



**iavi**  
International AIDS  
Vaccine Initiative

SCIENTIFIC BLUEPRINT 2000:

ACCELERATING

GLOBAL EFFORTS

IN

AIDS VACCINE DEVELOPMENT

JULY

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This document, *Scientific Blueprint 2000: Accelerating Global Efforts in AIDS Vaccine Development*, lays out a detailed global strategic plan to continue to accelerate the development of AIDS vaccines for use throughout the world.

This updated Blueprint is necessitated by the continued growth of the pandemic and by pronounced changes in the scientific landscape since The International AIDS Vaccine Initiative (IAVI) issued its original *Scientific Blueprint for AIDS Vaccine Development* at the World AIDS Conference in Geneva in 1998. The 1998 Blueprint laid out a global strategic plan to widen the vaccine development pipeline by creating international product development teams linking researchers from academia or industry with clinical researchers in developing countries.

It is gratifying that the applied research and product development-focused approaches advocated by the 1998 document have been widely embraced. IAVI itself has created and funded four international AIDS vaccine development partnerships, and additional product development efforts will receive IAVI's support by year's end. Industry has stepped up its commitment

to AIDS vaccine development, and national and transnational research agencies are also introducing AIDS vaccine product-development initiatives.

But the stepped-up efforts have not kept pace with the urgency of the pandemic. Nearly 12 million men, women, and children have been infected in the past two years. Over 95% of them live in developing countries, where there is little access to treatments that have prolonged life in industrialized countries. AIDS has now surpassed tuberculosis as the leading killer among infectious diseases. A globally accessible, preventive vaccine remains the best hope for ending this pandemic.

*Scientific Blueprint 2000* lays out an ambitious, comprehensive, and focused research and development agenda through 2007. This document proposes:

- Sharply compressing time lines for vaccine development by, among other things, collapsing Phases I and II of clinical trials into a combined Phase I/II
- Conducting parallel, rather than sequential, Phase III efficacy trials in several countries or regions hardest hit by AIDS
- Introducing a total of 25 new

vaccine designs into development, prioritizing among them by conducting head-to-head trials, and conducting between six and eight efficacy trials by 2007

- Spending an additional US\$900 million to \$1.1 billion above currently projected expenditures through 2007 to maximize the possibility of success

The new measures proposed here would dramatically shorten the time needed from product design to global licensure by as much as 50%, compared with standard product development paradigms. The conclusion that the world needs to introduce as many as 25 new vaccine designs to maximize the chance of success is based on a new survey contained in this report. The survey reveals that, of the numerous possible vaccine approaches, only a small percentage are being developed and even fewer are in clinical trials. The additional expenditures we propose would support this accelerated, intensified product development effort to move forward.

It is important to note that IAVI itself is not proposing to shoulder the entire new workload; rather, we aim to complement ongoing national, transnational

The new measures proposed here would shorten the time needed from product design to global licensure by as much as 50%.

and industrial efforts. However, to catalyze this comprehensive scientific agenda, this blueprint calls for IAVI to establish four to eight new vaccine development partnerships (in addition to the four ongoing IAVI-sponsored partnerships) with the goal of initiating efficacy trials of three of the most promising AIDS vaccines within 5-7 years.

As always, IAVI's scientific program will focus on vaccines that can be most useful in developing countries. Such vaccines would be inexpensive to manufacture, easy to transport, stable under field conditions, and require few follow-up doses. IAVI will prioritize novel approaches that have shown promise in animals and can be moved into human testing within two years. With 15,000 new infections a day, a full-fledged vaccine effort is essential. Even a six-month speed-up in the development and deployment of an AIDS vaccine would save millions of lives. However, creating a vaccine is not enough, we must assure that it is made immediately available to those who need it. This is the subject of another IAVI Blueprint, *AIDS Vaccines for the World: Preparing Now to Assure Access*.

This Blueprint, *Accelerating Global Efforts in AIDS Vaccine Development*, reviews the current status of worldwide efforts in AIDS vaccine development, and puts forth a comprehensive global scientific agenda to markedly accelerate the timetable for successful development of safe and effective AIDS vaccines for use throughout the world.

The need for a safe, effective, accessible, preventive AIDS vaccine for use throughout the world is critical. A total of 34.3 million adults and children were estimated by UNAIDS to be living with HIV/AIDS by the end of 1999, and more than 15,000 new infections are occurring each day, with over 95% of these new infections located in the developing world (**Figure 1, Adults and children living with HIV/AIDS**). AIDS has begun to destroy the family unit structure in several countries, with more than 13 million children worldwide having been orphaned. AIDS has also slashed life expectancy in many Sub-Saharan African countries. For example, in Botswana, Namibia, Swaziland, and Zimbabwe, life expectancy has fallen by more than 20 years (**Figure 2, The Impact of AIDS on Life Expectancy**). HIV is spreading fastest in new foci of the pandemic, including the former

Soviet Union, Eastern Europe, and Asia, with projections indicating that within three years more people will become infected annually in Asia than in the rest of the world combined. Prevention programs, including education, condom and clean needle distribution, and peer counseling, have had limited success when concentrated in targeted and focused campaigns to slow the spread of HIV, but on a global scale have not been successful at stopping the epidemic. The best hope for preventing the spread of an infectious agent such as HIV is the development, distribution, and use of a safe, accessible, affordable, and effective preventive vaccine.

Despite significant advances in understanding the molecular biology and pathogenesis of HIV, several challenges remain for successful development and delivery of safe and effective AIDS vaccines. The immune responses necessary for protection against HIV (for example, the relative roles of HIV-specific neutralizing antibodies, cellular immunity and mucosal immunity) remain unclear, as does the specific constitution of HIV antigens required to confer protective immunity. The durability and breadth of immune responses necessary to achieve protection under field conditions,

where highly variable subtypes of HIV are circulating, are also unclear. They will remain so until human field trials with a candidate AIDS vaccine demonstrate a sufficient level of protection so that studies assessing correlates of protective immunity may be undertaken. Moreover, the lack of an ideal animal model for AIDS further supports the need for expanded efforts in clinical development, prioritization of the most promising approaches, and expedited field testing of the best vaccine candidates.

The International AIDS Vaccine Initiative (IAVI) is an international, scientific non-governmental organization dedicated to ensuring the development of safe, effective, accessible, preventive AIDS vaccines for use throughout the world. IAVI is urgently pursuing this mission through three complementary strategies: building worldwide demand for AIDS vaccines by mobilizing growing public and government support for accelerated vaccine development; accelerating development of new and innovative AIDS vaccine designs, and prioritizing the best candidate vaccines for large-scale efficacy testing where the epidemic is spreading fastest in the developing world; and fostering an environment

FIGURE 1



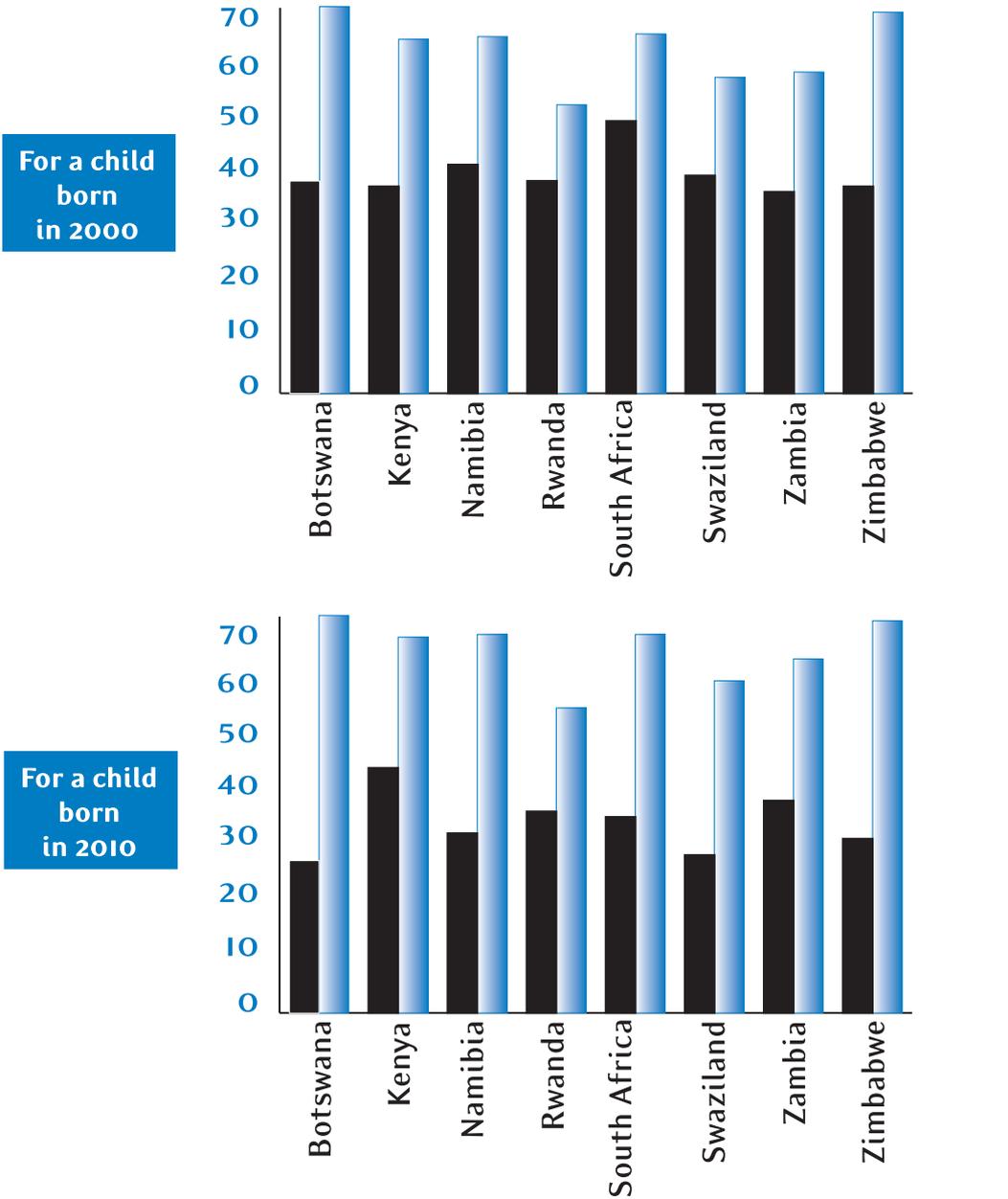
Adults & children living with HIV/AIDS - total: 34.3 million

source: UNAIDS *Report on the Global HIV/AIDS Epidemic*, June 2000

FIGURE 2

### The Impact of the AIDS epidemic on Life Expectancy

Because of the AIDS epidemic
  If there were no epidemic



Source: *World Population Profile*

**IAVI proposes that an additional US\$900 million to \$1.1 billion above current expenditures be allocated over the next seven years for accelerated product development and testing.**

for successful vaccine development by expanding public/private collaboration and investment in a global vaccine effort. It is now also necessary to begin to prepare for success—IAVI's new fourth strategy is to deal with the challenges of making these vaccines available to all those who need them as soon as feasible.

In June 1998 at the International AIDS Conference (Geneva, Switzerland), IAVI released *Scientific Blueprint for AIDS Vaccine Development*, which proposed a framework for accelerating AIDS vaccine development. This Blueprint praised the existing basic science effort and called for the design and testing of new candidate vaccines in the developing countries hardest hit by HIV and AIDS; the establishment of several HIV vaccine product development teams focused on innovative vaccine designs, bringing together research, manufacturing, and clinical trial expertise from both industrialized and developing countries; and solidifying the political commitment globally to ensure that the most promising vaccine approaches progress rapidly into human testing through safety, immunogenicity, and efficacy trials. Developing countries were selected because they are where the epidemic is spreading

the fastest, where other alternatives are limited, and where global vaccines can be most rapidly tested.

In the two years since the release of *Scientific Blueprint*, the global response has been overwhelmingly positive, and the landscape for AIDS vaccine development has finally begun to improve. Leading scientists have praised the strategy as scientifically sound; activists have endorsed the strategy; and funding agencies and philanthropic organizations have promptly and generously provided their support. The first Phase III efficacy trials of candidate HIV vaccines are now well under way; several new vaccine designs are being developed for clinical testing in the developing world through innovative public-private sector Vaccine Development Partnerships; industry commitment to AIDS vaccine research has been re-kindled; and government agencies have significantly increased their commitments to AIDS vaccine development while simultaneously enhancing the basic science effort.

Despite these advances, the AIDS pandemic continues to threaten the social, political, and economic infrastructure of an expanding list of nations. The scientific and logistical challenges associated

with successful development and utilization of AIDS vaccines demand an even more comprehensive and aggressive global scientific agenda to shorten the time required to design, develop, evaluate, and license safe and effective AIDS vaccines for use throughout the world. **IAVI proposes that an additional US\$900 million to \$1.1 billion above current expenditures be allocated over the next seven years specifically for accelerated AIDS vaccine product development and testing to:**

1. **Develop new and innovative AIDS vaccine designs applicable for use in the developing world**
2. **Prioritize candidate AIDS vaccines for accelerated progression to Phase III efficacy trials through head-to-head comparisons**
3. **Shorten time lines in all facets of the AIDS vaccine development process, but principally in clinical trials design and implementation, vaccine site preparedness, and expedited approval processes**

Successful implementation of this accelerated global strategy for AIDS vaccine development should enable 20 to 25 vaccine candidates, encompassing most if not all of the major AIDS vac-

**IAVI will establish four to eight new Vaccine Development Partnerships in addition to the four ongoing IAVI sponsored partnerships.**

cine strategies, covering the spectrum of HIV antigens and host immune responses, and representing the major and globally diverse circulating subtypes of HIV, to be developed and prioritized in clinical trials. The goal of this accelerated scientific agenda would be to have six to eight of the most promising AIDS vaccines in large-scale efficacy trials in regional clinical trials networks in high incidence populations of the developing world where the epidemic is most severe within the next 5–7 years, and at the same time significantly decrease the time required for safety, immunogenicity, and efficacy testing of such candidates, thereby markedly increasing the potential for successful AIDS vaccine development and utilization in the shortest time possible. To catalyze this comprehensive scientific agenda, IAVI will establish four to eight new Vaccine Development Partnerships (in addition to the four ongoing IAVI sponsored partnerships) with the goal of initiating efficacy trials of three of the most promising AIDS vaccines within 5–7 years.

**Current Status of Global Efforts in AIDS Vaccine Development**

The pipeline of candidate AIDS vaccines that eventually undergo

evaluation in human clinical trials for safety, immunogenicity, and, if promising, efficacy are selected from the range of experimental vaccines that have been studied during applied vaccine research and preclinical vaccine design and development programs. These programs generally include identification of antigen(s) of HIV and adjuvants(s) to include in the vaccine and to test in small animal screening safety and immunogenicity studies, prioritization of candidate vaccines for non-human primate safety and immunogenicity studies, development of pilot lot (small sample) manufacturing processes, production of the candidate vaccine under Good Manufacturing Practice (GMP), regulatory testing for safety, purity, identity, stability and potency, toxicology studies, and finally submission of the requisite data for initiation of clinical trials to regulatory agencies. The candidate vaccines are tested in human volunteers to determine their safety, immunogenicity, and eventually efficacy (**Figure 3, Vaccine Design to Access**).

Vaccine clinical trials are divided into three distinct stages:

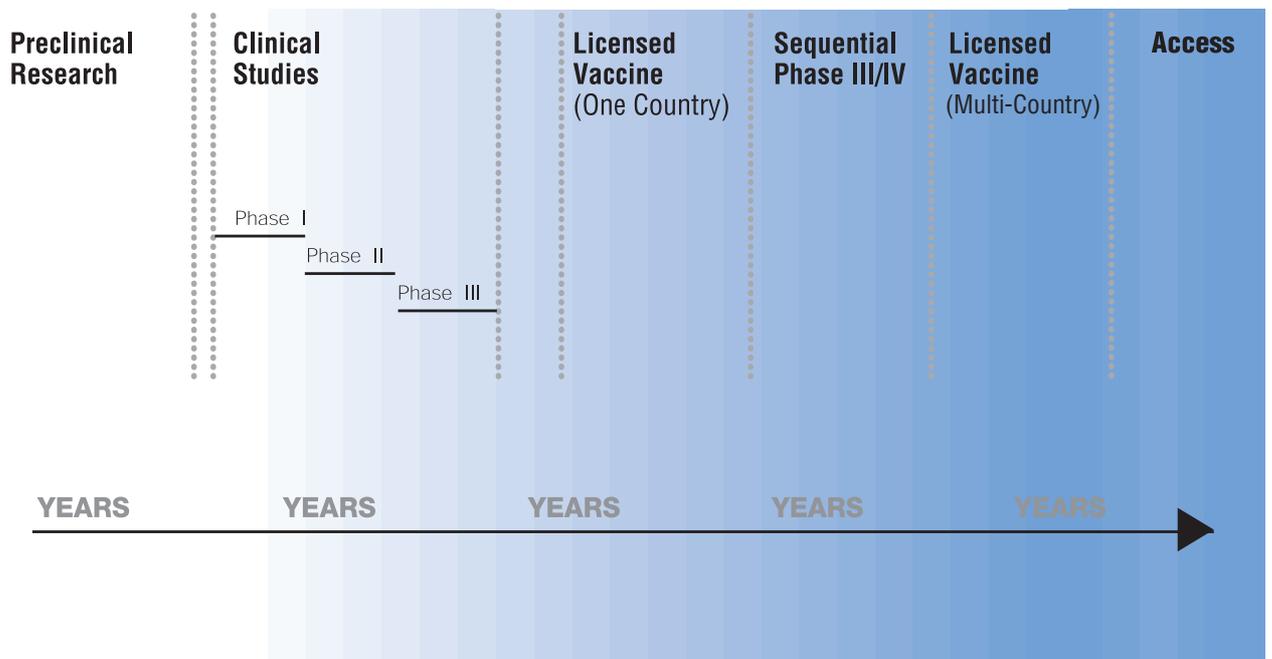
Phase I trials represent the first human trials of a candidate vaccine, and are generally conducted on small numbers (10–30) of

healthy adult volunteers, with the principal goals being evaluations of safety and immunogenicity of the vaccine. Preliminary dose escalation and schedules of immunizations are also evaluated in Phase I, which generally takes 12–18 months for completion.

Upon successful completion of Phase I testing, Phase II clinical trials of larger numbers of volunteers (50–500) are carried out in populations representative of those where eventual vaccine efficacy trials will be conducted, i.e., healthy subjects at relatively high risk for HIV infection. The goals of Phase II trials are to obtain additional safety data, refine the dosing and scheduling regimens of the vaccine, and if the trial is large enough, to obtain preliminary indications of efficacy of the vaccine. These trials generally take two years for completion, due in large part to the additional time required to screen and enroll larger numbers of subjects.

Based on successful outcomes of Phase II trials, large-scale efficacy trials (termed Phase III) are conducted in thousands of subjects, in which the vaccine is compared with a placebo in geographic areas where the incidence of HIV transmission is great enough to allow for a

### AIDS Vaccine Design to Access



| It is a tragedy that only one vaccine concept has reached the Phase III clinical trials stage. |

determination of the level of vaccine efficacy in preventing disease. Because Phase III trials are expensive and logistically challenging, they often pose a barrier for clinical development, particularly with HIV, where lack of ideal animal models has also impeded prioritization of the most promising vaccine approaches. Successful demonstration of efficacy in a Phase III trial will lead to an application for licensure of the vaccine for marketing and distribution. It is anticipated that Phase III trials of AIDS vaccines will take a minimum of 3–4 years for enrollment, immunizations and assessments of efficacy.

The current clinical pipeline in AIDS vaccine development is extremely narrow, and woefully inadequate given the urgency with which a safe and effective AIDS vaccine is needed to stem the HIV pandemic. After more than 15 years of research and development, it is a tragedy that only one vaccine concept, a recombinant subunit vaccine (termed gp120) has reached the Phase III clinical trials stage, and only two other vaccine concepts have even reached the stage of Phase II safety and immunogenicity trials. Moreover, on a global scale, only a handful of Phase I trials of candidate AIDS vaccines are currently ongoing,

with minimal activity in high-incidence areas of the developing world (**Table 1: AIDS Vaccine Candidates in Clinical Trials; Table 2: AIDS Vaccine Candidates in Clinical Trials in the Developing World**).

The list below summarizes the different types of vaccine concepts (**Figure 4, Overview of AIDS Vaccine Designs; Figure 5, Potential HIV Genes for Incorporation into an AIDS Vaccine**) currently under investigation for potential use as AIDS vaccines, and the stage of development/clinical trials which has been achieved for each concept:

**RECOMBINANT SUBUNIT:**

Recombinant subunits are vaccines that are produced by genetically engineering cells to produce one or more foreign genes, such as HIV genes. The recombinant subunit approach was first used against hepatitis B virus, where viral envelope produced in yeast cells proved effective in clinical trials. The envelope proteins of HIV are the targets of antibodies that neutralize, or prevent infection by, HIV and provided an obvious early target for vaccine design. The HIV surface glycoprotein (gp120) occurs in ‘spikes’ (each spike a trimer of gp120), protruding from the surface and attached to the core of the virus

particle via the gp41, the trans-membrane protein of HIV. Before the virus assembles itself into final form and buds from the infected cell, gp41 and gp120 are joined together in a larger protein called gp160. Beginning in 1989, several gp120 and gp160 proteins, manufactured in yeast, insect cell, or mammalian cell production systems, were tested in humans with a variety of adjuvants, and one of those products (VaxGen gp120 vaccine) forms a component of the only AIDS vaccine currently being evaluated in efficacy trials. Combination of multiple subunit proteins offers a strategy for expanding the breadth of immune responses induced by the vaccine. Subunits are also considered as a booster immunization in vector-prime, subunit boost vaccine strategies.

• Candidate recombinant subunit vaccines for AIDS in clinical trials:

- gp120: Phase III
- oligomeric gp140 Phase I
- p24: Phase I

**RECOMBINANT VIRAL VECTOR:**

HIV genetic material is placed into harmless viruses that then present pieces (e.g., proteins) of HIV to the immune system, which leads to the development of HIV-specific immune respons-

TABLE I

TABLE 1: AIDS VACCINE CANDIDATES IN CLINICAL TRIALS

Product	Company	HIV subtype	Phase
<b>Peptide:</b>			
C4-V3 peptide	Wyeth	B	1
V3 peptides	CIBG	B	1
p17	Cel-Sci	B	1
Lipopeptides: nef, gag,env	ANRS	B	1
<b>Recombinant subunit:</b>			
bivalent rgp120	VaxGen	B+E	3
bivalent rgp120	VaxGen	B	3
oligomeric gp140	Aventis	E	1
rgp120	Chiron	E	1
p24	Chiron	B	1
<b>DNA:</b>			
gag	Merck	B	1
env-rev	Wyeth	B	1
<b>Live viral vector:</b>			
vaccinia –env, gag, pol	Therion	B	1
vaccinia – multi - env	St.Jude's	B	1
canarypox – env, gag-pr	Aventis	B	1
canarypox – env, gag-pr, nef, pol	Aventis	B	1
<b>Live bacterial vector</b>			
Salmonella- env	Univ. Md.	B	1
<b>Combinations: (Vector prime + subunit boost)</b>			
canarypox –env, gag-pr,nef,pol	Aventis	E	2
• rgp 120	Chiron	E	
• rgp120	VaxGen	B+E	
• oligomeric rgp140	Aventis	E	
canarypox – env, gag-pr	Aventis	B	2
canarypox – env, gag-pr, nef, pol	Aventis	B	
• rgp120	VaxGen	B	
Salmonella- env	Univ. Md.	B	1
• rgp120	VaxGen	B	
<b>(DNA prime + vector boost)</b>			
DNA-gag,pol	Wyeth	B	1
• Canarypox-env, Gag-pr	Aventis	B	
DNA-env-rev	Wyeth	B	1
• Canarypox-env, Gag-pr	Aventis	B	

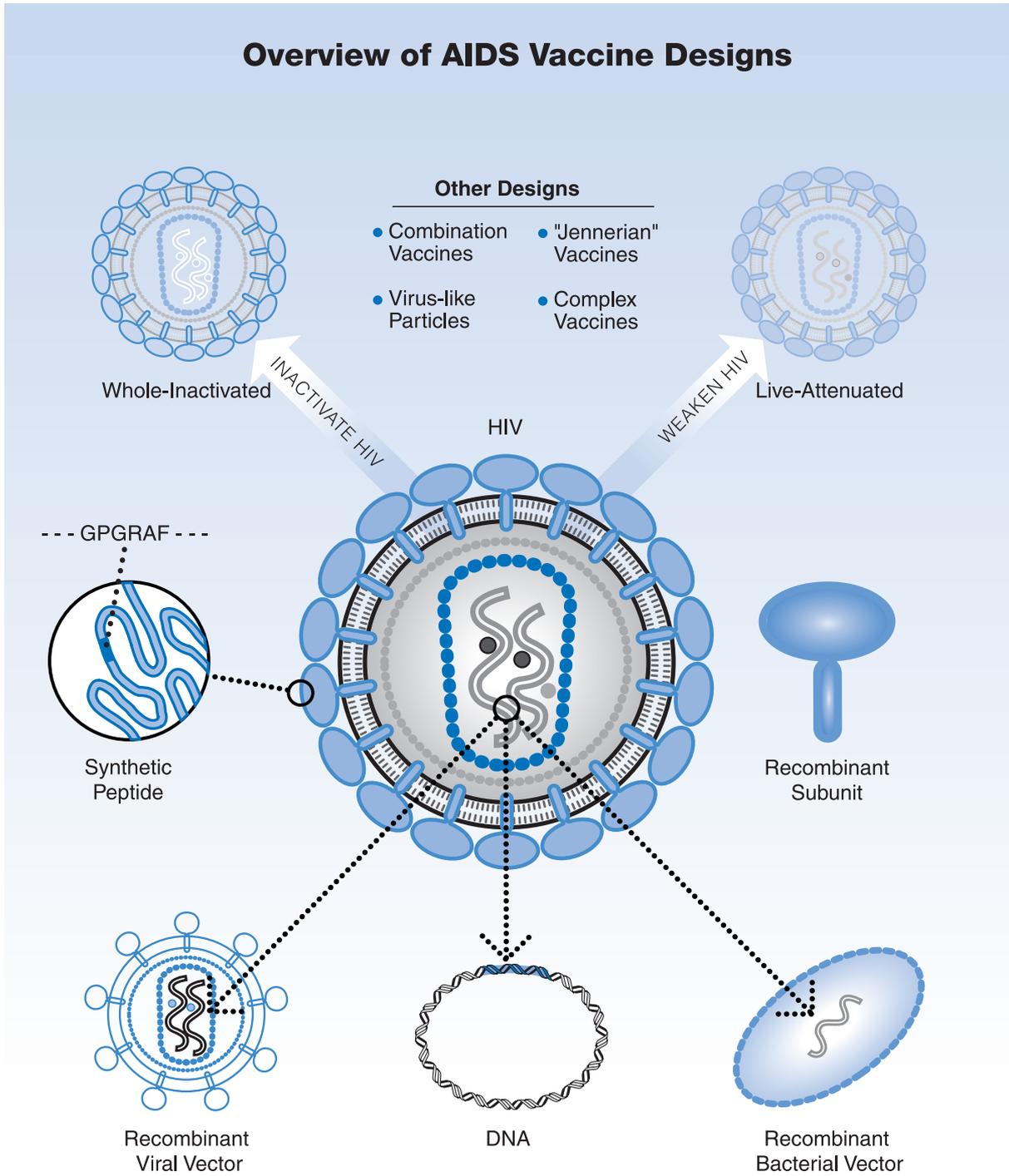
TABLE 2

**TABLE 2: AIDS VACCINE CANDIDATES IN CLINICAL TRIALS DEVELOPING WORLD**

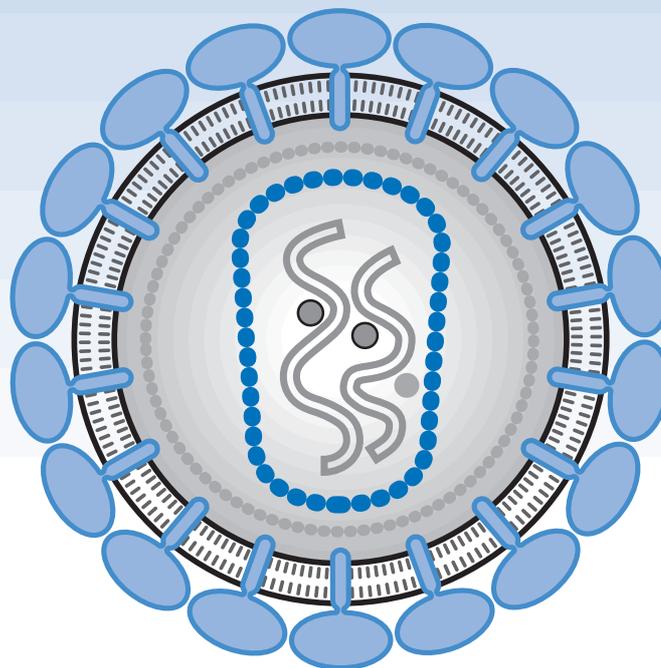
Product	Company	HIV subtype	Phase	Site
<b>Peptide:</b> V3 peptides	CIBG	B	1	Cuba
<b>Recombinant subunit:</b> bivalent rgp120	VaxGen	B+E	3	Thailand
<b>Live viral vector</b> canarypox – env, gag-pr	Aventis	B	1	Uganda
<b>Combinations: (Vector prime + subunit boost)</b> canarypox –env, gag-pr, nef,pol	Aventis	E	2	Thailand
• rgp 120	Chiron	E		
• rgp120	VaxGen	B+E		
• oligomeric rgp140	Aventis	E		
canarypox – env, gag-pr	Aventis	B	2	Haiti, Trinidad, Brazil
canarypox – env, gag-pr, nef, pol	Aventis	B		
• rgp120	VaxGen	B		

FIGURE 4

### Overview of AIDS Vaccine Designs



## Potential HIV Genes for Incorporation into an AIDS Vaccine



### HIV Genes

- env
- gag
- nef
- pol
- rev
- tat
- vif
- vpr
- vpu

HIV

Several bacterial systems are currently being evaluated in the early stages of AIDS vaccine design.

es elicited by the vaccine. The potential advantage of the viral vector strategy is to mimic as closely as possible the efficacy of live-attenuated vaccines, while at the same time offering much greater safety. Several viral vector systems are currently being utilized in the early stages of AIDS vaccine design, including alphavirus vectors (Venezuelan equine encephalitis; Sindbis or Semliki Forest viruses); adenovirus; adeno-associated virus (AAV); pox viruses (e.g., canarypox; fowlpox; modified vaccinia Ankara [MVA] and vaccinia); yellow fever virus; and polio virus. Despite this significant level of preclinical activity, only two viral vector strategies have thus far reached clinical trials, both of which are pox virus vectors. There has been a sequential evolution of the complexity of HIV genes incorporated into viral vector strategies, from single genes (e.g., HIV env gene) to multi-genes (e.g., HIV env, gag-pro, pol, and nef). The large number of potential viral vector systems, coupled with decision-making associated with which HIV genes to include in the vector and which subtype of HIV to base the vaccine on, highlights the need for strategies to prioritize the most effective vaccines and accelerate the best

products into efficacy trials.

- Candidate live recombinant viral vector vaccines for AIDS in clinical trials:

- Canarypox: Phase II
- Vaccinia: Phase I

**DNA:**

One of the newest technologies for vaccine design, DNA vaccines (also termed "naked DNA" or nucleic acid immunization) offer significant advantages in ease of manufacturing. Pieces of HIV DNA are incorporated into harmless plasmid DNA from bacteria and used to make the body's cells produce HIV proteins for the immune system to recognize and mount immune responses against. Preclinical studies with non-HIV vaccines have demonstrated the significant potential of this vaccine strategy, and recently DNA vaccines for AIDS have entered clinical trials. Moreover, several innovative strategies for presentation of DNA vaccines (e.g., within attenuated strains of bacteria) offer the potential for oral administration of such vaccines. Similarly, optimization of codons and attachment of DNA to synthetic particles offer strategies for enhancing the immunogenicity of DNA vaccines.

- Current status of DNA vaccines

for AIDS in clinical trials:

- Phase I

**RECOMBINANT BACTERIAL VECTOR:**

Similar in concept to viral vector vaccines, HIV genetic material is molecularly engineered into bacteria, which then serves as the vaccine. Several bacterial systems are currently being evaluated in the early stages of AIDS vaccine design, including Salmonella, Shigella, Listeria, and BCG. Bacterial systems offer several advantages including potential for oral administration, ease of production, and the capacity to be engineered with a full complement of HIV genes. With the exception of a single Salmonella vector in clinical trials, which expressed a single HIV env gene subtype B, all recombinant bacterial vector designs for AIDS vaccines have been preclinical.

- Candidate live recombinant bacterial vector vaccines for AIDS in clinical trials:

- Salmonella: Phase I

**SYNTHETIC PEPTIDE:**

Small portions of HIV proteins. Extensive basic research on potential cytotoxic T cell (CTL) and antibody epitopes of HIV have shown that the immune system will mount a response to very short peptide sections of a protein antigen when presented

**Live-attenuated SIV has proven to be the gold standard in protecting monkeys from SIV infection, however safety is a serious concern.**

appropriately to the immune system. Synthetic peptides can be linked to lipid molecules (e.g., lipopeptides) to facilitate induction of cellular immune responses such as CTLs. In addition, random libraries of peptides can be engineered to bind to antibody molecules, as a strategy to mimic (e.g., mimotope) the structure necessary to stimulate the desired antibody response. Finally, peptides can be combined as multi-peptide vaccines in a strategy to increase the breadth of the vaccine-induced response.

- Candidate synthetic peptide vaccines for AIDS in clinical trials:
  - p17: Phase I
  - Lipopeptides Phase I
  - V3-based Phase I

**COMBINATION VACCINES:**

Recognizing that protection from HIV may require a broad spectrum of immune responses including humoral (e.g., neutralizing antibodies), cellular (e.g., CTLs, cytokines, and chemokines), and mucosal immunity, scientists have designed combination regimens in attempts to elicit such broad-spectrum immunity.

- Current status of combination vaccines for AIDS in clinical trials

- Canarypox + gp120: Phase II

**LIVE-ATTENUATED:**  
Weakened (attenuated) live virus that is unable to cause disease, but is still able to infect cells and replicate within the body. The immune system is then potentially prepared to protect against future infection by pathogenic strains. Live-attenuated virus vaccines have been successfully used to protect against a great number of diseases, including polio and measles. Live-attenuated simian immunodeficiency virus (SIV) has proven to be the gold standard in protecting monkeys from SIV infection, to a greater degree than any other vaccine approach. Safety is a serious concern, however, because of well-documented instances of AIDS occurring in a small percentage of monkeys inoculated with live-attenuated SIV vaccines. Thus, a significant challenge for development of live-attenuated AIDS vaccines would be demonstrating that the attenuated vaccine would not revert back to a more virulent strain, capable of causing disease.

- Candidate live-attenuated AIDS vaccines in clinical trials:

- NONE

**WHOLE-INACTIVATED:**

This traditional approach combines the advantages of presenting a full complement of antigens in their native structure,

and has been successfully used for the development of vaccines for diseases such as polio and hepatitis A viruses. With regard to HIV, the conceptual advantage of the whole-killed approach is that the entire viral particle is presented to the immune system but it cannot infect and replicate, and thus has less safety concerns than live-attenuated vaccines. However, production issues of whole-inactivated vaccines in which the integrity of the virus particles is maintained in the face of chemical and physical inactivation modalities has thus far limited the development of this vaccine concept for AIDS vaccines.

Recent data demonstrating that primary (i.e., circulating) strains of HIV may retain their gp120 spike on the HIV virus particle through purification more effectively than laboratory-adapted strains, increases the potential for maintaining native structure throughout the purification process. In addition, several complementary modalities that allow for a greater threshold of safety are now available for inactivation of HIV.

- Candidate whole-inactivated AIDS vaccines in clinical trials:

- NONE

**VIRUS-LIKE PARTICLES:**

Incomplete viruses produced by

For nearly half of the potential vaccine strategies, no product has yet to enter clinical trials.

cells that are infected with parts of HIV DNA. Particulate antigens provide immunological advantages in presentation of multiple epitopes (e.g., antigenic sites) to the immune system, and provide safety advantages since they can be engineered to exclude the genes of the pathogen. For example, core particles of hepatitis B virus have been engineered and evaluated preclinically to present HIV antigens.

- Candidate virus-like particle vaccines for AIDS in clinical trials:

- NONE

#### "JENNERIAN" VACCINES:

In the 18th century, Edward Jenner discovered that immunization with cowpox protected against variola virus, the cause of smallpox. The concept of "Jennerian" vaccines is being explored for HIV utilizing vaccines based on the simian equivalent (simian immunodeficiency virus, SIV) and lentiviruses from other species, such as caprine arthritis encephalitis virus (CAEV).

- Candidate "Jennerian" vaccines for AIDS in clinical trials:

- NONE

#### COMPLEX VACCINES:

In contrast to developing vaccines which target HIV specific

proteins, some groups have focused on development of AIDS vaccines by directing immune responses against human host cell receptors which HIV utilizes as a port of entry for initial infection. Vaccines directed against the common host cell receptors, such as CD4 and CCR5, are often referred to as "host cell complex" or "complex vaccines."

- Complex vaccines for AIDS in clinical trials:

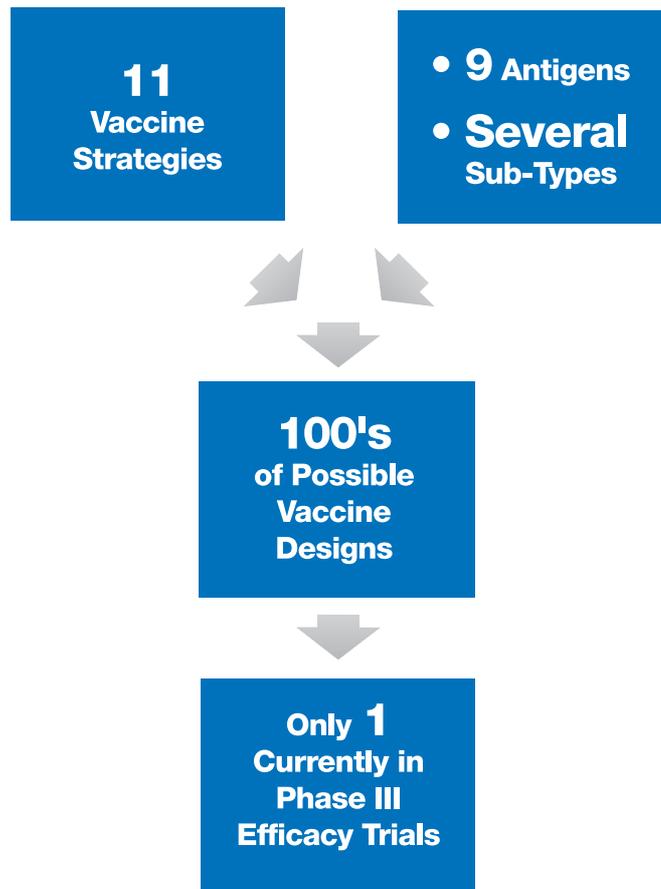
- NONE

The above list highlights the paucity of concepts for AIDS vaccines currently in clinical trials. By simple mathematics, over 1,000 potential vaccine designs are possible (11 AIDS vaccine strategies multiplied by 9 potential HIV antigens to include in a candidate vaccine multiplied by more than 10 potential subtypes of HIV circulating globally, (Figure 6, Challenges of AIDS Vaccine Development). From 11 potential vaccine strategies including combinations, there has been only minimal activity in clinical trials. For nearly half of the potential vaccine strategies, no product has yet to enter clinical trials. Moreover, as discussed below, the spectrum of HIV antigens used in these vaccines has been quite limited, with a disproportionate amount

of clinical effort focused on the HIV outer envelope antigen (e.g., HIV env, gp120), with much less resources focused on the use of core, regulatory and accessory antigens and development of multigenic vaccines.

In addition to this narrow clinical pipeline, AIDS vaccine development is further stymied by the fact that the overwhelming majority of candidate vaccines that have thus far entered clinical trials are focused on a single subtype of HIV (referred to as subtype B) currently circulating primarily in the industrialized world. Although the significance of global viral variation remains unclear, the emphasis of vaccine development on a single subtype highlights the need to both widen the pipeline of vaccines to diverse subtypes and to conduct efficacy trials with vaccines in multiple regions of the world where different subtypes are circulating, in order to determine the breadth of protection conferred by the vaccines. **The tragedy is that more than 15 years since the identification of HIV as the cause of AIDS, only one vaccine strategy, i.e., recombinant subunit, with two variants of the same HIV antigen, i.e., subtype B and subtype E gp120, has progressed to Phase III efficacy trials. There presently is no candidate AIDS vaccine in**

## Challenges of AIDS Vaccine Development



**15 Years / 53 Million Infections**

What is urgently needed is a rapid widening and expansion of the clinical pipeline of vaccines applicable for use in the developing world.

clinical trials focused on either of the two most prevalent subtypes of HIV that are circulating primarily in the developing world, and that together account for approximately two-thirds of all HIV infections worldwide.

In summary, the current status of AIDS vaccine development is characterized by an extremely narrow clinical pipeline of candidate vaccines, focused primarily on subtypes of HIV circulating in the industrialized world. However, during the past two years, there has been a significant widening of the preclinical pipeline in AIDS vaccine development, and more activity aimed at design of AIDS vaccines focused on strains of HIV circulating in the developing world. As discussed below, what is urgently needed is a rapid widening and expansion of the clinical pipeline of vaccines applicable for use in the developing world, prioritization of the best candidates into Phase III trials, and shortening the development time lines to accelerate the overall time required for development, licensure, and global deployment of a safe and effective AIDS vaccine.

#### Global Resources Dedicated to AIDS Vaccine Product Development

Despite close to US\$20 billion

being spent globally each year by national and international public sector agencies, biotechnology and pharmaceutical companies, and philanthropic non-governmental organizations on AIDS research, treatment, prevention and care, it is currently estimated that only approximately US\$350 million per year worldwide is currently being spent on AIDS vaccine development. Closer examination reveals that **less than one-third of that amount is being spent on product development**, while the remaining resources are focused on basic and applied research applicable to AIDS vaccine design, and the establishment of infrastructure for future clinical trials. Moreover, of the resources focused on product development, the majority is directed at vaccines applicable for use in the industrialized world, with **only limited global resources focused on product development of AIDS vaccines applicable for use in the developing world, where over 95% of new infections are occurring.**

AIDS vaccine research and development is supported by several national and international public sector agencies, private sector companies, international organizations and philanthropic groups. The recently reorganized WHO-UNAIDS program pro-

vides technical support for developing countries addressing issues in vaccine development, and addresses ethical, training, and clinical trials issues related to evaluation of candidate AIDS vaccines in the developing world. National and multi-national public sector agencies such as the US National Institutes of Health, UK Medical Research Council, French L'Agence Nationale de Recherches sur le SIDA, and European Commission (EC) support a broad spectrum of basic and applied vaccine research, and provide resources for infrastructure of clinical trial sites for evaluation of AIDS vaccines, with the vast majority of resources focused on HIV subtypes and vaccine products applicable for use in the industrialized world. Each of the major global vaccine companies, Merck, Wyeth-Ayerst, SmithKline Beecham, and Aventis-Pasteur, has programs in AIDS vaccine development, with the majority of their resources aimed at vaccines directed against subtype B of HIV-1, the major subtype circulating in the industrialized world. Large and small biotechnology companies, such as Chiron, VaxGen, and Therion, all have products in clinical trials, but only the VaxGen product has thus far

**IAVI helps ensure that its vaccines, if successfully developed, would be made available in reasonable quantities and cost in the developing world.**

progressed to Phase III efficacy trials (Table 3, Product Development Timeline: VaxGen Recombinant GP120 Candidate vaccine). During the past two years, the US NIH, Walter Reed Army Institute of Research (WRAIR), and EC have increased resources for vaccine product development, including pilot lot manufacturing, and clinical trials, and the WRAIR program has products in preclinical development focused on strains of HIV circulating in SE Asia and East Africa. NIH will soon be funding a new program, termed Vaccine Design and Development Teams, with the goal of providing supplemental funding to industrial product development efforts on AIDS vaccines, with the vast majority of resources aimed at development of vaccines against HIV subtype B, the most prevalent subtype of HIV circulating in the United States. Further, the NIH Vaccine Research Center will be focused on the iterative process of the preclinical/clinical trials interface, with the goal of improving the immunogenicity of novel vaccine designs.

Collectively, there are limited global resources directed at development of candidate vaccines applicable for use in the developing world, where the epidemic is spreading most rapidly.

As a result, IAVI has focused its efforts on complementing the activities of the national/international public sector agencies and the private sector, by providing support for development of new and innovative vaccine designs that are targeted at HIV subtypes circulating in the developing world. Through public-private sector linkages, termed Vaccine Development Partnerships, IAVI has established product-development teams connecting vaccine designers and manufacturers in the industrialized world with clinical researchers in the developing world. Via an innovative intellectual property model termed Social Venture Capital, IAVI helps ensure that the vaccine(s), if successfully developed, would be made available in reasonable quantities and cost to public sector authorities in the developing world. Thus, far, IAVI has forged four (4) Vaccine Development Partnerships, focused on vaccine development of DNA vaccines, recombinant viral vectors, and orally administered bacterial vaccines for eastern and southern Africa, with additional partnerships being formed aimed at accelerating vaccine development for India, China, and other regions of the developing world.

### **Current Challenges to Accelerating AIDS Vaccine Product Development**

Despite significant advances during the past few years in widening the preclinical pipeline for candidate vaccines that may eventually enter clinical trials, the current narrow scope and pace of the collective global effort in AIDS vaccine development clearly indicate that a more aggressive and focused agenda aimed at accelerating development of the most promising vaccines will be necessary to achieve the goal of successful development and use of safe and effective AIDS vaccines throughout the world in the shortest time frame.

Challenges to accelerating AIDS vaccine product development can be broadly grouped into three categories: Scientific, Operational and Regulatory.

#### **Scientific Challenges**

Several scientific challenges remain for successful development and delivery of safe and effective AIDS vaccines. The immune responses necessary for protection against HIV remain unclear, as does the specific constitution of HIV antigens necessary to confer protective immunity. The durability and breadth of immune responses necessary

TABLE 3

**TABLE 3: PRODUCT DEVELOPMENT TIMELINE:  
VAXGEN RECOMBINANT GP120 CANDIDATE VACCINE**

Year	Milestone
1985-1992	Vaccine Construction; Preclinical Development
1991-1993	Phase I Trials: (Clade B: IIIB and MN isolates)
1992-1994	Phase II Trial: (Clade B: MN Isolate)
1995-1997	2nd Generation Vaccine Construction, Preclinical Development <ul style="list-style-type: none"> <li>• Bivalent : clade B (MN+primary B isolate)</li> <li>• Bivalent: clade B+E (MN+ primary E isolate)</li> </ul>
1997-1999	Phase I/II Trials: <ul style="list-style-type: none"> <li>• Bivalent B and Bivalent B+E</li> </ul>
1998-2002	Phase III: Bivalent B+E: Thailand
1999-2002	Phase III: Bivalent B: US, Netherlands, & Canada

**There is renewed optimism that cross-reactive preventive vaccines may be designed against HIV subtypes.**

to achieve protection under field conditions, where highly variable subtypes of HIV are circulating, is also unclear, and will remain so until human field trials with a candidate AIDS vaccine demonstrate a sufficient level of protection so that studies assessing correlates of protective immunity may be undertaken. Thus, it is imperative that new and innovative vaccine designs capable of eliciting the broadest and most robust immune responses against HIV be considered for accelerated development, and that this development be framed in partnerships between vaccine designers, manufacturers, and clinical trial specialists from the countries where the vaccines will be tested in order to expedite clinical testing where the epidemic is most severe.

A number of recent and innovative scientific advances have had a significant impact on the strategies now being undertaken for AIDS vaccine design and development. The development of more specific and sensitive assays for assessing cellular immune responses, including tetramer-based, ELISPOT-based, and flow-cytometric intracellular cytokine assays, has significantly enhanced natural history studies, demonstrating a greater understanding of the importance of

HIV-specific cellular immune responses in controlling HIV infections. Similarly, demonstration of cross-reactive cellular immune responses from individuals vaccinated with viral-vector-based vaccines derived from one HIV subtype and assayed against targets from heterologous HIV subtypes provided renewed optimism that cross-reactive preventive vaccines may be designed against HIV subtypes circulating in different geographic locales. With respect to HIV neutralization, the recent structural biological data of the HIV envelope glycoproteins gp120 and gp41 provided new leads for design of immunogens focused on neutralization of HIV primary isolates, and currently, animal model studies are ongoing assessing such immunogens. Finally, data from several laboratories studying the roles of HIV regulatory and accessory genes have collectively suggested that one or more HIV regulatory and/or accessory genes may be important as components of an effective AIDS vaccine.

#### **Operational Challenges**

Several operational challenges are currently impeding efforts to accelerate AIDS vaccine product development. Vaccine designers, particularly those in academia and small biotechnology compa-

nies where the majority of new vaccine designs are conceived, generally do not have the financial and personnel resources to focus on critical project management, process development, scale-up and manufacturing issues necessary for development of vaccines. This lack of resources can often lead to significant delays in moving novel vaccine designs through the various stages of development. Education and advocacy efforts associated with preparations for AIDS vaccine trials in developing countries are a critical component to achieving success, but are often less than adequately supported, which can result in delays in obtaining the required political and ethics approvals necessary for conducting clinical trials in developing countries.

Comparative Phase I/II clinical trials of candidate AIDS vaccines offer the best opportunity for prioritizing vaccines for large-scale efficacy trials. Ideally, utilizing standard protocols, reagents and assays, clinical trials in similar study populations would enable comparative assessments of safety and immunogenicity among the various vaccine candidates. However, such head-to-head trials and comparative assessments have not always been easy to achieve due to different antigenic constitutions

## Comparative Phase I/II clinical trials of candidate AIDS vaccines offer the best opportunity for prioritizing vaccines for large-scale efficacy trials.

(e.g., HIV genes included in the vaccine) of the vaccines, commercial concerns related to failing an early-stage clinical comparative trial, and lack of defined endpoints to effectively make such comparisons. When head-to-head Phase I/II trials are not possible, prioritization of candidate vaccines could be achieved by reviewing data from Phase I/II trials conducted independently and supplementary comparative data from non-human primate studies.

Although there is not an ideal animal model for AIDS, more effective use of non-human primate models for AIDS could yield supplemental information in helping to guide vaccine development. However, it should be emphasized again that validation of the animal models awaits the demonstration in humans of a vaccine with protective efficacy, reinforcing the need for an accelerated clinical trials agenda. Thus, data from non-human primate studies should be considered only when sufficient numbers of animals are made available for such head-to-head comparisons of candidate vaccines and studies are conducted with standardized protocols and reagents, comparable to human trials.

Perhaps the two greatest operational issues impeding the accel-

eration of global efforts in AIDS vaccine product development relate to the standard progression of candidate vaccines through clinical development, and the current strategy of conducting sequential rather than parallel trials. Clinical development of vaccines generally progresses from small Phase I safety and immunogenicity studies to larger Phase II safety and efficacy studies. For AIDS vaccines, this standard sequential approach translates into approximately 1.5 years for Phase I trials, 1.5–2.0 years for Phase II trials and more than 3.5 years for Phase III trials (normally with additional and substantial time delays between phases), or a minimum of 7 years of clinical testing before initial consideration for licensure.

Strategies to compress Phase I and II trials would have a significant impact on accelerating overall development timetables. Similarly, although HIV is classified into several genetically diverse subtypes, it remains unclear whether there is any immunologic significance of the extensive genetic variation associated with HIV as it relates to AIDS vaccine design. Thus, while candidate vaccines progressing to efficacy trials have been based on the HIV subtypes

that predominate in the proposed trial population, this current model suggests that sequential efficacy trials in populations where genetically diverse subtypes of HIV are circulating will be necessary to assess the breadth of protection conferred by each vaccine. This could lead to extended delays before effective vaccines are licensed globally. Strategies focused on multiple and parallel efficacy trials would again have a significant impact on accelerating the overall development timetable for AIDS vaccines.

### Regulatory and Political Challenges

The current lack of international regulatory harmonization surrounding the development of AIDS vaccines not only impedes design of multi-country AIDS vaccine trials, but may significantly impede future decision-making surrounding potential worldwide licensure and accessibility of safe and effective AIDS vaccines. Regulatory strategies which take into account both the urgency of the AIDS epidemic where the vaccines will be evaluated and the urgency of the epidemic worldwide, and which may be harmonized regarding requirements for entry into clinical trials, progression through advancing stages of clinical tri-

**Developing countries should  
be full partners in moving  
vaccines forward.**

als, and licensure, would facilitate accelerated product development.

For a number of regulatory and ethical considerations, clinical trials of candidate AIDS vaccines have generally been undertaken initially in the country of origin, before being tested in developing countries where most efficacy trials will be done. Developing country leaders and scientists have, therefore, not been empowered to decide when trials should be initiated. Developing countries should be full partners in moving vaccines forward. Furthermore, this existing strategy may result in additional financial and time costs associated with product development, and thus consideration should be given to fast-tracking clinical trials in developing countries where the epidemic is the greatest while maintaining an effective balance between local cultural norms and recognized international standards of regulatory and ethical approvals processes.

In summary, a combination of scientific, operational, regulatory and political challenges, coupled with less than adequate resources directed at development of AIDS vaccines applicable for use in the developing world, have impeded the oppor-

tunities for accelerating global efforts in AIDS vaccine development and shorten the time lines for success utilization of safe and effective AIDS vaccines.

**Scientific Agenda for  
Accelerating Global Efforts in  
AIDS Vaccine Development**

The foregoing sections have discussed the current status of global efforts in AIDS vaccine development, and identified both progress and challenges in accelerating global efforts in AIDS vaccine development. Since the release of the *Scientific Blueprint* in 1998, significant progress has occurred including the start of the first Phase III efficacy trials of candidate HIV vaccines in both industrialized and developing countries, and the development of promising new vaccine designs including codon-optimized DNA, alphavirus replicon particles, modified vaccinia Ankara and adeno-associated virus vectors, and orally administered DNA vaccines carried via a bacterial vector. It is likely that within the next two years these new vaccine designs will be entering into clinical trials in the developing world, with the most promising progressing toward efficacy trials. The first few product development teams linking vaccine designers in industrialized countries with clinical

researchers in the developing world have been established, and there is greater commitment from both industry and government agencies to AIDS vaccine development. However, in order to significantly shorten the time lines for successful licensure and global utilization of safe and effective AIDS vaccines, a more comprehensive, aggressive and focused scientific agenda must be implemented.

The agenda for accelerating global efforts in AIDS vaccine development focuses on three major areas. First of all, there needs to be continued identification and development of the most promising AIDS vaccine designs focusing principally on vaccine strategies complementary to ongoing programs, and on vaccine strategies applicable for use in the developing world. Secondly, there needs to be mechanisms established to more effectively prioritize the most promising candidate vaccines, such that these candidates can be accelerated into efficacy trials. And finally, there needs to be renewed efforts to shorten time lines in all facets of the vaccine development process, but principally in clinical trials design, vaccine site preparedness, and approvals processes, with the goal of conducting parallel efficacy trials of multiple

There needs to be renewed efforts to shorten time lines in clinical trials design, vaccine site preparedness, and regulatory, political and ethics approvals processes.

vaccine candidates in several high-incidence areas of the developing world. IAVI proposes that an additional US\$900 million to \$1.1 billion (Table 4, Global Scientific Agenda for Accelerated AIDS Vaccine Development) above current expenditures be allocated over the next 7 years specifically for accelerated AIDS vaccine product development and testing for the following purposes:

1. *Identify and develop the most promising AIDS vaccine designs.*

In the absence of a clear roadmap for which individual or combination of HIV antigens are necessary to confer protective immunity, each and all of the respective HIV structural, regulatory and accessory genes may be considered as potentially important components of an effective AIDS vaccine. Since most vaccine candidates currently in the clinical pipeline generally include one or all of the HIV structural antigens (i.e., *env*, *pol*, and/or *gag*), more emphasis is required on determining whether non-structural accessory and regulatory genes provide value as components of candidate AIDS vaccines. Similarly, the absence of a clear understanding of which HIV-specific immune responses are required for protection against HIV suggests that

greater emphasis be given to vaccines that induce a broad spectrum of HIV-specific immune responses. Moreover, since the challenge is not only to create a safe and effective vaccine, but also to make it available to all of those who need it in a timely fashion, vaccine designers need to address the applicability of the vaccine strategy for use in the developing world, where the need is the greatest. IAVI proposes that additional resources on vaccine design be allocated to:

- **Identify and develop multi-genic AIDS vaccine designs, with greater emphasis placed on inclusion of additional HIV regulatory and/or accessory genes into the vaccines.**
- **Identify and develop AIDS vaccine designs that are capable of inducing broadly effective neutralizing antibodies against HIV. A consortium of scientists working together with adequate resources on this specific goal should be established in an effort to complement current global vaccine development activities which have predominantly focused on vaccines aimed at inducing HIV-specific cellular immunity.**
- **Identify and develop AIDS vaccine designs which com-**

**bine technologies to optimize both the effectiveness of the vaccine, such as novel adjuvants and delivery systems, and the applicability of the vaccine (s) for use in the developing world.**

2. *Prioritize the most promising AIDS vaccine candidates for accelerated efficacy trials in the developing world.*

The global effort in AIDS vaccine development will soon be entering into a new phase, where the previously narrow pipeline for candidate vaccines entering into clinical trials will be widening, and thus the decision-making process for which vaccines are accelerated into Phase III efficacy trials becomes of paramount importance. In the absence of an effective decision-making process for accelerating the best candidates through the clinical development process, time lines will inevitably be delayed. IAVI proposes that additional resources aimed at prioritizing the most promising AIDS vaccines be allocated to:

- **Conduct head-to-head comparative Phase I/II clinical trials of AIDS vaccine candidates, to prioritize for accelerating the most promising candidates into Phase III efficacy trials.**

## TABLE 4

**TABLE 4: GLOBAL SCIENTIFIC AGENDA FOR ACCELERATED AIDS VACCINE DEVELOPMENT<sup>a</sup>**

			US\$ Millions
<b>Applied Vaccine Research</b>		\$10M/yr	\$ 70
<ul style="list-style-type: none"> <li>• Assay development</li> <li>• Reagent development</li> <li>• Non-human primate studies</li> <li>• Core immunological infrastructure</li> <li>• Data management</li> </ul>			
<b>Vaccine Design/ Preclinical Development</b>	(n=25)	\$10M/ vaccine over 2.5yrs	\$250
<b>Clinical Trial Preparations</b>	(n=8 regional networks;	\$17M/network)	\$136
<ul style="list-style-type: none"> <li>• Cohorts</li> <li>• Lab infrastructure</li> <li>• Clinical Infrastructure</li> </ul>			
<b>Phase I/II Trials</b>	(n=20)	\$7M/vaccine over 2.5yrs	\$140
<b>Process Development/Scale-Up</b>	(n=10)	\$10M/vaccine	\$100
<b>Phase III Trials</b>	(n=8)	\$30M/vaccine over 3-4yrs	\$240
<b>Manufacturing/Engineering/ Plant Development</b>	(n=2)	\$50M/vaccine	\$100
			\$1036

<sup>a</sup> Represents additional resources (US\$1.036 billion over 7 years), for designing and developing 25 new candidate vaccines, conducting safety/immunogenicity clinical trials on 20 of these candidates, establishing infrastructure for efficacy trials in 8 geographic regions, and initiating 8 Phase III efficacy trials in the next 7 years (to be prioritized from candidates currently in development and/or new candidates).

**IAVI proposes conducting parallel efficacy trials of the most promising vaccines in multiple clinical trial sites.**

- Establish new mechanisms, including dedicated facilities, to provide access to AIDS vaccine designers for sufficient quantities of standardized reagents and assay validation protocols to more effectively compare candidate AIDS vaccines.
- Establish new mechanisms, including dedicated facilities, to provide access to AIDS vaccine designers for sufficient numbers of monkeys and reagents to more effectively undertake pre-clinical safety and immunogenicity studies in non-human primates.

*3. Compress the time lines for successful AIDS vaccine development.*

Although the design of more effective vaccines and development of more effective strategies for prioritizing these vaccines for efficacy trials in the developing world are critical components of the global scientific agenda for accelerating AIDS vaccine development, greater attention needs to be given to strategies aimed primarily at shortening the time lines for successful AIDS vaccine development. Primarily, there needs to be renewed efforts to shorten time lines in clinical trials design, vaccine site preparedness, and regulatory, political

and ethics approvals processes, with the goal of conducting parallel efficacy trials of multiple vaccine candidates in several high-incidence areas of the developing world. To compress the standard time lines for successful AIDS vaccine development, IAVI proposes that additional resources and policies be implemented to:

- Recruit and prescreen potential volunteers for AIDS vaccine trials in advance of the anticipated start date of the clinical trial, so as to shorten the overall time required for recruitment, enrollment and immunizations.
- Initiate clinical trials of AIDS vaccine candidates in either developing or developed country (or both), dependent on clinical development plans designed in partnership between vaccine developers, clinical researchers, and regulatory authorities in developing countries where eventual efficacy trials would be undertaken.
- Combine the Phase I and Phase II trials into Phase I/II, and conduct such trials in parallel in populations at lower risk for HIV infection, and in populations

where larger efficacy trials in high incidence areas of the developing world would most likely be conducted.

- Establish adequate infrastructure to conduct AIDS vaccine efficacy trials in 7–9 regional clinical trials networks, potentially including southern Africa, eastern Africa, western Africa, India, China, SE Asia, South America, Caribbean, and Russia/eastern Europe.
- Conduct efficacy trials of the most promising vaccines in multiple clinical trial sites in parallel, to address the breadth of protection against the diversity of HIV subtypes that are circulating in different geographic areas of the world.
- Provide additional resources for AIDS vaccine product development teams for project management, process development, manufacturing, and scale-up which most vaccine design groups lack, to enable each step in the vaccine development process to be accelerated.
- Provide additional resources for education and advocacy efforts associated with vaccine trial preparedness, including preparations for

The AIDS pandemic mandates new and innovative approaches to accelerating global efforts to shorten the time for successful development and delivery of AIDS vaccines

Phase I/II and large-scale efficacy trials. Such preparations for Phase I/II AIDS vaccine trials should begin at least one year prior to the anticipated start date trials, and 2–3 years prior to initiating efficacy trials.

- Harmonize regulatory requirements for entry of candidate AIDS vaccines into Phase I trials, to advance the most promising vaccines into efficacy trials. This would include simplification and standardization of requirements for licensure.

Figure 7, (Standard and IAVI time lines) outlines the standard timetable for vaccine development, from vaccine design and preclinical development through licensure, which generally takes 12–15 years. In the case of AIDS vaccines, this time line assumes product development in which the vaccine strain is matched against the subtype of HIV circulating in the population where the trial is conducted. For more universal licensing throughout the world, this standard time line assumes that additional post-licensure Phase III efficacy trials (or Phase IV effectiveness trials, if a validated surrogate marker for protection is identified in the Phase III trials) would be undertaken, to test the effica-

cy of the vaccine in populations where different HIV subtypes are circulating, or where the route of transmission of HIV is different (i.e., trials comparing vaccine efficacy in populations of injection drug use vs. sexually transmitted HIV). Such additional and sequential trials would add several years to the time lines for achieving the goal of accessibility of safe and effective AIDS vaccines throughout the world. At a minimum, the standard time line for design, development, and clinical testing of candidate AIDS vaccines for global distribution would be approximately 20 years by conventional processes.

In contrast, implementation of the IAVI proposals listed above to compress and accelerate the time lines for successful AIDS vaccine development would dramatically shorten the time necessary from product design to global licensure by several years and as much as 50% compared with standard product development paradigms (Figure 7, Standard and IAVI timelines). Time savings would occur by streamlining regulatory processes at each step of clinical development, combining Phase I and II trials into Phase I/II, conducting such trials in high-incidence populations where efficacy trials would be conducted, and, most

significantly, conducting multiple and parallel clinical trials of candidate AIDS vaccines in different regions of the world where protection against diverse subtypes of HIV could be assessed.

CONCLUSIONS

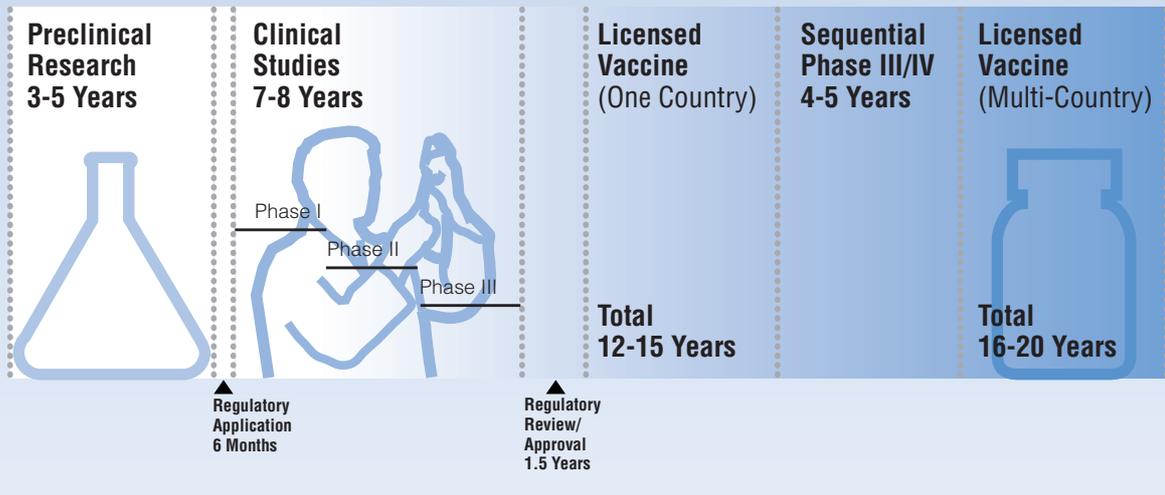
During the past two years, there has been a significant increase in the global investment in AIDS vaccine research and development, initiation of the first efficacy trials of candidate AIDS vaccines, development of promising new vaccine designs which will soon be entering clinical trials, and the recognition that innovative public-private partnerships linking vaccine designers and manufacturers with clinical trials and field researchers in the developing world represents a successful model for expediting development and testing of candidate AIDS vaccines.

However, the continued growth of the AIDS pandemic mandates that new and innovative approaches to accelerating global efforts to shorten the time for successful development and delivery of safe and effective AIDS vaccines for use throughout the world must be advanced as a global public health priority.

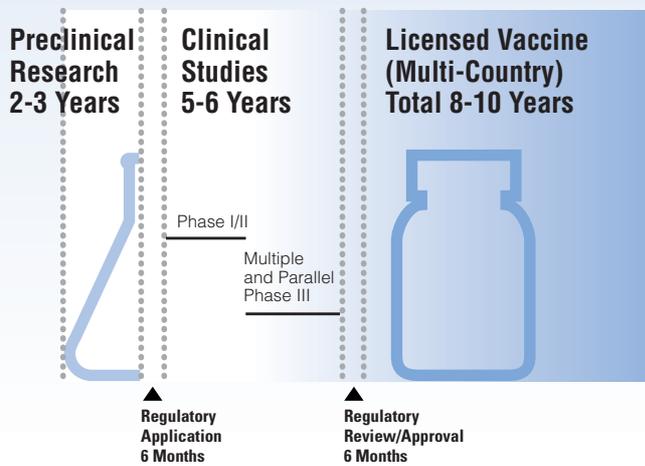
IAVI proposes that to accelerate global efforts in AIDS vaccine development, an additional US\$900 million to \$1.1 billion

FIGURE 7

**Standard Timeline: Research to Product Licensure**



**IAVI Timeline: Research to Product Licensure**



STANDARD TIMELINE

16-20 YEARS

IAVI TIMELINE

8-10 YEARS

An AIDS vaccine would be an international public good of the highest order.

above current expenditures should be allocated over the next 7 years, specifically to be used for accelerated AIDS vaccine product development and testing, focused on the three areas described above. This would significantly increase the potential for more rapid development of safe and effective AIDS vaccines. There needs to be continued identification and development by all of the agencies active in R&D of the most promising AIDS vaccine designs, focusing principally on vaccine strategies complementary to ongoing programs, and on vaccine strategies applicable for use in the developing world.

Secondly, there need to be appropriate mechanisms established to more effectively prioritize the most promising candidate vaccines, including head-to-head comparisons of vaccines in Phase I/II trials, standardization of protocols, reagents and assays to evaluate AIDS vaccines, and more effective use of non-human primate models of AIDS, with the principal goal of accelerating the most promising candidate vaccines into efficacy trials.

Finally, there need to be renewed efforts by all the relevant groups to shorten time lines in all facets of the vaccine development process, but principally in clini-

cal trials design, vaccine site preparedness, and regulatory, political, and ethics approvals processes, with the goal of conducting parallel efficacy trials of multiple vaccine candidates in several areas of the developing world.

Implementation of this comprehensive and global scientific agenda for accelerating AIDS vaccine development has the potential for dramatically shortening the time necessary from product design to global licensure of safe and effective AIDS vaccines by several years, and by as much as 50% compared with standard product development paradigms. **With over 15,000 new HIV infections each day, saving even one day in the AIDS vaccine development time line will have a significant impact. An AIDS vaccine would be an international public good of the highest order.** The world needs to come together and put in place the means to develop and distribute a safe and effective AIDS vaccine.

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