenge by live-attenuated SIV (Koff 2006) are another potential "milkmaid." A significant problem has been to secure the resources required to conduct NHP studies at a scale sufficient for elucidating the mechanism of that protection and, importantly, to build on the resulting observations through the design and testing of even more effective immunogens.

We propose that capacity be built so that sufficient numbers of NHPs dedicated exclusively to AIDS vaccine discovery and development are available to allow statistically significant studies. To achieve this, challenge viruses and more reagents will also be needed. An important advance would be identification of the immunologic mechanisms responsible for protection. It is likely that the immune responses elicited by live-attenuated SIV in the GALT and the immune targets (SIV antigens and epitopes) of cytotoxic T cells will be important components of the response.

*Interim Goal: Identify the differences in immunologic mechanisms induced by replicating live-attenuated and non-replicating single cycle SIV*

#### Implement a new clinical research program to determine optimal immunogens for eliciting CMI responses against HIV

Despite significant investment in clinical trials of AIDS vaccine candidates, the field has collectively failed to answer several fundamental questions applicable to the optimization of CMI responses against HIV, which can only be answered in human trials. Much of the focus has been on developing the vectors and delivery methods rather than on the immunogens themselves. We propose that dedicated



clinical research programs be undertaken to systematically assess the optimal immunogens to elicit CMI responses.

While some questions may be addressed using immunogens currently in hand—for example, the benefit of including Env in immunogens intended to elicit CMI responses—many will require the rapid development of new immunogens specifically for this clinical research. As new leads come from elite controllers, live-attenuated SIV models, and other studies informing vaccine design, additional immunogen development will be necessary. Assessing different routes of immunization, how to optimize the breadth of CMI responses, and the contribution of immunodominance of HIV antigens and/or epitopes in immunogens intended to elicit CMI responses will also be important. To do this it will be necessary to develop standardized, accepted approaches to clinical trials, including regulatory approval strategies, manufacturing, and community support for clinical research.

*Interim Goal: Develop a set of immunogens and a clinical testing strategy for assessing optimization of CMI responses against HIV*

### 5.1.3 Improve the pipeline

In order to successfully advance AIDS vaccine research, the current pipeline must be reprioritized using predetermined criteria, and the best of current as well as new and novel approaches must be assessed in small-scale efficacy trials.

#### Trim the product development pipeline of less promising candidates

The lack of efficacy evident in the first candidate testing the CMI hypothesis for AIDS vaccines in the Merck Ad5 trial suggests that it is time to review the current clinical pipeline and trim candidates that have a low probability of success. There is no universal agreement in the field on the benchmarks for success of candidate AIDS vaccines, but prioritization of resources is a critical component of any vaccine development enterprise. Consequently, we believe that stakeholders should review their portfolios and that candidates considered to have a low probability of success based upon comparison with the Merck Ad5 vaccine candidate should be dropped, with freed resources redirected towards more promising vaccine approaches.

It is imperative that the global clinical pipeline encompass a spectrum of scientific hypotheses and eventually include candidates that elicit broadly neutralizing antibodies against HIV, stimulate mucosal

immunity, employ an optimized set of HIV antigens, perform as well in SIV models as the live-attenuated SIV vaccine, and combine effective neutralizing antibody responses with robust and durable CMI responses.

Most of the candidates in the current clinical pipeline test DNA and viral vectors, alone and in combination, with the goal of suppressing viral load by stimulating CMI responses. Preclinical and clinical comparison against the Merck Ad5 vaccine would facilitate prioritization within the pipeline and should be encouraged.

*Interim Goal: Trim the AIDS vaccine pipeline of candidates considered to have a low probability of success, with resources redirected towards either more promising approaches or solving the key scientific challenges*

#### Broaden and rationalize approaches to vectors for use in AIDS vaccines

One area that has been underresourced but that holds great potential is the development of replicating viral vectors that more closely mimic live-attenuated vaccines (Koff 2008). Accelerating the development of live replicating vector-based vaccines while achieving the optimal balance of safety, efficacy, quality, speed, and innovation will require not only a comprehensive shift in focus and substantial commitment of resources but also close integration of community involvement, regulatory oversight, and international leadership. Accelerating their development will raise novel questions for regulatory agencies, making risk-benefit calculations particularly important.

A replicating vector-based AIDS vaccine discovery and development effort will require the establishment of dedicated programs through consortia, academia, and biotech that focus on the specific issues that will be required in the design and development of replicating viral vectors. A useful initial yardstick would be to test different vector candidates against the Merck Ad5 vector, each containing standard SIV immunogen inserts, against SIV challenge in the NHP model. These comparative studies could be reiterative, with the most promising candidates—those that meet a minimum determined efficacy in challenge studies in NHPs—advancing to clinical trials.

*Interim Goal: Advance to clinical development AIDS vaccine vectors that demonstrate improved efficacy against SIV challenge compared with the Merck Ad5 candidate*

### Conduct small efficacy trials on leading candidates that achieve predetermined criteria

Human efficacy data are an integral component of vaccine discovery. Since HIV's host range is limited to humans (and a few NHP species that HIV can infect without causing disease), clinical testing in humans is required. Since most candidates will fail in early clinical testing, novel clinical trial designs are required to initially, rapidly, and inexpensively assess potential efficacy. In 2006, IAVI proposed efficacy trials that are relatively small (600-1000 volunteers) Phase 2b trials that determine whether a candidate vaccine provides benefit, with the primary endpoints being suppression of viral load or prevention of infection (Excler 2007); the former endpoint may be more useful when testing vaccine candidates designed to elicit CMI responses, the latter for candidates designed to elicit neutralizing antibodies. These trials allow for relatively rapid set-up and completion, while not attracting widespread public attention that can be detrimental if a candidate proves not to be effective.

The outcomes of these efficacy trials would inform decisions regarding either advancement to large-scale efficacy trials of candidates that fulfill predetermined criteria or termination of development in the absence of efficacy. However, prioritization of the vaccine candidates to be tested in small efficacy trials, as well as the decisions on whether to advance candidates to large-scale trials, would greatly benefit from agreed-upon predetermined criteria. At a minimum, we suggest that candidates entering efficacy testing should elicit stronger or differing T-cell responses in humans and show better efficacy in NHPs than the Merck Ad5 candidate that was ineffective in the STEP trial, or meet the antibody neutralization criteria described earlier. Next-generation assays that better reflect immunologic responses relevant to HIV can also be validated in these small efficacy trials.

*Interim Goal: Develop universally accepted, predetermined criteria for advancing candidates from Phase I to small efficacy trials*

## 5.2 RECOMMENDATIONS FOR SUSTAINING THE EFFORT

Now more than ever, AIDS vaccine advocacy is crucial to ensuring that the technical, human, and financial resources are available to develop and license an AIDS vaccine. To sustain the effort, the field must come together and set

appropriate expectations for AIDS vaccine research and development, as well as educate governments, donors, and community leaders.

### Ensure adequate and appropriate clinical research and trial capacity

Clinical trial capacity to conduct Phase I and small efficacy trials is an essential component of the AIDS vaccine clinical research effort. Despite significant investment over the past two decades there are still only a limited number of centers in countries with high-incidence HIV infection rates capable of conducting clinical research programs relevant to AIDS vaccine discovery. Centers must have the capacity to conduct clinical HIV research that will inform vaccine design and prepare for small efficacy trials of AIDS vaccines, including incidence studies, molecular epidemiology of the transmitted virus, and population-based host immune response studies of HIV infection. The ability to ramp up to large-scale efficacy trials in the event of promising leads will also be required.

It is also critical that these centers provide career paths for young scientists and have long-term financial stability and effective data collection and management. Key elements for these centers would include but not be limited to clinical trials capacity; laboratory capacity, including accredited and validated labs; data management; epidemiology; training facilities; Good Participatory Practices training (Joint United Nations Programme of HIV/AIDS 2007); community links; national and international support; and high incidence of HIV infection in the community.

Clinical trial centers take a long time to develop and to attain a level of excellence in laboratory, data management, clinical, and other disciplines and cannot simply be "turned on and off." On the other hand, excess idle capacity in clinical trial centers during gaps in product development expends valuable vaccine discovery resources and risks disillusionment among principal investigators, clinical staff, and the community.

Between AIDS vaccine trials, the talent and infrastructure at clinical trial centers could be applied to clinical research programs required for AIDS vaccine discovery and to trials of vaccines against other diseases and trials of other AIDS prevention technologies. Stakeholders in the global AIDS vaccine effort should undertake an independent assessment of devoted clinical trials capacity and other potential opportunities to make

the necessary corrections. The advances made over the past decade in ensuring that a robust capacity is in place to conduct clinical evaluation of candidates in diverse areas of the world should not be halted, but rather maintained and developed further in strategic and cost-effective ways.

*Interim Goal: Undertake assessments of global clinical research and trial capacity to ensure that there are adequate established regional AIDS vaccine discovery and development centers in an appropriate worldwide distribution and that capacity is being utilized*

### Establish incentives that enhance innovation in AIDS vaccine discovery and development

Innovation is often stifled by peer review since it is a system more comfortable with incremental advances in knowledge than with radically new ideas. Yet innovation will be vital to successful AIDS vaccine development. Thus, mechanisms should be expanded or developed to encourage innovation. Inherently, pursuing innovative ideas will be risky, in that there will be a relatively low rate of success. Yet the ideas that do succeed have the potential to be high-yield. As noted earlier, in the past year a number of key stakeholders in the AIDS vaccine field have established innovation programs. It is too early to determine how successful these programs will be, but in any case current resources dedicated to fostering innovation are quite limited. Further, the passive request for proposal (RFP) process may not attract the truly novel ideas, especially from investigators and companies that are not active in AIDS vaccine research; proactive mechanisms—including incentives for their engagement—are necessary.

The AIDS vaccine field would also profit from closer integration with the basic immunology field, with efforts to develop other vaccines and with many of the cross disciplinary fields that are transforming biology, such as systems biology and computational biology. In particular, efforts should be made to proactively recruit novel technology to AIDS vaccine development. It should also be noted that innovation in AIDS vaccine trials, such as with adaptive and small efficacy trials, also enables accelerated and, ultimately, more informed decision making in clinical development.

*Interim Goal: Proactively identify novel technologies that offer promise to the AIDS vaccine field and create incentives for their use*

### Train the next generation of AIDS vaccine researchers

To expedite advances in AIDS vaccine development, measures should be taken specifically geared to persuade the best and brightest young scientists from all over the world to focus their careers on AIDS vaccine discovery and development. Training initiatives, career development, mentoring, and leadership opportunities must be made available to the next generation of scientists. Training is an absolutely essential element of accelerating AIDS vaccine development and can take many forms, including the training of graduate students and post-docs; training in specific new technologies developed within or external to the AIDS vaccine development field; increasing understanding of the multiple disciplines associated with vaccinology; and training in good laboratory, manufacturing, and clinical practices, among other things. Prizes could also be established for young investigators focused on solving key scientific challenges impeding AIDS vaccine development. Importantly, there should be specific incentives for young investigators from developing countries to establish careers in AIDS vaccine research.

*Interim Goal: Establish AIDS vaccine research graduate and post-doctoral fellowships for young investigators worldwide*

### Sustain and enhance financing for AIDS vaccine R&D

Achieving the goals and milestones of this *Blueprint* will require long-term and flexible financing built on renewed commitments from previous and present donors and contributions from new sources. This financing will need to match the duration of programs in AIDS vaccine R&D and must be flexible enough to allow for shifts in portfolios based on scientific results. The AIDS vaccine field will have to build a case for such funding, representing the shared priorities of all members of the Enterprise. Advocacy will be critical to keeping AIDS vaccine development on the agenda of policymakers and donors. At the same time, to enhance the stability and flexibility of the discovery and development process, funding for the AIDS vaccine field should be longer-term (5 to 10 years) than it has been. Lastly, the AIDS vaccine field should build partnerships with the malaria and TB vaccine fields, and possibly with other health technology fields, to help secure long-term funding for neglected disease R&D.

*Interim Goal: Ensure that AIDS vaccine funding is matched to R&D needs in size, duration, and flexibility, through analysis of needs and enhanced advocacy efforts*

## Establish a mechanism for monitoring progress in the AIDS vaccine field

It is vital for the field to monitor progress towards an AIDS vaccine and, when required, discuss reprioritization. There are several annual AIDS vaccine meetings.\* Leading researchers are often invited, and funders sometimes require them to attend many of these meetings. The proliferation of such meetings has resulted in the same researchers giving similar talks to similar audiences in many venues. These meetings are designed to promote information exchange, but the burden of meetings is now so heavy and accounts for such a disproportionate amount of time that many believe it is adversely affecting research progress. Collectively, significant time and financial resources are expended at these meetings that could be better spent on research. New paradigms are required that ensure maximum time for leading scientists to tackle the scientific challenges of AIDS vaccine development.

We propose a non-abstract-driven annual review meeting focused on accountability in which the progress of the field is evaluated and appropriate adjustments are made. A possibility is to alternate between an Enterprise special session at the International AIDS Vaccine meeting and the Keystone HIV Vaccine Symposium.

*Interim Goal: Beginning in 2009, annually monitor and update progress towards a safe and effective AIDS vaccine, including the achievement of milestones proposed in this Blueprint*

---

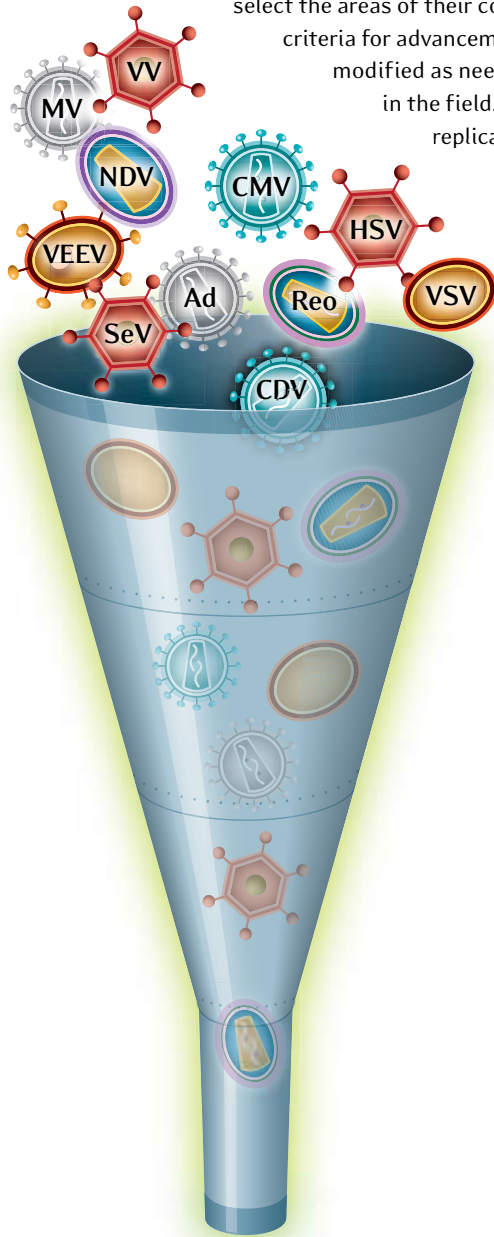
\***Annual HIV and AIDS Vaccine Related Meetings:** AIDS Vaccine 2008; 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; CROI; Immunology, Annual Meeting of The American Association of Immunologists (AAI)/Experimental Biology 2008; Mucosal Immunity and HIV/AIDS Vaccines; Challenges of Global Vaccine Development; World Vaccine Forum; Cancer Vaccines/Adjuvants/Delivery for the Next Decade (CVADD 2008); Clinical Update in Infectious Diseases (11th Annual); 21st International Conference on Antiviral Research; HVTN Conference; CHAVI Annual Meeting; CAVD Annual Meeting; Phacilitate's 7th annual European Vaccine Forum; 11th Annual American Society for Gene Therapy Meeting; American Society for Virology; HIV Implementers - Scaling Up Through Partnerships: Overcoming Obstacles to Implementation; BIO 2008 Annual International Convention; American Society for Reproductive Immunology (28th Annual); DNA Vaccines 2008, The Gene Vaccine Conference; 2nd International Symposium on Genetic and Immune Correlates of HIV Infection and Vaccine-Induced Immunity (GIC HIV); 35th Annual Meeting and Exposition of the Controlled Release Society; 9th International Veterinary Immunology Symposium; JP Morgan H&Q 26th Annual Healthcare Conference; Pharmaceutical Strategy Series' Sixth Annual R&D Executive Summit (part of Molecular Medicine Tri-Conference); HIV Vaccines: Progress and Prospects; Molecular Approaches to Vaccine Design, CSHL.

## 6 CONCLUSION

As challenging as the frontier ahead undoubtedly is for the AIDS vaccine field, those of us who are committed to it know that we have only one choice: to keep moving forward. The promise of an AIDS vaccine is too great to leave any other option. A vaccine offers the world's best hope for not just easing the AIDS pandemic but also ending it. The past has shown us the power of vaccines in changing the course of human history. Often, vaccines take decades to develop. Failure—sometimes of a spectacular sort—virtually always precedes success. We at IAVI believe in the power of science to solve human problems, in persistence, and in the learning opportunities afforded by failure. We believe that creating an AIDS vaccine requires a global effort employing the talents, resources, and passions of scientists, donors, policymakers, activists, advocates, and other stakeholders from both the developing and the developed worlds. We offer this *Blueprint* energized by the chance to work on an enormous scientific challenge at a moment of great dynamism, grateful for the opportunity to work with and alongside the many other stakeholders around the world who are committed to an AIDS vaccine, and eager for what we hope will be a productive debate on the suggestions made here.

## MILESTONES FOR THE DEVELOPMENT OF REPLICATING VIRAL VECTORS

In order to accomplish the interim milestones laid out in this *Blueprint*, IAVI encourages the field to select the areas of their core capabilities and construct development pathways with clearly defined criteria for advancement. These criteria should be based on the best science of today and be modified as needed to accommodate both novel advances in technology as well as changes in the field. As an example, IAVI has illustrated the pathway for development of replicating viral vectors.



Ad - Adenovirus 4/7 (National Cancer Institute) • CDV - Canine Distemper Virus (IAVI) • CMV - Cytomegalovirus (IAVI/Oregon Health Sciences Institute) • HSV - Herpes Simplex Virus (IAVI/Biovex, NIAID/Harvard Medical School) • MV - Measles virus (GSK, Crucell) • NDV - Newcastle Disease Virus (IAVI) • Reo - Reovirus (IAVI/ Harvard Medical School) • SeV - Sendai virus (IAVI/DNAVEC) • VEEV - Venezuelan equine encephalitis virus (IAVI/Global Vaccine Institute) • VSV - Vesicular Stomatitis virus (IAVI, Wyeth / Profectus) • VV -Vaccinia virus (National Center for AIDS Beijing)

### VECTOR SELECTION

- Minimal or no pre-existing immunity
- Special properties that may enhance immunity
  - Targets specific cell types or tissues
  - Elicits mucosal immunity
  - Persistent / long duration of antigen expression
  - Express membrane glycoproteins on viral particle
- Capacity to encode multiple foreign antigens

### TECHNICAL FEASIBILITY

- Expresses foreign antigen
- Genetically stable after 10 passages
- Propagation exceeds  $1 \times 10^6$  pfu/ml

### SMALL ANIMAL MODELS

- SAFETY**
- Causes minimal / no adverse reactions
  - Demonstrates no neuroinvasive properties
- IMMUNOGENICITY**
- Specific immune responses are detected in  $\geq 75\%$  of vaccinated animals at safe dose ranges

### NHP STUDIES

- SAFETY**
- Causes minimal / no adverse reactions
  - Demonstrates no neuroinvasive properties
  - Does not reveal any unexpected tissue tropism
- IMMUNOGENICITY**
- Immune responses are detectable in  $\geq 75\%$  of vaccinated animals
- EFFICACY**
- Relative protection against SIVmac239 challenge provided by vaccination
  - For CMI vaccine,  $> 2$  log reduction in set-point viral load
  - Elicits protection

### MANUFACTURE

- Supports production of clinical trial material
- Genetic stability confirmed after scale-up
- Stable for  $\geq 6$  months

### PHASE I/II CLINICAL TRIALS

- SAFETY**
- Causes minimal / no adverse reactions
- IMMUNOGENICITY**
- Specific immune responses in validated assays are detected in  $\geq 60\%$  of vaccinees

### SMALL EFFICACY TRIALS

**Figure 13** Milestones for the development of replicating viral vectors



**TABLE 5** Interim Goals and Milestones for Monitoring Progress in AIDS Vaccine Development

### SOLVE THE HIV NEUTRALIZING ANTIBODY PROBLEM

*Interim Goal: Identify and advance to clinical trials an immunogen that neutralizes a substantial proportion of circulating HIV strains, a suggested initial benchmark being at least 50 percent of moderately resistant HIV isolates*

#### Key Milestones

- Significantly scale up vaccine discovery efforts focused on solving the HIV Neutralizing Antibody Problem
- Establish high-throughput immunogen design and screening programs
- Identify and characterize new bnMAbs against HIV
- Determine the structures of these new bnMAbs in complex with Env
- Determine the structure of the native Env trimer

#### Supportive Milestones

- Establish an adjuvant screening program for Env immunogens, including ways of enhancing B-cell memory responses
- Determine the nature of the transmitted virus in MSM, heterosexual, IDU, and mother-to-child infections
- Develop new SHIVs to assess breadth of protection by Env-based immunogens in NHPs
- Determine whether non-neutralizing antibodies and mucosal antibodies provide benefit against SHIV in NHPs

### SOLVE THE HIV CELL-MEDIATED IMMUNITY PROBLEM

**Determine the antigens and immunologic mechanisms responsible for control of HIV infection by elite controllers**

*Interim Goal: Define the immune targets (HIV antigens and epitopes) of CD4+ and CD8+ T cells in elite controllers*

#### Key Milestones

- Establish appropriately scaled vaccine discovery efforts focused on determining the HIV antigens and immunologic mechanisms responsible for control of HIV infection in elite controllers
- Establish or expand large cohorts of elite controllers

#### Supportive Milestones

- Harness the tools of high-throughput drug discovery for definition of immune targets
- Define the predictable mutations that arise within the earliest targeted epitopes associated with CD8+ T-cell responses against HIV
- Determine the role of innate immunity in control of HIV infection and how this can be applied to AIDS vaccine discovery

**Determine the antigens and immunologic mechanisms responsible for control of SIV infection by live-attenuated SIV**

*Interim Goal: Identify the differences in immunologic mechanisms induced by replicating live-attenuated and non-replicating single cycle SIV*

#### Key Milestones

- Build dedicated NHP capacity sufficient to meet the needs of statistically significant experiments in AIDS vaccine discovery and development
- Determine the immune responses in the GALT conferred by live-attenuated SIV
- Define the immune targets (SIV antigens and epitopes) of CD8+ T cells for live-attenuated SIV

#### Supportive Milestones

- Determine the role of SIV Env in protection by live-attenuated SIV
- Develop new stocks of SIV challenge viruses to enable additional heterologous challenges in the SIV challenge model

**Implement a new clinical research program to determine the optimal immunogens for eliciting CMI responses against HIV**

*Interim Goal: Develop a set of immunogens and a clinical testing strategy for assessing optimization of CMI responses against HIV*

#### Key Milestones

- Integrate the clinical research agenda with studies to elucidate the antigens and immunologic mechanisms that control HIV infection in elite controllers
- Assess different routes of immunization to optimize CMI responses and to elicit CMI responses at mucosal sites

#### Supportive Milestones

- Screen adjuvants with a standard immunogen to assess potential capacity for enhancing magnitude and durability of CMI responses
- Assess potential immunodominance of HIV antigens and/or epitopes in immunogens intended to elicit CMI responses
- Assess the benefit of including Env in immunogens designed to elicit CMI responses
- Assess the potential of multiple copies of single or related antigens to enhance CMI responses
- Prioritize most promising approaches to induce HIV-specific immune responses, and compare across different regions where HLA differences may affect response

**TABLE 5** continued...

## IMPROVE THE PIPELINE

Trim the product development pipeline of less promising candidates

*Interim Goal: Trim the AIDS vaccine pipeline of candidates considered to have a low probability of success, with resources redirected towards either more promising approaches or solving the key scientific challenges*

### Key Milestones

- Ensure that the clinical pipeline has candidates in development that assess different specific scientific hypotheses for prevention and control of HIV infection
- Create algorithms for comparing candidates in the pipeline using data from SIV challenge studies, mechanisms of action, and comparison to Merck Ad5.

Broaden and rationalize approaches to vectors for use in AIDS vaccines

*Interim Goal: Advance to clinical development AIDS vaccine vectors that demonstrate improved efficacy against SIV challenge compared with the Merck Ad5 candidate*

### Key Milestones

- Ensure adequate AIDS vaccine discovery and development programs focused on the design and development of vaccine candidates using replicating viral vectors
- Assess standard vectors with different SIV antigens to determine minimal antigen set required for efficacy, compared with Merck Ad5 and live-attenuated SIV
- Develop vectors that express Env immunogens to elicit neutralizing antibodies and CMI responses

### Supportive Milestones

- Establish standard panels of SIV antigens to insert into vectors for comparative studies
- Assess vectors for systemic and mucosal administration
- Develop vector-specific assays to assess antivector immunity and conduct seroepidemiology studies of vectors targeted for clinical trials
- Evaluate adjuvants to enhance the immunogenicity of vectors
- Establish infrastructure for effective process development of leading vector-based immunogens, to be ready when clinical development milestones are achieved to address scale up related issues.

Conduct small efficacy trials on leading candidates that achieve pre-determined criteria

*Interim Goal: Develop universally accepted, predetermined criteria for advancing candidates from Phase I to small efficacy trials*

### Key Milestones

- Ensure clinical trial site capacity to conduct small efficacy trials in different regions of the world
- Develop additional adaptive clinical trial designs to accelerate the screening of AIDS vaccine candidates

### Supportive Milestones

- Develop new assays, including functional T-cell assays, to assess cell-mediated, mucosal, and innate immune responses, that are more predictive of a vaccine candidate's efficacy, and validate them in small efficacy trials
- Develop criteria for advancing candidates from small efficacy trials to Phase III licensing trials

## RECOMMENDATIONS FOR SUSTAINING THE EFFORT

Ensure adequate and appropriate clinical research and trial capacity

*Interim Goal: Undertake assessments of global clinical research and trial capacity to ensure that there are adequate established regional AIDS vaccine discovery and development centers in an appropriate worldwide distribution and capacity is being utilized*

### Key Milestones

- Conduct a portfolio analysis of global AIDS vaccine trial site capacity
- Ensure the capacity to conduct multiple Phase I and small efficacy trials of AIDS vaccines in different regions of the world
- Ensure the capacity to ramp up clinical trials site capacity when a candidate meets criteria for advancing from small efficacy trials to Phase III efficacy trials
- Utilize any transient excess AIDS vaccine trial site capacity to conduct clinical trials of other vaccines and/or AIDS prevention modalities
- Strengthen the capacity of regulatory agencies in these countries to rigorously evaluate, approve, and monitor AIDS vaccine clinical trials

### Supportive Milestones

- Ensure that an optimum number of cohorts are available to support a vigorous vaccine effort
- Define key social science research projects to inform more efficient strategies for future trials
- Link clinical research programs to focused efforts on solving the scientific challenges impeding AIDS vaccine development to enhance training and access to new technologies



**TABLE 5** continued ...

**RECOMMENDATIONS FOR SUSTAINING THE EFFORT (cont'd)**

**Establish incentives that enhance innovation in AIDS vaccine discovery and development**

*Interim Goal: Proactively identify novel technologies that offer promise to the AIDS vaccine field and create incentives for their use*

**Key Milestones**

- Enhance mechanisms for supporting early-stage biotech companies working on AIDS vaccines and for facilitating collaboration between industry and academia
- Develop proactive mechanisms for identifying and engaging promising new technologies that have not yet been applied to AIDS vaccine efforts

**Supportive Milestones**

- Establish Innovations Units in vaccine discovery programs with the flexibility and resources to evaluate high-risk yet possibly high-reward opportunities
- Conduct an analysis of lessons learned from successful innovation programs in other fields
- Evaluate ongoing AIDS vaccine discovery innovations programs after five years and implement improvements

**Train the next generation of AIDS vaccine researchers**

*Interim Goal: Establish AIDS vaccine research graduate and post-doctoral fellowships for young investigators worldwide*

**Key Milestones**

- Ensure adequate research funding targeted to young investigators to enable viable careers in AIDS vaccine research
- Following the model of the Howard Hughes Medical Institute's early career development awards, establish a program for young investigators working in fields related to AIDS vaccine discovery
- Establish a course, patterned after the Fondation Mérieux's course in Advances in Vaccinology, focused specifically on AIDS vaccine discovery and development
- more effective courses in GCP, GLP, and GMP

**Supportive Milestones**

- Establish prizes for young investigators focused on solving the key scientific challenges impeding AIDS vaccine development
- Develop specific incentives for young investigators from the developing world to establish careers in AIDS vaccine discovery and development
- Identify opportunities for collaboration between young investigators and seasoned scientists in the global South
- Strengthen mechanisms in developing countries to share knowledge about AIDS vaccine research and ensure the long-term funding to do so even when trials are not under way
- Utilize advances in distance learning programs to establish more effective courses in GCP, GCLP, and GMP

**Sustain and enhance financing for AIDS vaccine R&D**

*Interim Goal: Ensure that AIDS vaccine funding is matched to R&D needs in size, duration, and flexibility, through analysis of needs and enhanced advocacy efforts*

**Key Milestones**

- Identify gaps and inefficiencies in current financing and explore possible solutions, including new financing mechanisms
- Carry out a new analysis of resource needs for AIDS vaccine discovery and development in light of new priorities

**Supportive Milestones**

- Advocate for policies that enhance the stability and flexibility of AIDS vaccine discovery and development funding
- Build partnerships with the malaria and TB vaccine fields to help secure sustainable, flexible long-term funding for neglected disease R&D
- Build a sustainable enabling environment for AIDS vaccine R&D on the ground by creating and implementing plans for community support in countries even when trials are not under way

**Establish a mechanism for monitoring progress in the AIDS vaccine field**

*Interim Goal: Beginning in 2009, annually monitor and update progress towards a safe and effective AIDS vaccine, including the achievement of milestones proposed in this Blueprint*

**Key Milestones**

- Reduce the number of annual meetings focused on or related to AIDS vaccine discovery and development
- Conduct an annual review of the AIDS vaccine field at a meeting that is non-abstract-driven

# APPENDIX I: MAJOR PLAYERS IN VACCINE R&D

The following is IAVI's attempt to create a snapshot of major players in AIDS Vaccine R&D. It must be noted that the field is constantly changing and as such this list may change significantly from the time of publication. We apologize in advance if we have omitted any references.

## PUBLIC SECTOR

### United States

The US National Institutes of Health (NIH; [www.nih.gov](http://www.nih.gov)) is the largest public sector source for funding of AIDS vaccine R&D. It supports basic and applied research and conducts clinical trials. The lead agency for NIH in AIDS vaccine R&D is the National Institute for Allergy and Infectious Diseases (NIAID; [www3.niaid.nih.gov](http://www3.niaid.nih.gov)). 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.hvtn.org](http://www.hvtn.org)), an international network of clinical trial 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](http://www.vrc.nih.gov)) focuses on DNA and adeno vector approaches. NIH has established the Partnership for AIDS Vaccine Evaluation (PAVE; [www.hivpave.org](http://www.hivpave.org)), a volunteer consortium of US government agencies and key government-funded organizations. The US Military HIV Vaccine Research Program (USMHRP; [www.hivresearch.org](http://www.hivresearch.org)), a member of PAVE, focuses on vaccine development in Thailand and East Africa. With the Thai government and sanofi-aventis, USMHRP is conducting a Phase III trial of a canarypox vector prime plus gp120 boost vaccine candidate. USMHRP has an MVA vector program and is developing trial centers and conducting clinical trials in East Africa.

The US Centers for Disease Control and Prevention ([www.cdc.gov](http://www.cdc.gov)) is building clinical and laboratory infrastructure at international centers, including one in Kenya. The US Agency for International Development (USAID; [www.usaid.gov](http://www.usaid.gov)) supports all phases of HIV vaccine R&D through the President's Emergency Plan for AIDS Relief, and specifically supports IAVI's efforts to prepare communities and build clinical trial centers and laboratory capacity for HIV vaccine trials in developing countries. USAID encourages public policy research aimed at accelerating HIV vaccine discovery and development while addressing issues central to vaccine introduction, and future access. Bridging HIV prevention, care, and treatment programs with HIV vaccine clinical research is an ongoing USAID mandate.

### European Union

The EU ([www.europa.eu.int](http://www.europa.eu.int)) funds HIV/AIDS research on new drug treatments, microbicides, and vaccines through new collaborative efforts within Europe and with developing countries. The European Commission funds AIDS vaccine research via its Framework Program (FP), the EU's main instrument for funding research in Europe. Among the many AIDS vaccine development projects supported by the EC Framework Program, the most notable have been FP6's European Vaccine/Microbicide Enterprise (EUROPRISE) consortia and FP5's European Vaccine Effort against HIV/AIDS (EuroVacc). The EU also funds the AIDS Vaccine Integrated Project (AVIP; [www.avip-eu.org](http://www.avip-eu.org)) and Mucosal Vaccines for Poverty-Related Diseases (MUVAPRED; [www.mucosalimmunity.org/muvapred](http://www.mucosalimmunity.org/muvapred)). The EU supports expanded efforts in building clinical trial center capacity through the Director General Development and the European and Developing Countries Clinical Trials Partnership (EDCTP; [www.edctp.org](http://www.edctp.org)). The EDCTP continues to link European and African researchers, providing research capacity in developing countries.

### WHO-UNAIDS

The WHO-UNAIDS HIV Vaccine Initiative (HVI; [www.who.int/vaccine\\_research/diseases/hiv/en/](http://www.who.int/vaccine_research/diseases/hiv/en/)) is a joint activity of the World Health Organization (WHO; [www.who.int](http://www.who.int)) and the Joint United Nations Programme on HIV/AIDS (UNAIDS; [www.unaids.org](http://www.unaids.org)). Under the banner of the Initiative for Vaccine Research (IVR), the HVI mission is to promote the development, facilitate evaluation, and address the future availability of preventive HIV vaccines, with a focus on the needs of developing countries. HVI also promotes expanding AIDS vaccine research and development capacity in Asia and exploring the opportunities for an AIDS Vaccine Asian Network.

HVI activities include: advocacy, information, education and policy dialogue; guiding and coordinating international efforts; developing norms and standards; promoting development of vaccines appropriate for global use, especially in developing countries; facilitating the conduct of vaccine trials in developing countries, through training and capacity building; and addressing issues of future availability and access.

HVI is guided by a WHO-UNAIDS Vaccine Advisory Committee (VAC; [www.who.int/vaccine\\_research/diseases/hiv/en/](http://www.who.int/vaccine_research/diseases/hiv/en/)), which provides a unique forum for coordination. Scientists from different agencies and disciplines, from both the global north and south, can exchange information and identify common grounds for collaboration. The

WHO-UNAIDS program coordinates 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 HIV Vaccine Initiative hosts and supports the African AIDS Vaccine Programme (AAVP; [www.who.int/vaccine\\_research/diseases/hiv/aavp/en](http://www.who.int/vaccine_research/diseases/hiv/aavp/en)).

### Australia

The Australian government ([www.health.gov.au](http://www.health.gov.au)) provides funding to the National Centre in HIV Social Research, the National Centre in HIV Epidemiology and Clinical Research (NCHECR; [www.nchechr.unsw.edu.au](http://www.nchechr.unsw.edu.au)), the Australian Centre for HIV and Hepatitis Virology Research (ACH2; formerly the National Centre for HIV Virology Research; [www.hiv.edu.au/](http://www.hiv.edu.au/)), and the Australian Research Centre in Sex, Health, and Society, as well as providing several other research grants. Partially funded by the NCHECR, the HIV Netherlands Australia Thailand Research Collaboration ([www.hivnat.org/Current.html](http://www.hivnat.org/Current.html)) is conducting a Phase I trial of a DNA and fowlpox prime-boost vaccine candidate.

### Brazil

The Brazilian government was an early supporter of AIDS vaccine research. It issued one of the world's first national AIDS vaccine plans (1992), which has been updated three times to address changes in the landscape. Over the years, the National AIDS Program of Brazil/Ministry of Health ([www.aids.gov.br](http://www.aids.gov.br)) has supported multiple national research projects directly or indirectly related to AIDS vaccines. Since 2006 the investment has been expanded and now includes a portfolio of efforts in discovery, pre-clinical investigation, clinical center development, and epidemiology.

### Canada

The Canadian government ([www.acdi-cida.gc.ca](http://www.acdi-cida.gc.ca)) continues to support AIDS vaccine research and development at home and internationally. The Canadian HIV Vaccine Initiative (CHVI; [www.chvi-icvv.gc.ca/index-eng.html](http://www.chvi-icvv.gc.ca/index-eng.html)) represents the first comprehensive strategy for AIDS vaccine research, advocacy, and funding to be created in a developed country. Funding under the CHVI is administered by the Public Health Agency of Canada ([www.phac-aspc.gc.ca/index-eng.php](http://www.phac-aspc.gc.ca/index-eng.php)), Health Canada ([www.hc-sc.gc.ca/index-eng.php](http://www.hc-sc.gc.ca/index-eng.php)), the Canadian Institutes of Health Research ([www.cihr-irsc.gc.ca/e/193.html](http://www.cihr-irsc.gc.ca/e/193.html)), Industry Canada (IC; [www.ic.gc.ca](http://www.ic.gc.ca)); the Canadian International Development Agency ([www.acdi-cida.gc.ca/index-e.htm](http://www.acdi-cida.gc.ca/index-e.htm)), and the BMGF (see philanthropic

sector section). Its goals are to: strengthen HIV vaccine discovery and social research capacity; strengthen clinical trial capacity and networks; increase global pilot scale manufacturing capacity for HIV vaccine clinical trial lots; address policy and regulatory approaches for HIV vaccines; and promote the community and social aspects of HIV vaccine research and delivery.

### China

Through the Chinese Center for Disease Control and Prevention ([www.chinacdc.net.cn](http://www.chinacdc.net.cn)), the government of China and other government and private research institutions sponsor and conduct the design and manufacture of new AIDS vaccine candidates. The research priorities of the Chinese Academy of Medical Sciences ([english.cas.cn/eng2003/page/S&T/Introduction.htm](http://english.cas.cn/eng2003/page/S&T/Introduction.htm)) are basic prevention and treatment technologies for emerging epidemics and HIV/AIDS. The academy maintains a collaboration among institutions to research and develop novel AIDS vaccines. China has conducted a Phase I clinical trial in Nanning, Guangxi Province, with a vaccine candidate developed at Johns Hopkins University's Bloomberg School of Public Health and manufactured in Changchun, Jilin Province. Another Phase I clinical trial is ongoing in Beijing with another vaccine candidate developed by the Chinese Center for Disease Control and Prevention. Other teams from the academic, pharmaceutical, and biotechnology sectors are working on various AIDS vaccine approaches at preclinical stages.

### Denmark

The Danish government supports national AIDS vaccine R&D at several universities and at the Statens Serum Institute ([www.ssi.dk](http://www.ssi.dk)). This government-owned institute is engaged in the prevention and control of infectious diseases and congenital disorders. The vaccine R&D portfolio at the Statens Serum Institute includes research on how to optimize design of HIV DNA vaccines. The Ministry of Foreign Affairs ([www.um.dk/en](http://www.um.dk/en)) supports international AIDS vaccine R&D programs.

### France

The French government ([www.sante.gouv.fr](http://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 et les hépatites virales (ANRS; [www.anrs.fr](http://www.anrs.fr)) supported a significant proportion of AIDS vaccine efforts at sanofi-aventis. For more than 15 years, the ANRS has been committed to a strong research program on AIDS vaccines that includes among others things, the development of mucosal immunity assays as part of

clinical trials of lipopeptides administered via the mucosal route. Furthermore, the ANRS supports partnerships with national and international scientists and vaccine networks in order to diversify vaccine research and encourage initiation of vaccine trials at ANRS clinical centers in developing countries.

### Germany

The Ministry of Health ([www.bmg.bund.de](http://www.bmg.bund.de)) and the Ministry of Education and Research ([www.bmbf.de/en](http://www.bmbf.de/en)) fund AIDS vaccine research. The Robert Koch Institute ([www.rki.de](http://www.rki.de)), financed by the Ministry of Health, works on neutralizing antibody concepts and studies the SIV model in nonhuman primates. The Paul-Ehrlich Institute ([www.pei.de](http://www.pei.de)), also supported by the Ministry of Health, conducts research on vaccines based on MVA vectors. The Ministry of Education and Research co-sponsors HIV vaccine clinical trials conducted by the University of Munich at the Mbeya Medical Research Center in Tanzania. The ministry also supports research at the University of Regensburg, which collaborates with EuroVacc researchers to develop and test AIDS vaccine candidates.

### India

The Indian government, through the Indian Council of Medical Research (ICMR; [www.icmr.nic.in](http://www.icmr.nic.in)) and the National AIDS Control Organization (NACO; [www.naco.nic.in](http://www.naco.nic.in)), is committed to developing an AIDS vaccine and conducting clinical trials of vaccine candidates. Two Phase I clinical trials have been conducted with two vaccine candidates at the National AIDS Research Institute, Pune (NARI, [www.nari-icmr.res.in](http://www.nari-icmr.res.in)), and the Tuberculosis Research Centre, Chennai ([www.trc-chennai.org](http://www.trc-chennai.org)). The Department of Biotechnology (DBT; [www.dbtindia.nic.in/index.asp](http://www.dbtindia.nic.in/index.asp)), the Council of Scientific and Industrial Research (CSIR; [www.csir.res.in/](http://www.csir.res.in/)), and the Ministry of Science and Technology ([www.dst.gov.in/](http://www.dst.gov.in/)), are exploring areas of upstream research that can accelerate vaccine development in India and globally, including the design of immunogens capable of inducing neutralizing antibodies against primary isolates and identification of new bnMAbs.

### Ireland

The Irish government, through Irish Aid ([www.irishaid.gov.ie](http://www.irishaid.gov.ie)), supports international AIDS vaccine R&D efforts from early stage applied research through to clinical trials.

### Italy

The Italian government, mainly through the Italian Istituto Superiore di Sanita (National Institute of Health,

[www.iss.it](http://www.iss.it)), carries out work in AIDS vaccine research nationally as well as in developing countries as part of its research into the prevention and treatment of HIV and AIDS. Since March 2005, the ISS has funded clinical trials of candidate AIDS vaccines.

### Japan

The Japanese government ([www.nih.go.jp](http://www.nih.go.jp)) funds research at the National Institute for Infectious Diseases (which houses the AIDS Research Center; [www.nih.go.jp/niid/index-e.html](http://www.nih.go.jp/niid/index-e.html)), Tokyo University Institute of Medical Science, and a handful of other major universities. These activities include basic HIV retrovirology, pathogenesis of AIDS, development of HIV animal models, early stage development of HIV vaccines and therapeutic agents, and the evaluation of HIV laboratory diagnosis and current antiretroviral therapy.

### Netherlands

The Dutch government—through several ministries including the Ministry of Health ([www.minvws.nl/en](http://www.minvws.nl/en)) the Ministry of Science ([www.minocw.nl](http://www.minocw.nl)), and the Ministry of Foreign Affairs ([www.minbuza.nl](http://www.minbuza.nl))—funds numerous HIV/AIDS organizations, researchers, government authorities, and interest groups. Their work covers scientific research, including national and international AIDS vaccine R&D, as well as information and prevention programs, and projects in developing countries. The Aids Fonds ([www.aidsfonds.nl](http://www.aidsfonds.nl)) also supports Dutch HIV/AIDS researchers, including those who work on AIDS vaccines.

### Norway

The Norwegian government allocates funds to support Norwegian-based research through the Norwegian Research Council ([www.forskningsradet.no](http://www.forskningsradet.no)) with the aim of strengthening knowledge in vaccine science and development. The government has allocated funding for a Norway-India bilateral collaboration to support global health and vaccination research. The Ministry of Foreign Affairs ([www.regjeringen.no/en/dep/ud.html?id=833](http://www.regjeringen.no/en/dep/ud.html?id=833)) supports international AIDS vaccine R&D programs.

### Russia

The Russian government has allocated funding from its federal budget to support a national AIDS vaccine research center that brings together leading research institutes. The AIDS vaccine development team that is part of this initiative consists of three research centers: the Institute of Immunology in Moscow, the St. Petersburg Biomedical Centre, and the State Research Center of

Virology and Biotechnology in Novosibirsk. The Institute of Immunology recently initiated a Phase I trial testing an HIV protein vaccine candidate.

### South Africa

The Department of Science and Technology (DST; [www.dst.gov.za](http://www.dst.gov.za)), funds the R&D of AIDS vaccines. South Africa established the South African AIDS Vaccine Initiative (SAAVI; [www.saavi.org.za](http://www.saavi.org.za)), which supports a variety of programs in vaccine design, exploration of host response (including mucosal), and the role of chemokines in HIV immunity as well as adjuvants. SAAVI funds the HIV vaccine ethics group at the University of KwaZulu Natal and supports behavioral science and community involvement projects throughout the country. SAAVI has funded the development of clinical trial centers in South Africa and is expanding this infrastructure.

### Spain

The Spanish government and the Catalan Autonomous Government provide support through several public agencies for basic and applied research projects on preventive AIDS vaccines and therapeutic immunization. Public agencies and ministries involved include the Health Research Fund (the former Ministry of Science and Education), the intramural research program of the Carlos III Health Institute ([www.isciii.es/htdocs/en/index.jsp](http://www.isciii.es/htdocs/en/index.jsp)), and the Ministry of Health via the National AIDS Plan, as well as the Spanish Foundation for AIDS Research and Prevention. Spain also supports international efforts to develop and test AIDS vaccines.

### Sweden

The Swedish government supports national and international AIDS vaccine research from the early stages of applied science through clinical research activities. One of the leading medical universities, the Karolinska Institute ([www.ki.se](http://www.ki.se)), runs a program dedicated to understanding the mechanisms underlying the induction of immune responses with the aim of eliciting broadly neutralizing antibodies. Clinical work is focused on developing DNA vaccine candidates, which are also being tested in developing countries in Africa.

### Switzerland

The Swiss government recently supported the initiation of the Swiss Vaccine Research Institute ([www.swissvaccinerearch.ch](http://www.swissvaccinerearch.ch)), a collaboration among five leading Swiss research centers. The main goal of the institute is to develop preventive vaccines against HIV, TB, malaria, and other major infectious diseases, and to give access to all those who need these vaccines.

### Thailand

Thailand has led the developing world for AIDS vaccine clinical development and capacity building over the past 15 years. The Ministry of Public Health ([www.eng.moph.go.th](http://www.eng.moph.go.th)) is fully committed to this effort and has established strong partnerships among Thai institutions and such entities as the US Military HIV Research Program ([hivresearch.org/global-efforts/thailand.html](http://hivresearch.org/global-efforts/thailand.html)), the Armed Forces Research Institute of Medical Sciences ([www.afrims.org](http://www.afrims.org)), Mahidol University ([www.mahidol.ac.th](http://www.mahidol.ac.th)), and the HIV Netherlands-Australia-Thailand Research Collaboration ([www.hivnat.org/Current.html](http://www.hivnat.org/Current.html)). Multiple AIDS vaccine clinical trials have been conducted, including the first Phase III clinical trial in a developing country, testing the VaxGen's gp120 AIDSVAX candidate. The largest community-based Phase III trial is still ongoing.

### United Kingdom

The UK government is a strong supporter of AIDS vaccine R&D, from early stage applied research to clinical research through the Department for International Development (DFID; [www.dfid.gov.uk](http://www.dfid.gov.uk)). The Medical Research Council (MRC; [www.mrc.ac.uk](http://www.mrc.ac.uk)) provides support through competitive grants for basic and applied research, and has long-standing collaborations in developing countries that help develop local infrastructure for AIDS vaccine clinical trials.

## PRIVATE SECTOR

### GlaxoSmithKline

GSK ([www.gsk.com](http://www.gsk.com)) focuses its AIDS vaccine development efforts on recombinant protein vaccine candidates and has conducted trials of a gp120 plus NefTat fusion protein. An HIV-measles candidate vaccine, developed in the past few years in collaboration with the Institut Pasteur, is expected to enter clinical trials in 2009.

### Merck

Merck ([www.merck.com](http://www.merck.com)) has focused its AIDS vaccine research program on replication-defective recombinant adenovirus vectors. Merck has tested a series of DNA candidates in trials, evaluating copolymer and alum adjuvants aimed at enhancing the immunogenicity of DNA vaccines in humans. Merck has teamed with Sanofi Pasteur to evaluate a vaccine strategy of an adenovirus vectors prime and canarypox vectors boost candidate. Merck announced in September 2007 that it had discontinued vaccinations



in trials of its adenovirus-based vaccine candidate after an interim analysis concluded that the candidate was not efficacious.

#### sanofi pasteur

sanofi pasteur ([www.sanofipasteur.com](http://www.sanofipasteur.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. Data from this trial are expected in 2009.

#### Wyeth

Wyeth ([www.wyeth.com](http://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. Wyeth's DNA gag vaccine is currently in clinical trials conducted by the HVTN.

### BIOTECHNOLOGY COMPANIES

#### Alpha Vax

AlphaVax ([www.alphavax.com](http://www.alphavax.com)) is developing vaccine technology with broad applications against infectious disease, cancer, and biodefense threats which could redefine vaccines and their role 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

Crucell ([www.crucell.com](http://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 ([www.hms.harvard.edu/hms/home.asp](http://www.hms.harvard.edu/hms/home.asp)). Crucell has entered into an exclusive license agreement with IAVI to develop this technology and a cell line for production of adenovector based vaccines.

#### FIT Biotech

FIT Biotech ([www.fitbiotech.com](http://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 immunotherapies and gene therapies. FIT Biotech's HIV DNA therapeutic vaccine candidate has advanced to a Phase II trial in collaboration with the Chris Hani Baragwanath Hospital, Pediatric Research Centre in Soweto, South Africa ([www.chris-hanibaragwanathhospital.co.za/bar/index.jsp](http://www.chris-hanibaragwanathhospital.co.za/bar/index.jsp)).

#### Bavarian Nordic

Bavarian Nordic ([www.bavarian-nordic.com](http://www.bavarian-nordic.com)) is a biopharmaceutical company developing an innovative vaccine to prevent and treat HIV based on a novel MVA virus strain. MVA-BN® multiantigen is an MVA vaccine expressing eight whole or truncated antigens from HIV with the aim of eliciting a very broad immune response. MVA-BN® multiantigen is in Phase I clinical trials.

#### GeoVax

GeoVax ([www.geovax.com](http://www.geovax.com)) is a biotechnology company developing vaccines for HIV and other infectious agents. Successful Phase I clinical trials of a DNA vaccine have demonstrated its safety. Phase IA/IB trials are ongoing for testing various combinations of DNA and MVA AIDS vaccines in volunteers for safety and immunogenicity. A Phase II clinical trial testing three different regimens is in the planning stages.

#### Pharmexa

Pharmexa ([www.pharmexa.com](http://www.pharmexa.com)) is conducting Phase I trials in connection with several HIV vaccines, either preventive or therapeutic, that were initially developed through Pharmexa-Epimmune. Several of these trials are being funded principally through various divisions of the NIH. Pharmexa is leading a consortium consisting of Bavarian Nordic ([www.bavarian-nordic.com](http://www.bavarian-nordic.com)), SRI International ([www.sri.com](http://www.sri.com)), and Althea Technologies ([www.altheatech.com](http://www.altheatech.com)).

#### Mymetics

Mymetics ([www.mymetics.com](http://www.mymetics.com)) is developing vaccines and therapies to combat HIV. Its lead HIV vaccine candidate combines a gp41-derived HIV 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

Targeted Genetics ([www.targetedgenetics.com](http://www.targetedgenetics.com)) is a biotechnology company focused on the development of innovative targeted molecular therapies. It 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). Targeted Genetics is planning a Phase I clinical trial with the HVTN to test its AAV-1 and AAV-2.

## PHILANTHROPIC SECTOR

### Bill & Melinda Gates Foundation

The Bill & Melinda Gates Foundation (BMGF; [www.gatesfoundation.org](http://www.gatesfoundation.org)) is the largest private foundation supporting AIDS vaccine research and development. BMGF does this through grants to individual investigators, programs such as the Grand Challenges ([www.gatesfoundation.org/GlobalHealth/BreakthroughScience/GrandChallenges/default.htm](http://www.gatesfoundation.org/GlobalHealth/BreakthroughScience/GrandChallenges/default.htm)), and most significantly, the Collaboration for AIDS Vaccine Discovery (CAVD; [www.cavd.org](http://www.cavd.org)), an international network of 13 vaccine discovery consortia (VDCs) and five central service facilities (CSFs) formed to apply new technologies, concepts, and approaches to the design of safe and effective preventive vaccines against HIV/AIDS. BMGF also served as the secretariat for the Global HIV Vaccine Enterprise ([www.hivvaccineenterprise.org](http://www.hivvaccineenterprise.org)).

### amfAR

The American Foundation for AIDS Research ([www.amfar.org](http://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](http://www.utac.org)) has been providing ongoing support for the global AIDS vaccine effort through its funding of IAVI since 1996.

## NGONGOVERNMENTAL ORGANIZATIONS

### AIDS Vaccine Advocacy Coalition

The AIDS Vaccine Advocacy Coalition (AVAC; [www.avac.org](http://www.avac.org)) is a nonprofit, community and consumer-based organization that uses public education, policy analysis, advocacy, and community mobilization to accelerate the ethical development and global delivery of AIDS vaccines and other HIV prevention possibilities.

### African AIDS Vaccine Programme

The mission of the African AIDS Vaccine Programme (AAVP; [www.who.int/vaccine\\_research/diseases/hiv/aavp/en](http://www.who.int/vaccine_research/diseases/hiv/aavp/en)) is to advocate for and support a coordinated effort

towards global HIV vaccine development goals, with the objective of developing appropriate and affordable vaccines for Africa in the shortest possible time. The AAVP, as a WHO-UNAIDS-supported program, was conceived in 2000 as a network of African experts working together to promote and facilitate HIV vaccine research and evaluation in Africa through capacity building and regional and international collaboration.

### The Global HIV Vaccine Enterprise

The Global HIV Vaccine Enterprise is an alliance of independent organizations around the world dedicated to accelerating the development of a preventive HIV vaccine by:

- implementing a strategic plan for HIV vaccine research that spans vaccine discovery, product development and manufacturing, and clinical trials;
- mobilizing significant new funding for achieving the scientific plan; and
- promoting more efficient, faster ways for researchers to share successes and failures and avoid duplication of efforts.

### IAVI

The International AIDS Vaccine Initiative (IAVI; [www.iavi.org](http://www.iavi.org)) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines 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 for enhancing R&D and eventual vaccine access; and accelerating R&D. IAVI's R&D team designs, develops, and clinically evaluates HIV vaccine candidates applicable for use in the developing world through a range of partnerships and agreements with more than 40 academic, biotechnology, pharmaceutical, and government institutions around the globe.

### Wellcome Trust

The Wellcome Trust ([www.wellcome.ac.uk](http://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.

## APPENDIX 2: AIDS VACCINE GLOSSARY

### 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.

**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 *ALVACHIV™*; *vector*.)

**CD4<sup>+</sup> 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<sup>+</sup> T-cells help orchestrate the immune response, including antibody responses as well as killer T-cell responses. (See also *T-cell*.)

**cell-mediated immunity (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 be used also 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.

**elite controllers:** also called long-term non-progressors. People infected with the human immunodeficiency virus (HIV) whose bodies have kept the microbe at undetectable levels in their bloodstreams without treatment.

**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 (Env):** 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.

**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

**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.

**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 trial 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 IIb vaccine trial:** A possible intermediate step is a Phase IIb test-of-concept trial. A test-of-concept trial is about finding out if the vaccine concept or the type of vaccine being tested will be effective. A test-of-concept trial is not designed to establish the efficacy of a particular candidate but rather to help researchers decide if a candidate is worth testing in larger Phase III trials. These intermediate studies are also referred to as proof-

of-concept trials. The number of volunteers required for such trials is smaller, only around 2,000 to 5,000 volunteers, compared to over 10,000 for Phase III trials.

**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.

**preventive HIV vaccine (AIDS 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

**Screening Test-of-Concept Trial (STOC):** A STOC trial is an approach developed by IAVI to obtain efficacy data from human subjects in a shorter time frame and with fewer volunteers. STOC trials involve relatively small cohorts (300-600 individuals from higher-risk communities) and expedite preliminary indications of potential efficacy, helping guide product development for new vaccines that represent a marked improvement over existing candidates.

**serostatus:** positive or negative results of a diagnostic test for a specific antibody.

**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 2007. [www.niaid.nih.gov/factsheets/GLOSSARY.htm](http://www.niaid.nih.gov/factsheets/GLOSSARY.htm) (accessed June 28, 2008).



## APPENDIX 3: LIST OF ABBREVIATIONS

Ad5.....	adenovirus type 5
AIDS.....	acquired immunodeficiency syndrome
ANRS.....	Agence nationale de recherches sur le sida et les hépatites virales
BMGF.....	Bill & Melinda Gates Foundation
bnMAbs.....	broadly neutralizing monoclonal antibodies
CAVD.....	Collaboration for AIDS Vaccine Discovery
CCR5.....	chemokine receptor 5
CHAVI.....	Center for HIV/AIDS Vaccine Immunology
CMI.....	cell-mediated immunity
DNA.....	deoxyribonucleic acid
ELISPOT.....	enzyme-linked immunosorbent spot
FDA.....	Food and Drug Administration
GALT.....	gut-associated lymphoid tissue
GCLP.....	good clinical laboratory practices
GCP.....	good clinical practices
HIV.....	human immunodeficiency virus
HVTN.....	HIV Vaccine Trials Network
IAVI.....	International AIDS Vaccine Initiative
IDU.....	injecting drug user
MSM.....	men who have sex with men
MVA.....	modified vaccinia Ankara
NAC.....	Neutralizing Antibody Consortium
NCVDG.....	National Cooperative Vaccine Development Groups for AIDS
NHP.....	nonhuman primate
NIAID.....	National Institute of Allergy and Infectious Diseases (US)
NIH.....	National Institutes of Health (US)
PAVE.....	Partnership for AIDS Vaccine Evaluation
R&D.....	research and development
SAAVI.....	South African AIDS Vaccine Initiative
SHIV.....	simian human immunodeficiency virus
SIV.....	simian immunodeficiency virus
TB.....	tuberculosis
WHO.....	World Health Organization

# REFERENCES

- Allen, T.M., and D.I. Watkins. 2001. "New Insights into Evaluating Effective T-Cell Responses to HIV." *AIDS* 15 Suppl 5: S117-26.
- Bernstein, A. 2008. "AIDS and the Next 25 Years." *Science* 320, no. 5877: 717.
- Betts, M.R., C.M. Gray, J.H. Cox, and G. Ferrari. 2006. "Antigen-Specific T-Cell-Mediated Immunity after HIV-1 Infection: Implications for Vaccine Control of HIV Development." *Expert Rev Vaccines* 5, no. 4: 505-16.
- Calarese, D.A., C.N. Scanlan, M.B. Zwick, S. Deechongkit, Y. Mimura, R. Kunert, P. Zhu, M.R. Wormald, R.L. Stanfield, K.H. Roux, J.W. Kelly, P.M. Rudd, R.A. Dwek, H. Katinger, D.R. Burton, and I.A. Wilson. 2003. "Antibody Domain Exchange Is an Immunological Solution to Carbohydrate Cluster Recognition." *Science* 300, no. 5628: 2065-71.
- Esparza J, Osmanov S. 2003. HIV Vaccines: a global perspective. *Curr Mol Med* 3(3):183-93.
- Excler JL, Rida W, Priddy F, Fast P, Koff W. 2007. "A Strategy for Accelerating the Development of Preventive AIDS Vaccines." *AIDS* 21, no. 17: 2259-63.
- Feinberg, M.B., and J.P. Moore. 2002. "AIDS Vaccine Models: Challenging Challenge Viruses." *Nat Med* 8, no. 3: 207-10.
- Hanke, T., and A.J. McMichael. 2000. "Design and Construction of an Experimental HIV-1 Vaccine for a Year-2000 Clinical Trial in Kenya." *Nat Med* 6, no. 9: 951-5.
- Joint United Nations Programme on HIV/AIDS, World Health Organization. 2007. *AIDS epidemic update: December 2007*. (Document UNAIDS/07.27E). Geneva: World Health Organization.
- Joint United Nations Programme on HIV/AIDS, World Health Organization, and AIDS Vaccine Advocacy Coalition. 2007. *Good participatory practice guidelines for biomedical HIV prevention trials*. Document UNAIDS /07.30E). Geneva: World Health Organization.
- Jones, S.M., H. Feldmann, U. Stroher, J.B. Geisbert, L. Fernando, A. Grolla, H. D. Klenk, N.J. Sullivan, V.E. Volchkov, E.A. Fritz, K.M. Daddario, L. E. Hensley, P. B. Jahrling, and T.W. Geisbert. 2005. "Live Attenuated Recombinant Vaccine Protects Nonhuman Primates against Ebola and Marburg Viruses." *Nat Med* 11, no. 7: 786-90.
- Klausner, R.D., A.S. Fauci, L. Corey, G.J. Nabel, H. Gayle, S. Berkley, B.F. Haynes, D. Baltimore, C. Collins, R.G. Douglas, J. Esparza, D.P. Francis, N.K. Ganguly, J. L. Gerberding, M.I. Johnston, M.D. Kazatchkine, A.J. McMichael, M. W. Makgoba, G. Pantaleo, P. Piot, Y. Shao, E. Tramont, H. Varmus, and J.N. Wasserheit. 2003. "Medicine. The Need for a Global Hiv Vaccine Enterprise." *Science* 300, no. 5628: 2036-9.
- Koff, W.C., P.R. Johnson, D.I. Watkins, D.R. Burton, J.D. Lifson, K.J. Hasenkrug, A.B. McDermott, A. Schultz, T.J. Zamb, R. Boyle, and R.C. Desrosiers. 2006. "HIV Vaccine Design: Insights from Live Attenuated SIV Vaccines." *Nat Immunol* 7, no. 1: 19-23.
- Koff, W.C., C.L. Parks, B. Berkhout, J. Ackland, S. Noble, and I.D. Gust. 2008. "Replicating Viral Vectors as HIV Vaccines Summary Report from IAVI Sponsored Satellite Symposium, International AIDS Society Conference, July 22, 2007." *Biologicals* (2008).
- Silverman, M.F., and D.B. Silverman. 1985. "AIDS and the Threat to Public Health." *Hastings Cent Rep* 15, no. 4: suppl 19-22.
- Telenti, A., and D.B. Goldstein. 2006. "Genomics Meets HIV-1." *Nat Rev Microbiol* 4, no. 11: 865-73.
- Tobey, T.W., S.A. Dubey, K. Anderson, D.C. Freed, K. S. Cox, J. Lin, M.T. Prokop, K. . Sykes, R. Mogg, D. V. Mehrotra, T.M. Fu, D.R. Casimiro, and J.W. Shiver. 2006. "A Comparison of Standard Immunogenicity Assays for Monitoring HIV Type 1 Gag-Specific T Cell Responses in Ad5 HIV Type 1 Gag Vaccinated Human Subjects." *AIDS Res Hum Retroviruses* 22, no. 11: 1081-90.
- VaxGen. "VaxGen announces results of its phase 3 HIV vaccine trial in Thailand: vaccine fails to meet endpoints." News release, November 12, 2003.
- Weiss, R.A. 2003. "HIV and AIDS: Looking Ahead." *Nat Med* 9, no. 7: 887-91.
- Yan, Q. 2008. "Bioinformatics Databases and Tools in Virology Research: An Overview." *Silico Biology*. 8: 8.

---

# NOTES

---



IAVI gratefully acknowledges the generous support provided by the following major donors.\*



Provided with the support of the European Union



Canadian International Development Agency



Government of Ireland



Ministry of Foreign Affairs



NORWEGIAN MINISTRY OF FOREIGN AFFAIRS

Alfred P. Sloan Foundation  
Basque Autonomous Government  
Becton, Dickinson and Company (BD)  
Bill & Melinda Gates Foundation  
Bristol-Myers Squibb (BMS)  
Broadway Cares/Equity Fights AIDS  
Canadian International Development Agency  
Continental Airlines  
European Union  
Foundation for the National Institutes of Health  
Google Inc.  
The Haas Trusts  
Henry Schein, Inc.  
Irish Aid  
James B. Pendleton Charitable Trust  
The John D. Evans Foundation  
Kathy Bole & Paul Klingenstein  
Merck & Co., Inc.

Ministry of Foreign Affairs and Cooperation, Spain  
Ministry of Foreign Affairs of Denmark  
Ministry of Foreign Affairs of The Netherlands  
Ministry of Foreign Affairs of Sweden  
The New York Community Trust  
Norwegian Royal Ministry of Foreign Affairs  
Pfizer Inc  
The Rockefeller Foundation  
Swedish International Development Cooperation Agency  
U.K. Department for International Development  
Until There's a Cure Foundation  
The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development  
The William and Flora Hewlett Foundation  
The World Bank through its Development Grant Facility



**USAID**  
FROM THE AMERICAN PEOPLE



\* As of 04/08

And many other generous individuals from around the world.



