AIDS VACCINE BLUEPRINT 2006

Actions to Strengthen Global Research and Development

EXECUTIVE SUMMARY

International AIDS Vaccine Initiative

A 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.

This executive summary is reproduced from the *AIDS Vaccine Blueprint 2006: Actions to Strengthen Global Research and Development* (ISBN - 0-9773126-5-8). The full text of this report is also available online at the IAVI website at: http://www.iavi.org/blueprint.

IAVI gratefully acknowledges the valuable contributions of its colleagues that made it possible to accurately assess the field and provide recommendations to catalyze change to improve AIDS vaccine development. IAVI, as a founding member of the Global HIV Vaccine Enterprise, sought feedback from members of the Enterprise Coordinating Committee 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 Wordfirm Inc.
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AIDS VACCINE BLUEPRINT 2006: ACTIONS TO STRENGTHEN GLOBAL RESEARCH AND DEVELOPMENT

EXECUTIVE SUMMARY

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

The ultimate goal is an AIDS vaccine that prevents infection from the wide spectrum of globally diverse HIV isolates and is applicable for use in the developing world where the need is the greatest (Figure 1, Figure 2).

However, a vaccine that suppresses viral load and slows progression to AIDS or suppresses and blunts transmission of HIV would have significant public health impact (Figure 3). To achieve that, a host of scientific, public policy, and political actions must be taken in a coordinated, interlinked fashion to make all of the necessary resources available (Figure 4). While scientific challenges continue to be the main obstacle in the search for an AIDS vaccine, countless examples of successful technology breakthroughs show that political will matters enormously. It is vital to enlist political leadership, non-governmental organizations, community groups, and a range of strategic coalitions that can

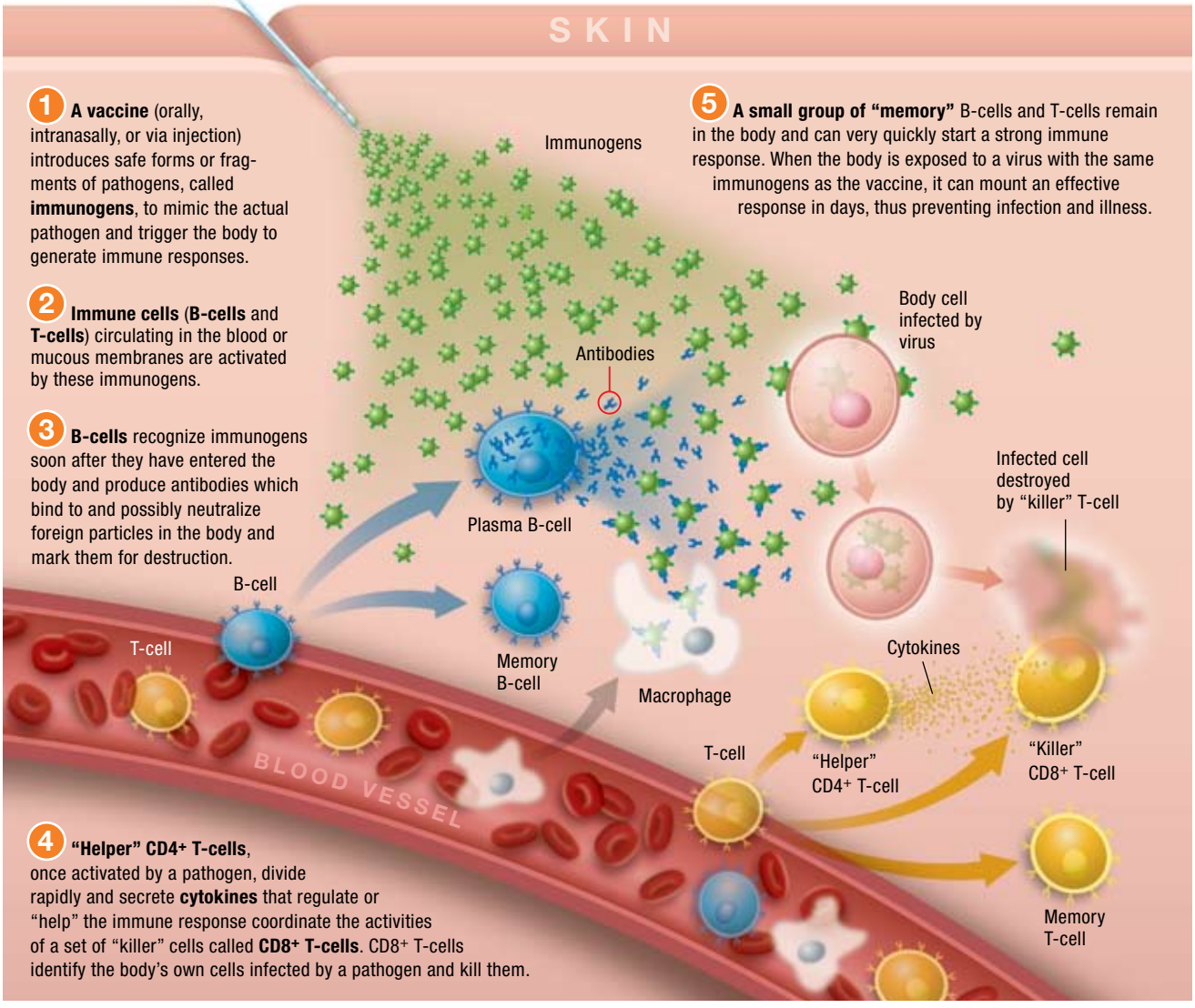

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Figure 1 How Vaccines Work Against Viruses

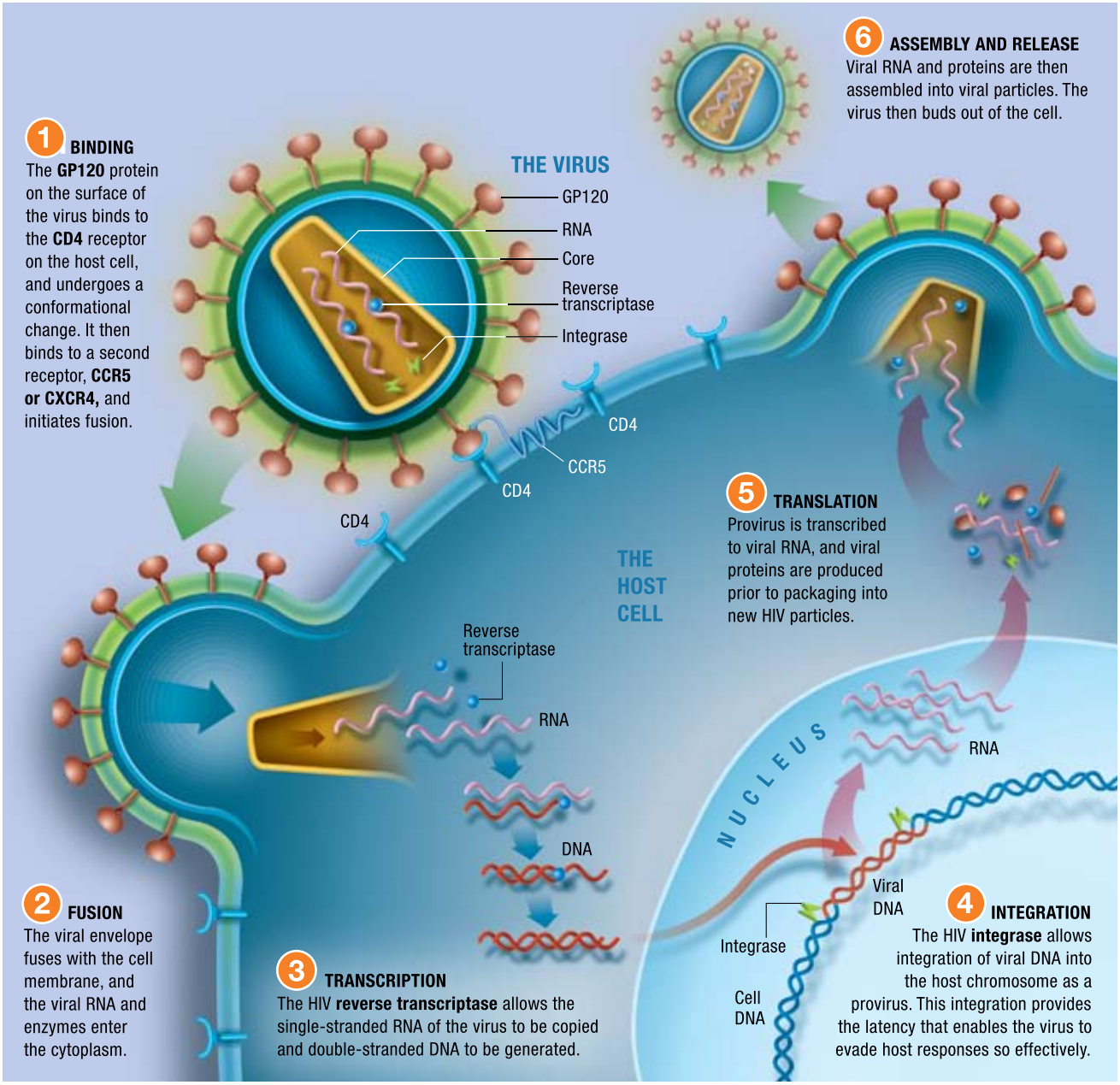

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Figure 2 **The HIV Replication Cycle**

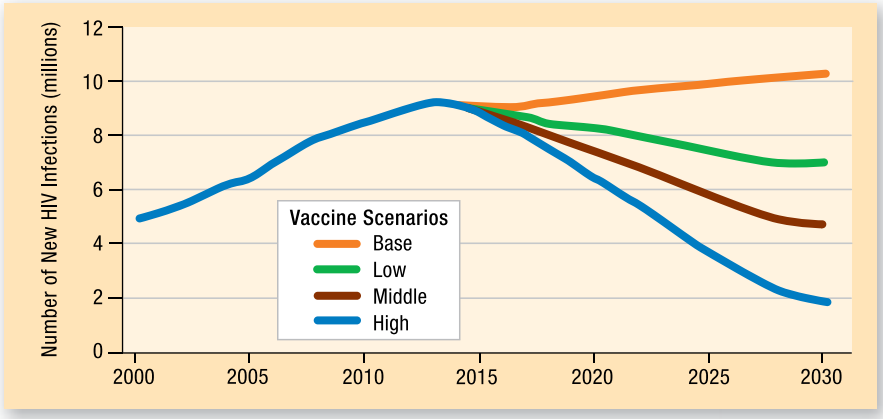

Figure 3 **The Impact of an AIDS Vaccine on New HIV Infections**

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

amplify and reinforce support for AIDS vaccines.

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

THE AIDS VACCINE LANDSCAPE

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

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

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

Since the XV International AIDS Conference in Bangkok, July 2004, steps have been taken towards the implementation of a more integrated vaccine design effort. Three of the founding members of the Enterprise have launched programs to design vaccines to elicit broadly neutralizing antibodies, elucidate the

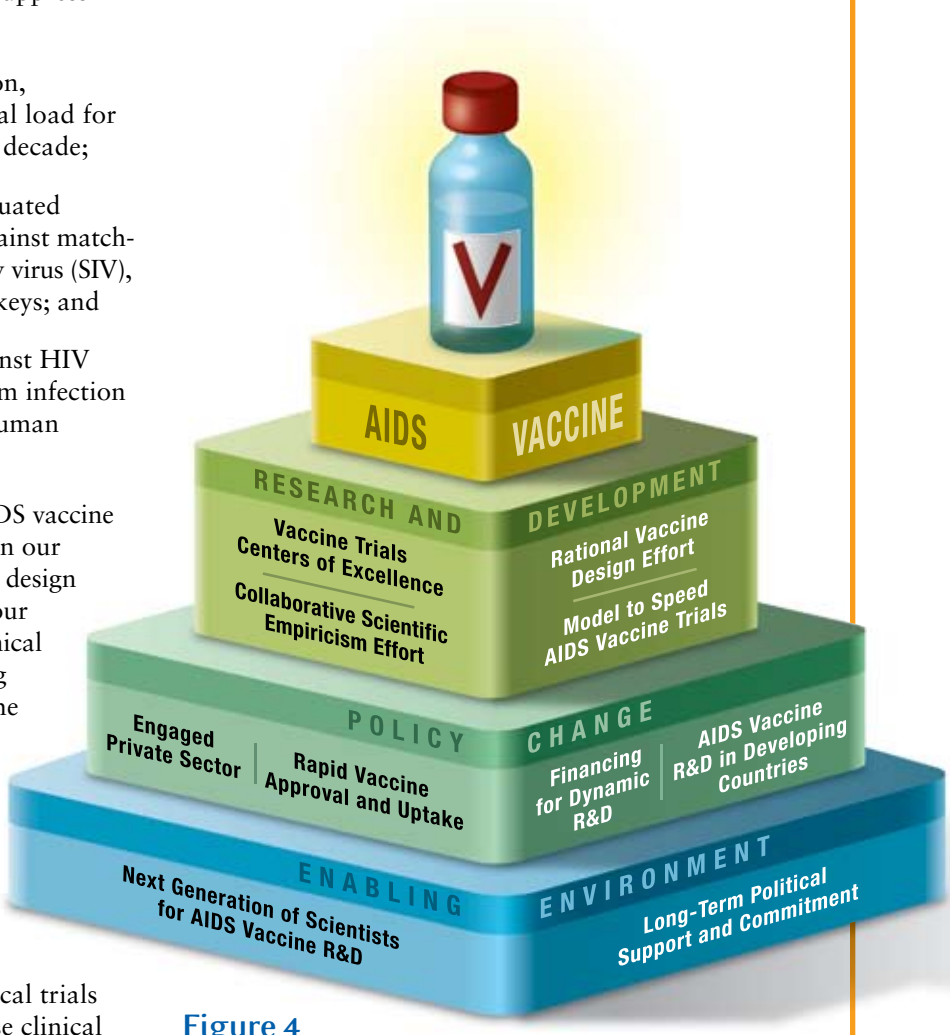

Figure 4
Elements Required to Accelerate an AIDS Vaccine

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

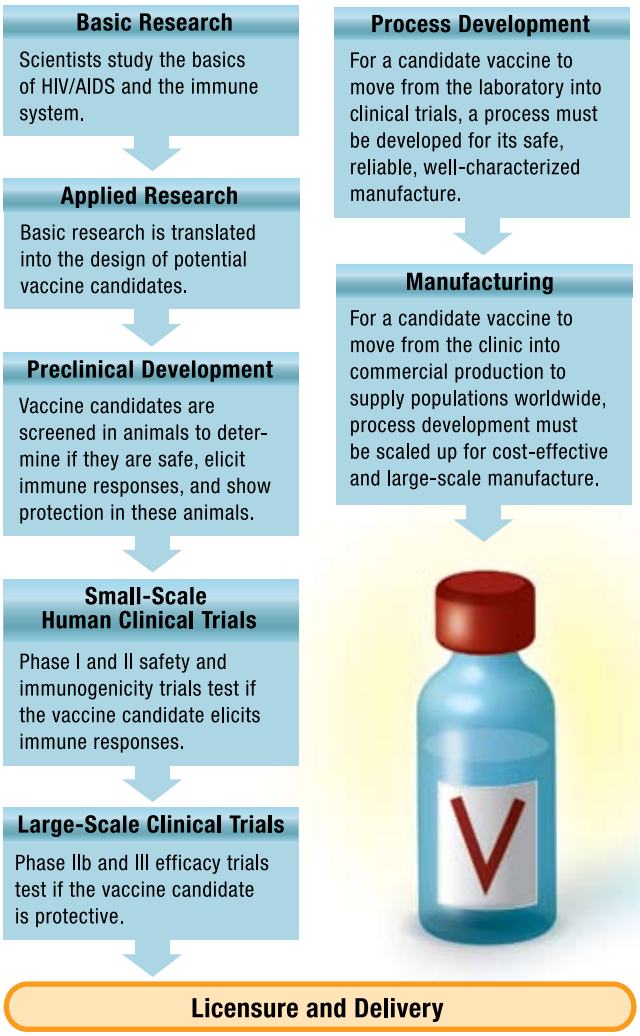

Figure 5 **AIDS Vaccine Research and Development**

correlates of protective immunity, and address the scientific challenge of HIV variability:

- The Bill & Melinda Gates Foundation established the Collaboration for AIDS Vaccine Discovery (CAVD), a network of 11 vaccine-discovery consortia focused on designing AIDS vaccines that elicit durable and broad-spectrum cellular, neutralizing antibody, and mucosal immune responses, supported by five centralized facilities that provide standardized laboratory analysis and statistical support;

- The US National Institute of Allergy and Infectious Diseases (NIAID) established the Center for HIV/AIDS Vaccine Immunology (CHAVI) to study the virologic, genetic, and immunologic responses to acute HIV infection, to elucidate correlates of human protection through a range of human and nonhuman primate studies, and to translate this knowledge into the design of AIDS vaccines; and

- The International AIDS Vaccine Initiative (IAVI) expanded its Neutralizing Antibody Consortium (NAC) to focus on solving the neutralizing antibody problem, establish new consortia to elucidate the correlates of protective immunity, and establish an industrial-style AIDS Vaccine Development Laboratory to provide enhanced capabilities for the field in process development, systematic optimization and prioritization of candidate vaccines, and new approaches to vaccine design.

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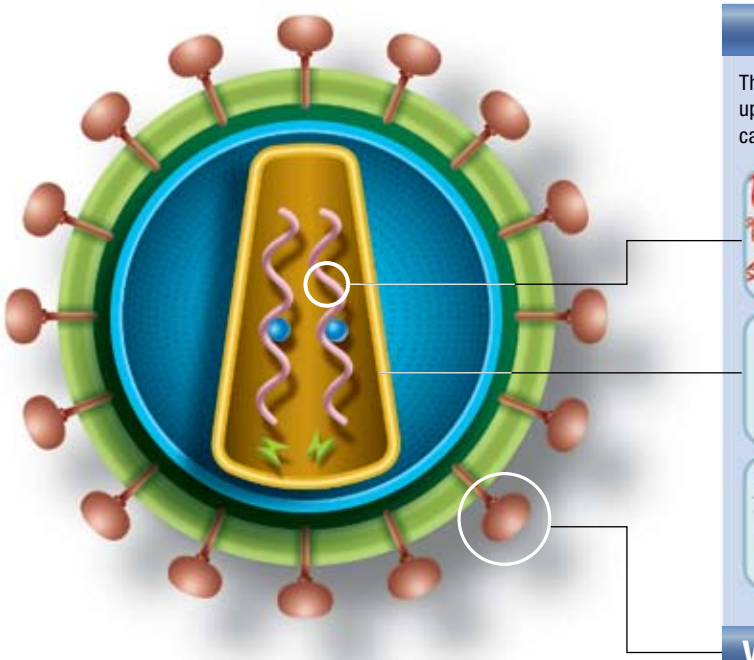
Table 2 HIV Vaccine Candidates in Phase I/IIa Trials

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

Table 3 HIV Vaccines in/Soon to Be in Phase IIB and/or Phase III Clinical Trials

Candidate	Scientific Question	Status
gp120	Protection against infection was observed in chimpanzees immunized with gp120, and the vaccine stimulated neutralizing antibodies against laboratory-adapted isolates of HIV.	Completed two efficacy trials of gp120. Both trials showed the vaccine had no effect in preventing HIV infection and no effect in suppressing viral load in those immunized subjects who subsequently became HIV infected.
Canarypox vector prime (Sanofi-Pasteur) + subunit gp120 boost (VaxGen)	gp120 alone failed to prevent HIV infection or suppress viral load in previous human efficacy trials. This clinical trial will assess whether priming with a canarypox vector and then subsequently boosting with gp120 provides additional benefit, e.g., prevents HIV infection or suppresses viral load.	Phase III. The trial is being conducted in Thailand and is fully enrolled with over 16,000 trial volunteers. Data from this trial are expected in 2008–09.
Replication defective Adeno-subtype 5 vector (Merck)	This trial is designed as a proof of concept to evaluate whether cell-mediated immune responses elicited by the Ad5 vectors containing three HIV genes (gag-pol-nef) confers any benefit. Phase I/II clinical trials with this candidate demonstrated that the vaccine is safe and that subjects not previously exposed to Adeno-subtype 5 (i.e., no significant antivector immunity) generated significant cell-mediated immune responses to the HIV antigens gag, pol, nef.	Phase IIB. This trial is enrolling 3000 subjects, and initial data are expected in late 2007 or early 2008. This will be the first test of the vaccine, which should determine if any efficacy is conferred and provide the initial information on the potential impact of anti vector immunity. At the time of this writing, a 2nd Phase IIB trial is being considered for this candidate, to be undertaken in South Africa, in order to assess the efficacy of this Clade B vaccine vs. Clade C isolates of HIV circulating in southern Africa.



VACCINES FROM HIV GENES

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

Naked DNA
The vaccine consists of HIV gene(s).

Viral vectors
The vaccine consists of a weakened virus unrelated to HIV, into which HIV gene(s) are inserted. The virus delivers HIV gene(s) to human cells.

Bacterial vectors
HIV gene(s) are delivered via weakened bacteria.

VACCINES FROM HIV PROTEINS

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

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

VACCINES FROM WHOLE HIV

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

Whole inactivated HIV
The vaccine contains killed HIV.

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

COMBINATION

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

SAMUEL VELASCO / SW INFOGRAPHIC

Figure 6 AIDS Vaccine Designs

Table 4 Potential Outcomes—Phase IIB Trial of Replication Defective Ad5-HIV Vaccine

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

Although the overall funding landscape in AIDS vaccine development has substantially improved, increasing to $759 million in 2005 (Figure 7), a comparison of investment in preventive AIDS vaccine R&D as a percentage of GDP highlights that countries are not contributing equally (Figure 8). In addition, though pharmaceutical and biotechnology companies are playing a part in AIDS vaccine research and development today, they are only contributing 10% of the total spending from their own resources. Policy discussions have focused on mechanisms such as "push" and "pull" incentives to reduce the risk of early-stage investment in R&D and to ensure viable markets for AIDS vaccines (Figure 9). However, we need to assess whether these mechanisms will actually increase resources for AIDS vaccine research.

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

CHALLENGES FACING AN AIDS VACCINE

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

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

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

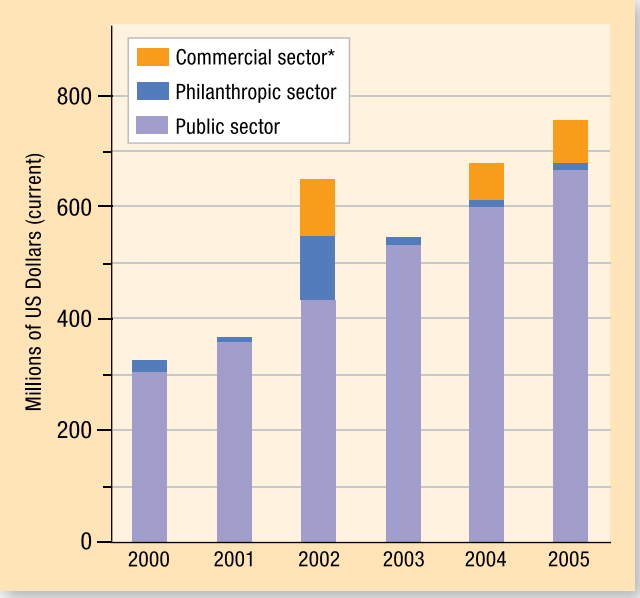


Figure 8 Funding Sources for Preventive HIV Vaccine R&D (2000–2005)

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

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

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

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

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

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

Figure 9 "Push" and "Pull" Mechanisms to Incent AIDS Vaccine R&D
While "push" mechanisms remain the primary means to incent research and development, other mechanisms are complementary.

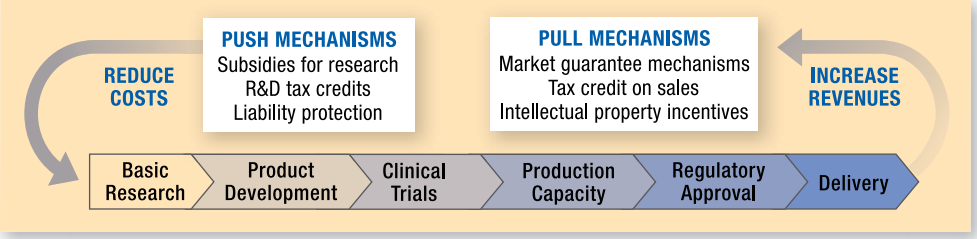


Table 5	Scientific Challenges in the Development of an AIDS Vaccine
Virus	• HIV isolates worldwide are hypervariable • HIV antigens required for protection remain undefined • HIV infects, suppresses, and destroys key cells of the immune system • Limitations in the animal models for HIV/AIDS
Immune Response	• Natural immune responses do not eradicate HIV • Correlates of protective immunity remain undefined • The role of innate immunity remains poorly explored • Superinfection with a second isolate of HIV is possible
HIV Transmission & Pathogenesis	• Multiple forms: HIV is transmitted as cell-free and cell-associated virus • Multiple routes: HIV is transmitted sexually, intravenously, and orally (breast-feeding) • HIV replication cycle includes integration into the host cell genome • Short window of opportunity: Regardless of route of transmission, HIV rapidly targets gut-associated lymphoid tissue followed by amplification and seeding of other lymphoid organs • HIV incidence, time to set point, and required follow-up combine to make AIDS vaccine efficacy trials very complex and long (4–5 years)

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

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

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

Retrovirus: HIV is a retrovirus that integrates its genetic material into the human genome and establishes a persistent and life long infection. After this integration, the resting HIV-infected cells appear no different from uninfected cells and avoid immune defense mechanisms. The goal for an AIDS vaccine is to prevent the genome integration and establishment of persistent infection, which occurs within the first seven to ten days after HIV exposure. This brief window of opportunity creates challenges for optimizing the magnitude, durability, and localization of vaccine-induced immune responses.

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

Correlate of Protective Immunity: In many other viral infections, persons can be identified who become infected with the pathogen, spontaneously generate immune responses, and clear the infection. Analysis of these individuals leads to identification of a correlate of protective immunity, which facilitates vaccine development. For HIV there is no documented case of "recovery" from infection and the immunological correlates of protection remain unknown. In the absence of a correlate of protection the field does not

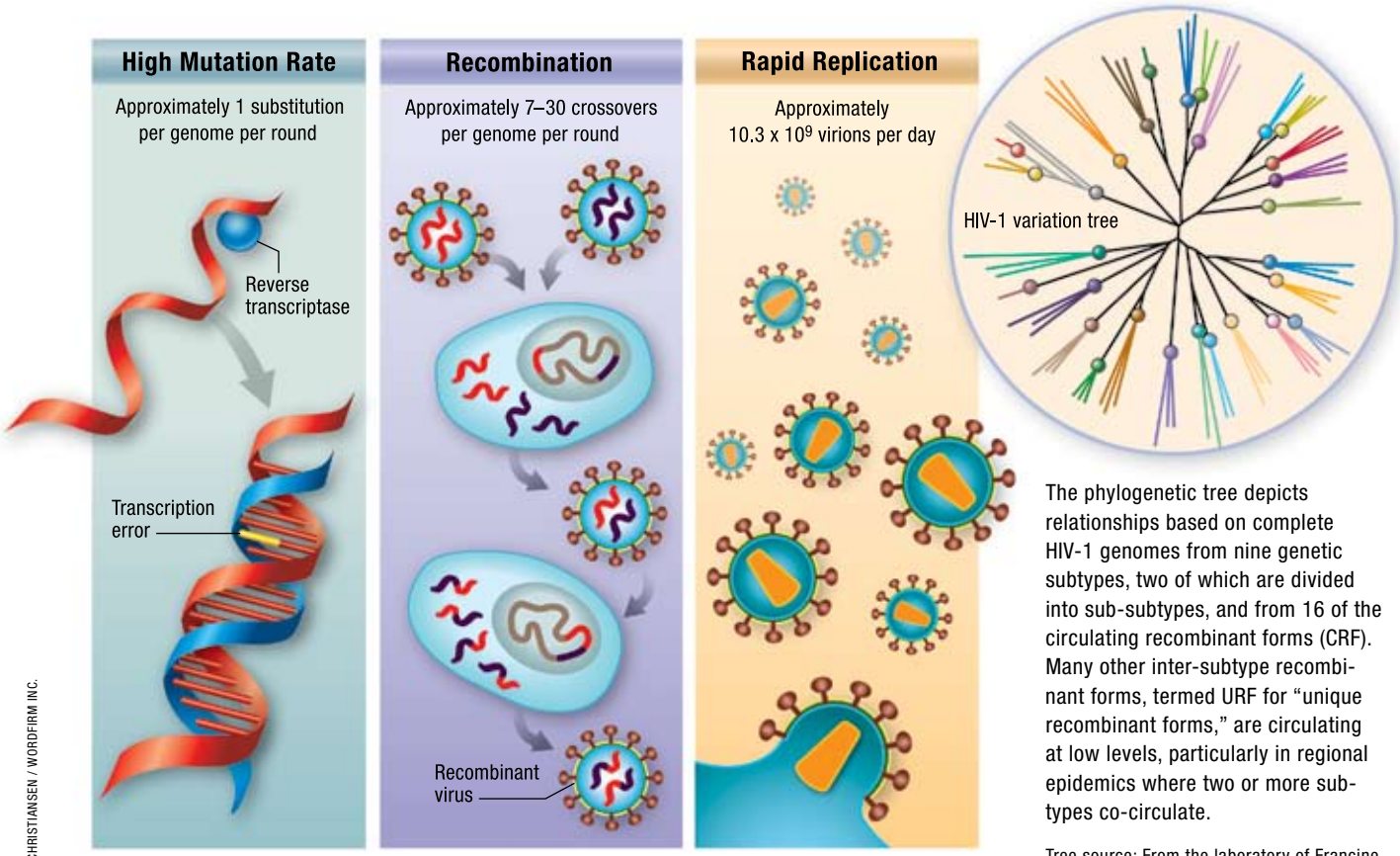


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Figure 10 Causes of HIV Variability and Impact on the Circulating Virus

The phylogenetic tree depicts relationships based on complete HIV-1 genomes from nine genetic subtypes, two of which are divided into sub-subtypes, and from 16 of the circulating recombinant forms (CRF). Many other inter-subtype recombinant forms, termed URF for "unique recombinant forms," are circulating at low levels, particularly in regional epidemics where two or more subtypes co-circulate.

Tree source: From the laboratory of Francine McCutchan, Henry M. Jackson Foundation.

have a validated marker for determining whether one vaccine candidate is a significant improvement over another. It is unclear whether one or more of innate, neutralizing antibody, cell-mediated, or mucosal immune responses is required for eliciting protective immunity (Figure 13). In particular, mucosal immunity may be required to prevent the earliest stages of HIV infection.

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

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

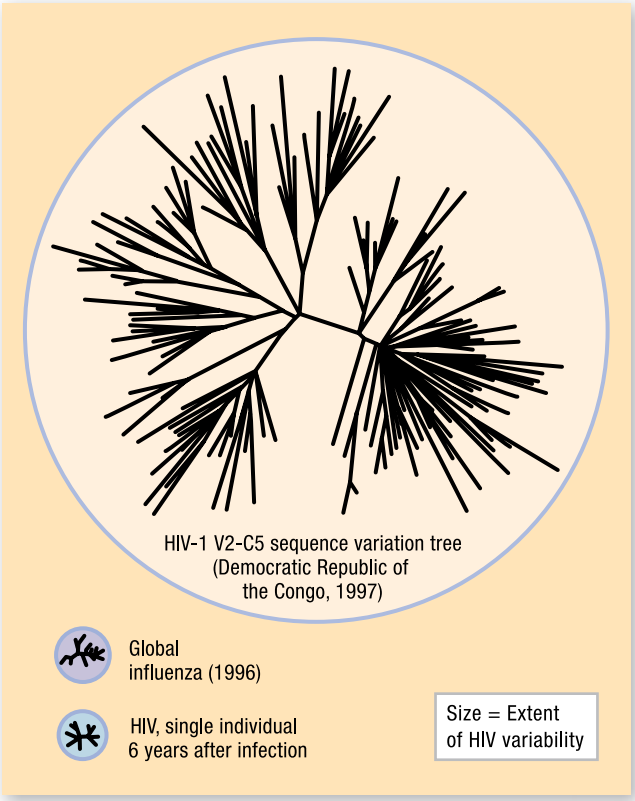

Figure 11 The Scale of HIV Variability

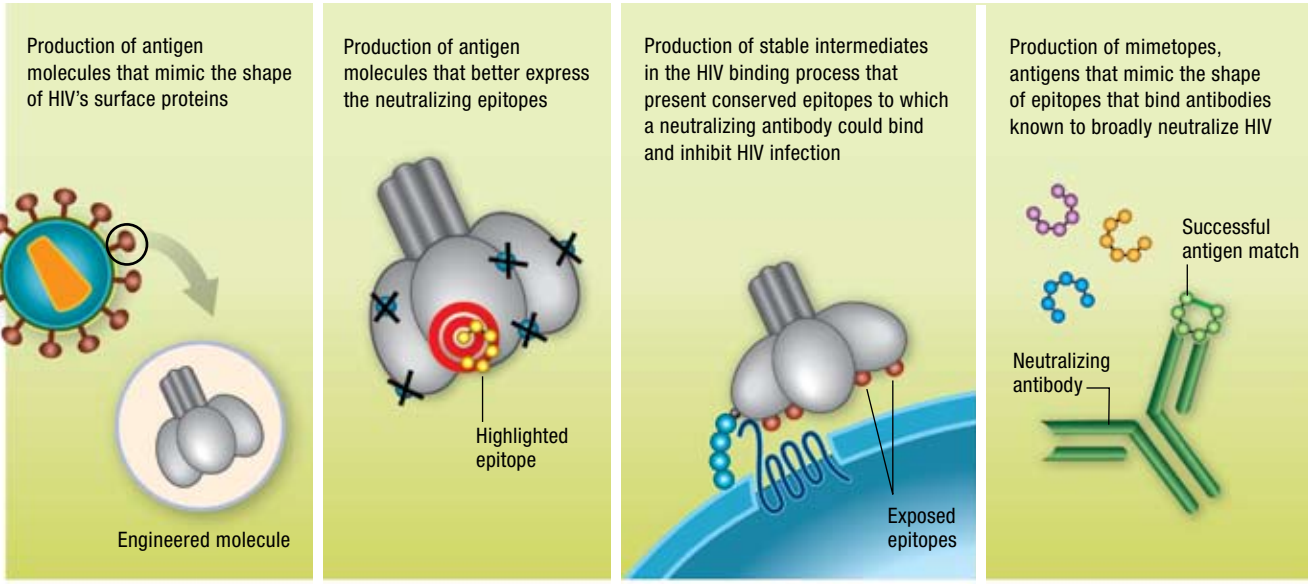

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Figure 12 Current Strategies to Address the Neutralizing Antibody Problem

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

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

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

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

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

ADDRESSING THE CHALLENGES

Scientific empiricism alone is unlikely to yield an effective vaccine. An integrated approach that incorporates rational vaccine design to address key scientific challenges to improve antigen development along with a more streamlined evaluation and testing procedure is required to accelerate AIDS vaccine development. In addition to the formidable scientific barriers to more rapid progress in AIDS vaccine R&D existing today, there are also major policy obstacles which must be overcome in order to speed scientific progress. This report recommends a series of new initiatives with five-year interim milestones, which, if reached, would likely and significantly advance the search for an effective AIDS vaccine.

Integrated Program for Accelerating AIDS Vaccine Development: There needs to be a coordinated paradigm shift to move more novel candidates targeting different immune responses into the pipeline and to accelerate feedback on their efficacy. The required components of this paradigm shift are: rational vaccine design applied towards resolving the unanswered questions and translating

answers into novel vaccine candidates; coordinated scientific empiricism to test only those candidates that are significantly better than the leading candidate in the pipeline; and accelerated clinical trials to yield efficacy and safety data to prioritize within the field. This shift in focus must be supported by policy choices that make available the necessary resources—sufficient and flexible funding and expertise—to successfully develop an AIDS vaccine.

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

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

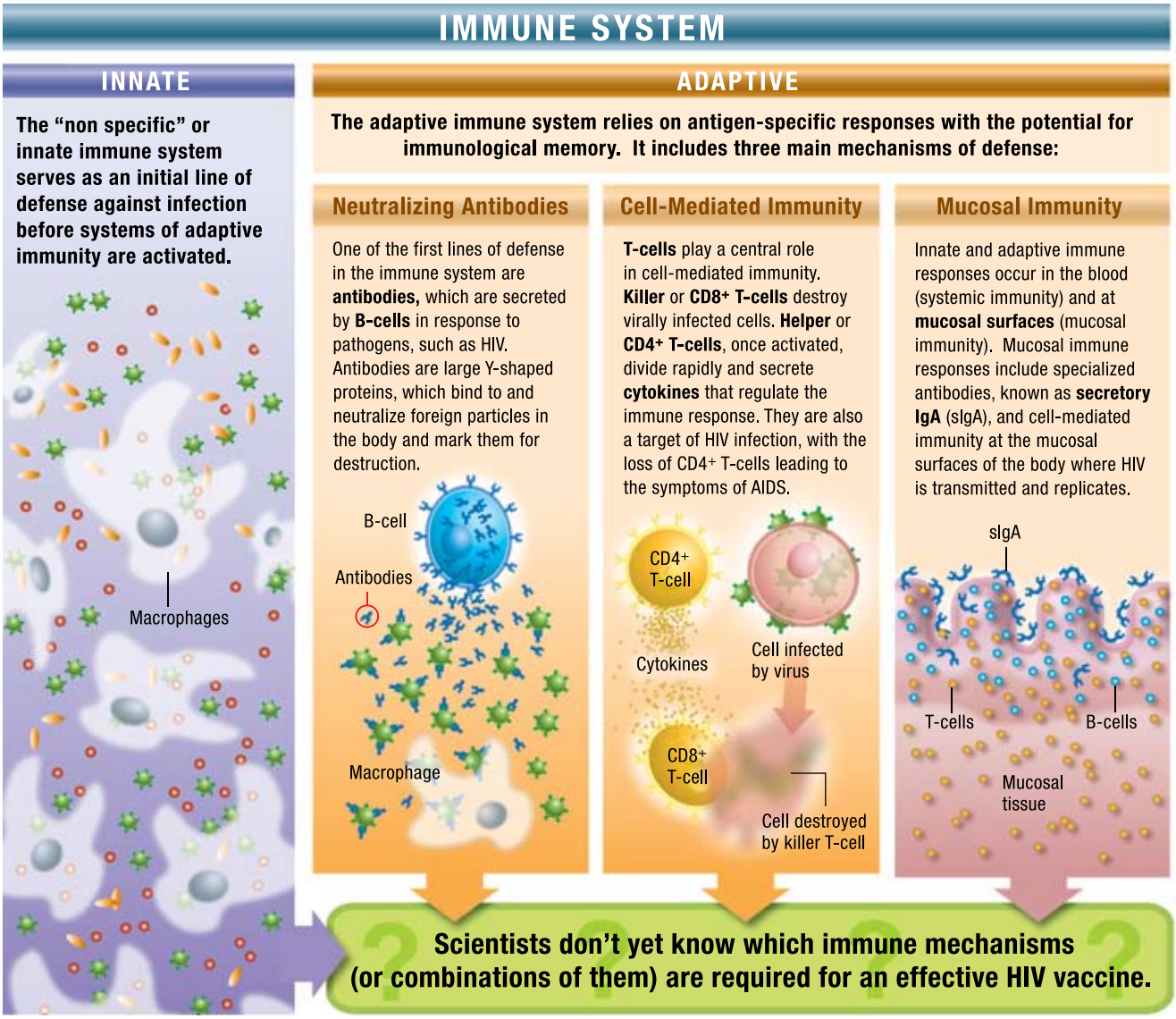

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Figure 13 **Potential Correlates of Protection Against HIV**

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

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

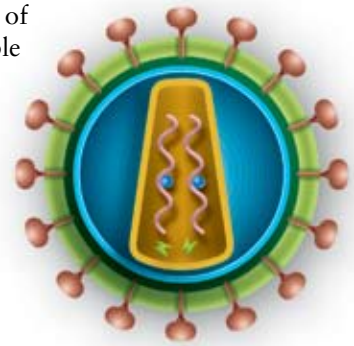
A Collaborative Scientific Empiricism Effort should focus on the design and clinical efficacy testing of candidates that qualitatively or quantitatively improve upon the best current candidates and eliminate the unnecessary duplication that currently plagues the AIDS vaccine pipeline. The focus must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

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

- Phase I trials of candidates which qualitatively or quantitatively are superior to the current leading candidate vaccines should be conducted in small numbers (<50) of subjects at sites where Phase II trials would be conducted;
- Candidates that fulfill the criteria should be advanced immediately to Phase II trials of about 500 subjects at high risk for HIV infection, such as discordant couples or people living in areas where HIV incidence rates exceed 4% per year and there is a strong track record of compliance in clinical trials. The expected 20–25 new infections per year would be comprehensively assessed for anti-HIV immune responses, viral load at acute infection and set point, and host genetics. This would greatly speed the collection of efficacy data and allow for many candidates to be tested at the same cost as a single Phase IIb trial in the current funding paradigm; and
- Based on preliminary efficacy data from these proposed accelerated Phase II efficacy trials, an algorithm must be established for terminating work on the candidate, modifying/improving the candidate, or advancing the candidate to Phase III trials.

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

In order to increase the engagement of pharmaceutical and biotechnology companies, their R&D investment risk needs to be reduced. A variety of "push" and "pull" incentive mechanisms are needed to lower the cost of R&D and to ensure viable markets for future AIDS vaccines. A number of innovative proposals have been developed and discussed—now these incentives need



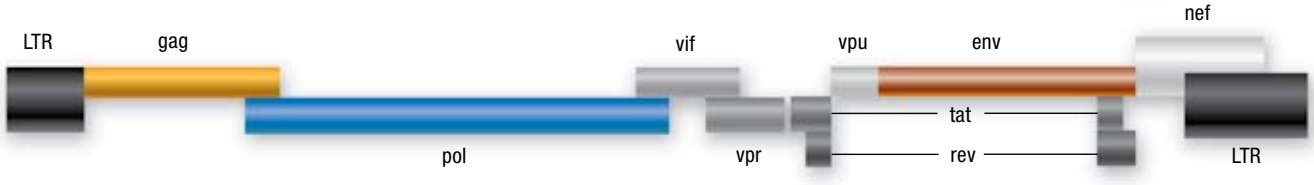


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Figure 14 **HIV Genome and Major Antigens**

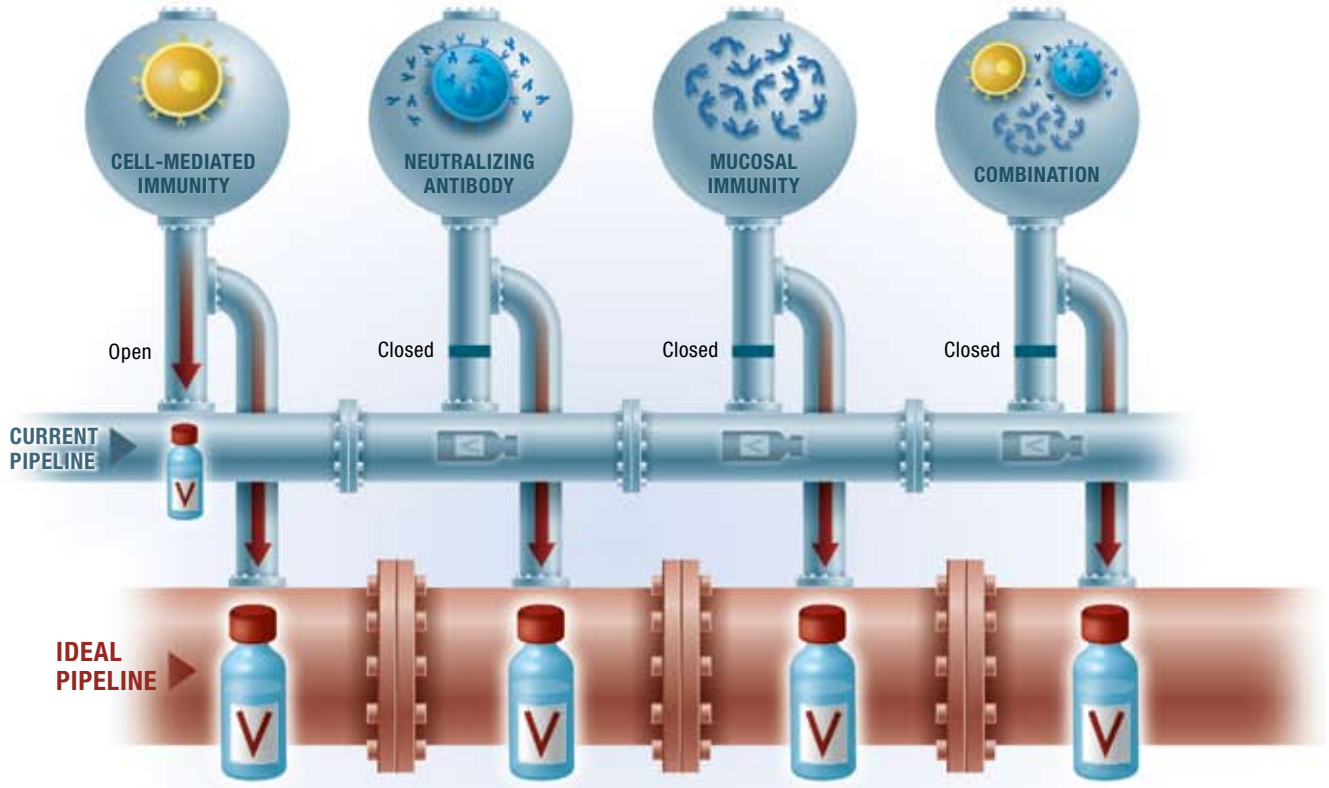

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Figure 15 **The AIDS Vaccine Pipeline**

to be introduced and tested. Additionally, novel forms of partnership and product development schemes should be created to tap private sector expertise in areas such as high-throughput technologies, project management, process development, and manufacturing.

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

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

Establishing Vaccine Trial Networks of Excellence in developing countries by enhancing existing centers and creating new centers will fully utilize resources and provide maximum long-term benefit to the local communities. These networks should be able to conduct the required clinical research and multiple Phase IIb and III AIDS vaccine trials, as well as have the capacity to conduct vaccine trials for other diseases such as tuberculosis and malaria. Key components include: clinical trial capacity; accredited and validated laboratory capacity; data management; epidemiology expertise; training facilities; community linkages; and national and international support. Vaccine Trial Networks of Excellence incorporating agreed-upon standards to enable multi center clinical trials should be established in the regions of eastern Africa, southern Africa, western Africa, India, China, Russia/Eastern Europe, southeast Asia, Latin America, and the Caribbean, where circulating HIV isolates vary.

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

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

Preparing today for rapid vaccine approval and

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

Critical Actions to Build and Sustain Long-Term Political Support and Commitment: Implementing the recommendations outlined above will require enormous commitment from many groups, from grassroots to global, and this commitment must be sustained until vaccines are accessible to all those who require them. Policy research is critical in providing a solid base for advocacy, and the relevance of AIDS vaccines to other issues should be emphasized to engage a wider range of constituencies. Ultimately, those allocating resources must be convinced and engaged for the long-term. Recent political statements reflect the awareness and priority these countries assign to AIDS vaccines, but more needs to be done to turn these declarations into real resources and tangible results.

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

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

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