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Todd
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FOR IMMEDIATE RELEASE: December 1, 1998
Contact: Victor Zonana
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IAVI Hails Clinton's 33% Increase in Vaccine Research Funding

Seth Berkley, M.D., president of the International AIDS Vaccine Initiative, issued the following statement upon learning of President Clinton's decision to increase the National Institutes of Health's AIDS vaccine research spending by 33%, to $200 million:

"For too long, AIDS vaccine research has been a poor stepchild to other AIDS activities. This is particularly true for vaccine research aimed at developing countries.

"Therefore, we applaud President Clinton's decision to increase AIDS vaccine research spending by 33%, to $200 million, and for recognizing the international dimensions of this pandemic.

"We are encouraged that the Administration has concluded that a vaccine offers the best hope of ending the global AIDS pandemic.

"We look forward to working with our colleagues at the National Institutes of Health to maximize the impact of this investment.

"We also look forward to working with the Administration to ensure that AIDS vaccines, once available, are made accessible to those who need them most: people living in developing countries."

######

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DATE: December 1, 1998

TO: Todd Summers

CC:

FAX NUMBER: 202-456-2438

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FROM: Victor Zonana

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IAVI REPORT

A Newsletter on International AIDS Vaccine Research — Vol.3 No.1 January-March 1998

INTERNATIONAL AIDS VACCINE INITIATIVE

Using Recombinant Vectors as HIV Vaccines

A wide range of vectors are being studied, but so far only a few have moved into human studies

by Alan Schultz, Ph.D.

Vector-based HIV vaccines consist of harmless viruses or bacteria into which HIV genes have been genetically (recombinantly) inserted. When an individual is immunized with a vector-based (or "live vector") HIV vaccine, HIV proteins or peptides are produced in the body by the vector as it replicates. This will, hopefully, elicit immune responses that can protect those who receive the vaccine if they are subsequently exposed to HIV.

Researchers around the world are studying a wide range of recombinant vectors for use in HIV vaccines. Only a relatively small number of these, however, have moved into human studies. Yet one of the recombinant vector vaccines (Pasteur-Mérieux-Connaught's canarypox construct, given with a gp120 boost) is among the approaches most likely to reach Phase III efficacy studies by the end of the decade.

continued on page 2

Vaccines High on the Agenda at AIDS in Africa Meeting

More than 5,000 researchers, healthcare professionals and activists gathered in Abidjan, the capital of the Ivory Coast, for the 10th International Conference on Sexually Transmitted Diseases and AIDS on 7-11 December 1997. The need for a more aggressive and well-funded HIV vaccine research effort was a key topic of discussion at the meeting.

Speaking at the opening ceremonies, French President Jacques Chirac called for massive new efforts to bring better treatments and a preventative vaccine to developing countries. President Chirac stressed that an HIV vaccine was the only way to eradicate the disease in many parts of the world, including Africa. According to new UNAIDS estimates, more than two-thirds of the world's 30.6 million HIV-infected people live in Africa.

"I realize how difficult it is to develop a vaccine, but this is a goal of such overwhelming importance that everything must be done to achieve it," the French President said. He stressed that France would do whatever was required to secure the support of its European partners in promoting access to treatment and funding for vaccine research. President Chirac also promised to push hard for concrete action at the next meeting of the G-8.

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Starr Foundation Becomes IAVI Founding Partner

As the *IAVI Report* goes to press, we have learned that the Starr Foundation has joined the Rockefeller and Sloan Foundations as Founding Partners of IAVI. In doing so, the Foundation, which is based in New York City, is providing IAVI with an unrestricted grant of US$4 million over three years. We will provide further information on the Starr Foundation and its commitment to advancing the global HIV vaccine effort in our next issue.

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IAVI REPORT

A Newsletter on International AIDS Vaccine Research — Vol.3 No.4 October-December 1998

INSIDE THIS ISSUE

Geneva Overview

Vaccines at the 12th World AIDS Conference

by David Gold

There was certainly no shortage of data at the 12th World AIDS Conference. The meeting, held on 25 June-3 July 1998 in Geneva, featured more than 5,000 abstracts and 400 oral presentations. While vaccine issues were somewhat more visible this year, for the most part they remain a side-issue at the international AIDS meetings. Moreover, the conference agenda presented few opportunities to bring together researchers and experts to discuss key challenges in the field and how to move promising vaccine approaches forward.

That said, the Geneva conference did include an array of interesting vaccine-related presentations. In this overview, we describe many of these.

Wigzell plenary talk on vaccines

In a plenary talk on vaccines, Hans Wigzell of the Karolinska Institute provided a review of AIDS vaccine research and called for an expanded effort in both basic and clinical vaccine research.

Wigzell said that a vaccine that could protect against disease was far more likely than one that

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Remembering Mary Lou Clements-Mann

Loss of leading vaccine researcher, IAVI SAC member leaves large void

The tragic loss of Mary Lou Clements-Mann and her husband, AIDS and human rights pioneer Jonathan Mann, in the Swissair crash on 2 September 1998 leaves a large gap in the overall effort to develop a safe and effective AIDS vaccine.

Clements-Mann, the founding director of the Center for Immunization Research at Johns Hopkins University and a member of IAVI's Scientific Advisory Committee (SAC), was en route to Geneva to attend a series of UNAIDS vaccine-related meetings.

A passionate and tireless advocate for more rapid AIDS vaccine development and testing, Clements-Mann was also an extremely well-respected researcher. And, unlike many AIDS researchers, she had extensive experience in the clinical evaluation of vaccines for other human diseases.

Seth Berkley, IAVI's President, noted that "Mary Lou was a distinguished vaccine researcher and cherished IAVI colleague. Jonathan was a world-renowned AIDS leader and an unyielding defender of human rights and the right to health care for people around the world. Their deaths leave a large void in the ranks of those working to control this global pandemic."

As a founding member of IAVI's SAC, Clements-Mann played a key role helping shape the Initiative's scientific program.

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IAVI REPORT

A Newsletter on International AIDS Vaccine Research — Vol.2 No. 3 October – December 1997

INSIDE THIS ISSUE

INTERNATIONAL AIDS VACCINE INITIATIVE

Proposed Live HIV Vaccine Trials Face Safety, Production Hurdles

U.S. and Australian groups hope to initiate human studies

by David Gold

While a physicians' group and a University of Massachusetts researcher each proposed human studies of a live attenuated HIV vaccine, other researchers warned of the risks posed by the studies and a U.S. company said it could be two years before a product was even ready for testing. At the same time, an Australian research team said human studies of its live attenuated HIV vaccine could begin within 18 months.

The flurry of activity surrounding live attenuated HIV vaccines began in September, when the Chicago-based International Association of Physicians in AIDS Care (IAPAC) announced that more than 50 individuals had volunteered to participate in a study of a live attenuated vaccine, first described by Ronald Desrosiers of the Harvard Medical School (see interview page 6).

Desrosiers and other research teams have shown that live attenuated SIV vaccines could provide impressive protection in monkeys. But concerns began to mount with reports that some newborn and adult monkeys developed simian AIDS from the vaccines (see *IAVI Report*, vol. 2, nos.1 and 2).

To date, at least four research groups report monkeys that show signs of immune suppression after receiving a live attenuated SIV vaccine. These groups include the Aaron Diamond AIDS Research Center, the Dana-Farber Cancer Institute, the Walter Reed Army Institute of Research and Desrosiers' own lab at the New England Regional Primate Center. The

continued on page 2

2,500 Meet in Manila for AIDS in Asia Congress

by James Snodgrass

On 25-29 October, 1997, more than 2,500 delegates gathered in Manila, the Philippines, for the 4th International Congress on AIDS in Asia and the Pacific. Key areas of discussion at the meeting included the explosive spread of HIV in many parts of the region and the need to move candidate HIV vaccines into human studies.

According to IAVI's scientific director, Peggy Johnston, Thailand could well be the location of the first large-scale efficacy trials of candidate HIV vaccines - and sooner than many might think. Speaking at an IAVI-sponsored media briefing, she suggested that "if everything is safe and works...the first efficacy trial could start in Thailand, perhaps by the year 2000." Johnston also strongly praised the Thai effort, noting that the country "has shown international leadership in developing HIV vaccines."

Prasert Thongcharoen, a virologist at Mahidol University in Bangkok, also speaking at the briefing, noted the urgent need for a vaccine in Asia. The Thai researcher suggested that many in his country were willing to volunteer for a vaccine efficacy trial. "We cannot wait for Western

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International AIDS Vaccine Initiative

Scientific Blueprint for AIDS Vaccine Development

June 1998

ADVANCE COPY

NOT FOR DISTRIBUTION

EMBARGOED TO 28 JUNE 1998

International AIDS Vaccine Initiative

Scientific Blueprint for AIDS Vaccine Development

June 1998

International AIDS Vaccine Initiative, New York

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CONTENTS

Executive Summary

Introduction

This *Scientific Blueprint* lays out a detailed global scientific program to put AIDS vaccine development efforts on the fast track. The goal is to identify an AIDS vaccine as soon as possible.

The need for an AIDS vaccine is compelling and urgent. In the past two years, this issue has received a notable increase in international attention. The resources and academic talent devoted to the field of HIV vaccine research is growing. However, efforts to accelerate product development and clinical testing to identify an effective vaccine have not kept pace. The vaccine development pipeline has been likened, appropriately, to a pipette. Few novel vaccine designs have entered clinical trial in the past two years. No efficacy trial of a candidate vaccine has been initiated anywhere in the world, although the first efficacy trial is scheduled to begin in June 1998.

In sum, the world is not on track to meet the bold goal set by the U.S. President, Bill Clinton, to identify a safe and effective vaccine by the year 2007. Further, the effort to ensure worldwide applicability of and access to an AIDS vaccine, once developed, remains largely unattended.

The International AIDS Vaccine Initiative (IAVI) is dedicated to ensuring the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI believes that the goal of identifying an effective HIV vaccine can be achieved in the shortest period of time if additional resources are applied to vaccine development and clinical trials, including the design, development and testing of vaccines for developing countries. Specifically, we believe that multiple efficacy trials of different vaccine approaches around the world must begin within the next four years in order to achieve our goal. The purpose of this *Scientific Blueprint* is to explain the rationale behind IAVI's strategy of increasing support for scientific projects, particularly those more applied and developmental in nature. This document also proposes a new model for international collaboration in HIV vaccine development.

There Is an Urgent Need that Is Possible to Meet

A vaccine is the only way we will end this epidemic, and most scientists now agree that a safe and effective vaccine to stop AIDS is possible. Despite progress in prevention interventions and the advent of powerful drug combinations to treat HIV infection, approximately 16,000 people become infected every day, 90% of whom live in developing countries. An effective vaccine, given prior to exposure to HIV, would help the body control HIV and prevent AIDS and/or transmission of HIV to others. A vaccine that is effective in all high-risk populations worldwide against all circulating HIV isolates is the best hope for halting the AIDS epidemic.

A vaccine is the only way we will end this epidemic, and most scientists now agree that a safe and effective vaccine to stop AIDS is possible.

The Current Multiprong Approach Needs More Prongs

There have been tremendous advances in our understanding of HIV's basic biology. This progress has resulted in large part from the support of national research programs, which generally support basic and targeted research on HIV, develop clinical trial infrastructures, conduct clinical trials, and train researchers.

Despite the desire to have a balanced, multiprong approach of research and development of multiple vaccine designs, support for basic research continues to dominate national AIDS programs. While over 25 candidates have moved into clinical trials, only three have advanced into the second phase of clinical testing, and only one has advanced, just recently, to the stage at which efficacy can be determined.

The current product pipeline is flowing slowly, if at all. There are few novel designs entering phase I trials, and fewer still that have been designed for testing and use in developing countries. A rational and thorough approach would be to continue vigorous support for new, potentially improved designs, while at the same time evaluating the most promising of the known vaccine design options and combinations.

The current product pipeline is flowing slowly, if at all.

Fortunately, there are novel, safe vaccine approaches shown to induce immune responses that could offer protection against AIDS. Those approaches must be developed and moved forward into clinical trials. Those already in clinical trials must also advance.

Almost all designs that have entered human trial have been produced by private sector laboratories, which are generally recognized as the only source of the technical expertise required for vaccine development. This includes construction and formulation of the vaccine for human use, and ensuring that the product is made reproducibly and to acceptable levels of purity, potency, consistency, and stability. Very few manufacturers have been willing to commit to testing multiple vaccine concepts in human trials. The reasons include: the long time frame necessary to accomplish these tasks; the question of whether the product will prove efficacious; the financial risk associated with manufacturing; and several non-scientific disincentives (*i.e.*, uncertainties about market size, and liability and political concerns).

Further, where corporate sponsorship does exist, candidates are being developed for evaluation and use in the United States and Europe. Only a small number of companies are considering the design of vaccines for testing and use in developing countries.

With few exceptions, national programs do not support activities within the private sector that are necessary to bridge the research and development environments and bring products forward for clinical evaluation. It remains unclear to what extent newer programs–including the Vaccine Center at the U.S. National Institutes of Health (NIH), and the European Union focus on vaccines–will result in the entry of innovative vaccine designs into clinical trials, particularly trials in developing countries.

The urgency of the epidemic demands that all reasonable avenues be explored. A linear, stepwise approach is unacceptable. A more aggressive, multipronged strategy is far more likely to rapidly solve scientific problems and identify promising approaches.

Increased Involvement of Developing Countries Is Essential

Developing countries–in which the need for a preventive HIV vaccine is greatest–have been only peripherally involved in the HIV vaccine development process. A few countries, with the assistance of UNAIDS and/or the U.S. NIH, have been active in preparing sites for the field testing of HIV vaccines. Fewer still (Thailand, Brazil, China, Cuba) have actually conducted a phase I trial of a candidate HIV vaccine,

and only one country currently shows evidence of significant contributions to all stages of vaccine development. Thailand is distinct in that it has evaluated multiple designs in phase I/II trials; will initiate an efficacy trial in the coming year; and has multiple, active collaborations designed to advance newer vaccine designs into clinical trial.

Multiple efficacy trials of candidate HIV vaccines will be necessary, and these trials will be best conducted in populations at highest risk. Such populations generally reside in developing countries. Unlike the development of most established vaccines, which were first found efficacious in industrialized countries, achievement of an HIV vaccine will require developing countries to become active and long-term partners throughout the development process.

Further, full involvement of developing countries is the most likely route to ensuring that intellectual property arrangements will be structured to provide accessibility and use of eventual products in locations where they are most needed. Involvement of developing countries in all stages of vaccine development will also allow them to consider and solve, on their own terms, the difficult issues of risk/benefit analysis and ethics.

Scientific Issues that Have Limited Developing-Country Participation Can Be Addressed

This key scientific uncertainty has thwarted trials in developing countries: the continued uncertainty about the relevance of different genetic clades to HIV vaccine development. With few exceptions, manufacturers have based their vaccines on laboratory isolates of clade B HIV, the subtype of HIV that predominates in North America and Europe. A long time frame and commitment to process development and manufacturing accompanies a private company's decision to develop a candidate vaccine. For these reasons, it is difficult, time consuming, and costly for a company to adapt a design to the more recently described "primary isolates" of HIV, or to isolates from other clades of HIV. Nonetheless, a few companies are now developing candidate vaccines based on primary isolates and/or clades that predominate worldwide. Biotechnology companies, which are better positioned for risk taking, have generally been unable to raise the venture capital to support aggressive HIV vaccine-development programs. This is particularly true of designs based on the most prevalent HIV clades.

It may be that the 10 or so genetic clades of HIV will prove irrelevant to HIV vaccine design. Recent evidence has shown that CTLs (immune cells that recognize and destroy cells with signs of HIV infection) isolated from people infected with clade B HIV can kill at least some isolates from at least some other clades. However, "universal killing," in which CTLs kill cells infected with any isolate from all clades, has yet to be described. In addition, while there appear to be conformational epitopes that are shared among the various clades, researchers have yet to design antigens that induce antibodies against those epitopes.

In the absence of definitive knowledge about the immunologic significance of genetic subtypes or a clear definition of immunotypes on which a vaccine can be logically based, candidate vaccines tested in individuals at risk for HIV infection should be based on the HIV subtype(s) that predominate in the proposed trial population. Alternatively, there could be justification to advance to larger trials a "mismatched" vaccine

Multiple efficacy trials of candidate HIV vaccines will be necessary, and these trials will be best conducted in populations at highest risk.

that has been shown to induce strong immune responses in the proposed trial population against the spectrum of viruses that circulate in that population.

However, this approach is potentially time consuming. For example, if the "mismatched" vaccine fails to induce adequate immunity, the question would remain as to whether the vaccine lacked efficacy because of the design itself, or because the design was not based on circulating virus isolates. If new and novel vaccines are to be pursued toward clinical trial, there is no apparent reason why those vaccines should not be based on the HIV subtypes that are most prevalent worldwide.

Involvement of developing countries in all stages of vaccine development will allow them to consider and solve, on their own terms, difficult issues of risk/benefit analysis and ethics.

A "Thoughtful Empiricism" Approach to HIV Vaccine Development– the Rapid, Definitive Testing of Candidate Vaccines–Is Needed

There are significant scientific and technical questions that bring a great deal of uncertainty to the development of HIV vaccines. Foremost among them are the lack of validated correlates of immune protection and the absence of an ideal animal model of HIV disease. While these questions remain, it will not be possible to definitively conclude from small clinical studies or animal studies whether any specific candidate vaccine is effective. Appropriately designed larger clinical trials in humans will be required to determine if and to what extent a vaccine works.

HIV vaccine research and development is at a crossroads. The scientific community could step back and put its full weight behind tackling these basic research obstacles, and move candidate vaccines forward when there is consensus that the vaccine is likely to be protective. This approach might be defensible if the rate of spread of HIV were low or tapering off. However, worldwide statistics demonstrate otherwise. Further, there are a number of examples in which other vaccines have proven successful without ever knowing the correlate of immune protection, and/or in which an ideal animal model was lacking.

Given the urgency of the epidemic and the failure of other measures to control the spread of HIV, it is time to give significantly more weight to HIV vaccine development. In particular, more human research on more candidate vaccines is needed, including vaccines designed for and tested in developing countries. All reasonable candidate vaccine designs should enter phase I trials to evaluate safety and immunogenicity. The best designs that prove safe and that induce immune responses that could reasonably be argued might be protective should advance into phase II clinical studies in individuals at higher risk for HIV infection, and eventually into larger trials to determine efficacy.

This rapid, definitive testing of candidate vaccines is called "thoughtful empiricism." Its value is twofold: First, such trials will help identify efficacious vaccines. Second, they will to generate immunologic data that can lead to improved vaccine designs. The only truly "failed" trials are those that do not yield useful scientific information.

This process will take years and millions of dollars in addition to what is already being spent on basic and targeted research, and on smaller clinical trials.

A Sense of Urgency Must Prevail

When President Clinton set the goal of identifying an effective vaccine by the year 2007, leaders of the Group of 8 (the world's largest economies) followed with their own pledge: to provide the necessary resources to accelerate HIV

vaccine research. Leaders from other countries should accept this challenge.

The goal appears to have been largely ignored in the new grant programs heralded by the U.S. NIH and others. National programs have fostered basic research on HIV and HIV vaccine designs, but have not increased the development and clinical trials efforts needed to meet this goal.

The time required for the mandatory preclinical and clinical evaluation of experimental HIV vaccines is quite long, approximately seven to eight years. Unless there is an immediate breakthrough in vaccine design, it is highly unlikely that new basic knowledge will contribute to an effective vaccine by 2007. If an effective vaccine is to be identified by then, only those products already in or near the preclinical stage have any chance of fulfilling the goal. All designs that have shown promise in preclinical and clinical studies should advance through the pipeline as rapidly as possible.

New Models of International Cooperation in HIV Vaccine Development Are Needed

IAVI believes that new mechanisms should be established to foster true international partnerships in HIV vaccine research and development. Toward that end, IAVI has developed a distinctive scientific strategy for the world. Specifically, we propose creation of international product development teams, which would bring together vaccine designers, vaccine developers/companies, and clinical researchers from both industrialized and developing countries to work together on all stages of the development process. Each team would focus on one specific vaccine approach.

This worldwide strategy has been designed to complement, not compete with, existing programs at UNAIDS, NIH, the French National AIDS Research Agency, and other national and international organizations. The approach, at a cost of approximately US$350 million-$500 million above current expenditures over the next nine years, emphasizes cooperation with industry and has evolved from extensive consultations with leaders of national and international organizations and industry.

IAVI's strategy is unique in that it focuses exclusively on accelerated product development and testing through international collaborations. The challenge in executing a fast-track HIV vaccine development strategy is to ensure that the most promising new candidate vaccines are tested as rapidly as possible in the best clinical and field study sites. While this tactic may seem obvious, there is no ready mechanism whereby researchers with an exciting new vaccine can identify and establish direct collaborations with clinical and field researchers and populations in epidemic locations.

IAVI's strategy is unique in that it focuses exclusively on accelerated product development and testing through international collaborations.

The need to match vaccine approaches with epidemic locations for testing can be met by creation of international product development teams. This is the concept: Assemble a team of vaccine researchers, manufacturers, and clinical researchers around a candidate vaccine product *before* a pilot lot is produced. In this way, a comprehensive and seamless vaccine development plan can be formulated and adhered to. Such a team should have an international composition because new technical approaches traditionally derive from laboratory research in industrialized countries, while the epidemic locations with the highest incidence of HIV are typically in developing countries. The exact institutional composition of

each team would vary according to the range of expertise among team members. Scientists from the developing country would be expected to work closely with scientists from industry.

Conclusions

Even given the ongoing and planned efforts of the private and public sectors, critical gaps in HIV vaccine development must be filled if an effective vaccine is to be ready within nine years. Foremost among these is the need for enhanced global political commitment to ensure that every promising new vaccine approach is clinically evaluated for safety, immunogenicity, and efficacy as rapidly as possible. Several promising new approaches should be designed for and tested in developing countries hardest hit by HIV and AIDS, and plans should be laid for several phase III efficacy trials.

The need to match vaccine approaches with epidemic locations for testing can be met by creation of international product development teams.

The urgency of the worldwide AIDS epidemic relative to ongoing vaccine development and clinical-trial efforts begs for creation of new models of international collaboration. Models that include developing-country participation throughout the vaccine-development process have the best chance for success and will best address worldwide needs. Toward this end, IAVI proposes the model of international HIV vaccine product development teams that bring together research, manufacturing, and clinical-trial expertise to accelerate development and evaluation of promising vaccine designs.

I. Introduction

The need for an HIV vaccine is compelling and urgent. In the past two years, this issue has received a notable increase in international attention. The resources and academic talent devoted to the field of HIV vaccine research are growing. However, efforts to accelerate product development and clinical testing to identify an effective vaccine have not kept pace. The vaccine development pipeline has been likened, appropriately, to a pipette. Few novel vaccine designs have entered clinical trial in the past two years. No efficacy trial of a candidate vaccine has been initiated, although the first is scheduled to begin soon.

In sum, the world is not on track to meet an important goal set by the U.S. President, Bill Clinton: to identify a safe and effective vaccine by the year 2007. Further, efforts to address the international imperative for an HIV vaccine remain largely unattended.

The International AIDS Vaccine Initiative (IAVI) is dedicated to ensuring the development of safe, effective, accessible, preventive vaccines for use throughout the world. IAVI is urgently pursuing this objective through three complementary strategies:

- **Build worldwide demand for HIV vaccines** by mobilizing growing public and government support for accelerated vaccine development
- **Advance scientific progress toward a vaccine** by identifying gaps, working to fill them, and advancing promising candidate vaccines
- **Foster an environment for successful vaccine development** by expanding public/private collaboration and investment in a global vaccine effort

IAVI believes that the goal of identifying an effective HIV vaccine can be achieved in the shortest period of time if additional resources are applied to vaccine development and clinical trials, including trials in developing countries. The purpose of this *Scientific Blueprint* is to explain the rationale for the second of IAVI's strategies–to advance progress through increased support for scientific projects, specifically those that are applied and developmental. IAVI also proposes a new model for international collaboration to further HIV vaccine development.

II. The Urgent Global Need for an AIDS Vaccine

The need for a preventive HIV vaccine is compelling. Recent UNAIDS statistics estimate that a worldwide total of 30.6 million people were living with HIV in 1996, and that an additional 16,000 people become infected every day. Most new infections (approximately 90 %) are occurring in developing countries, where non-clade B HIV strains predominate (Figures 1, 2). The economic impact alone of HIV in several African countries could amount to a loss of more than 10% of potential economic production by the year 2000. Behavior-change education and access to prevention tools such as condoms have been shown to help people markedly decrease risk of HIV transmission. However, these interventions do not reduce risk to zero, nor will they ever be fully accessible worldwide. Such prevention measures will therefore not, by themselves, halt the epidemic. In addition, while microbicides are being developed that are woman-controlled and potentially inexpensive, they will require frequent use and neither their efficacy in controlled clinical trials nor their utility for long-term impact on a viral epidemic has been demonstrated.

Innovative treatments for HIV infection and associated opportunistic infections

The resources and academic talent devoted to the field of HIV vaccine research are growing. However, efforts to accelerate product development have not kept pace.

Figure 1. Persons Living with HIV/AIDS, And Most Prevalent Clades

(Thousands)

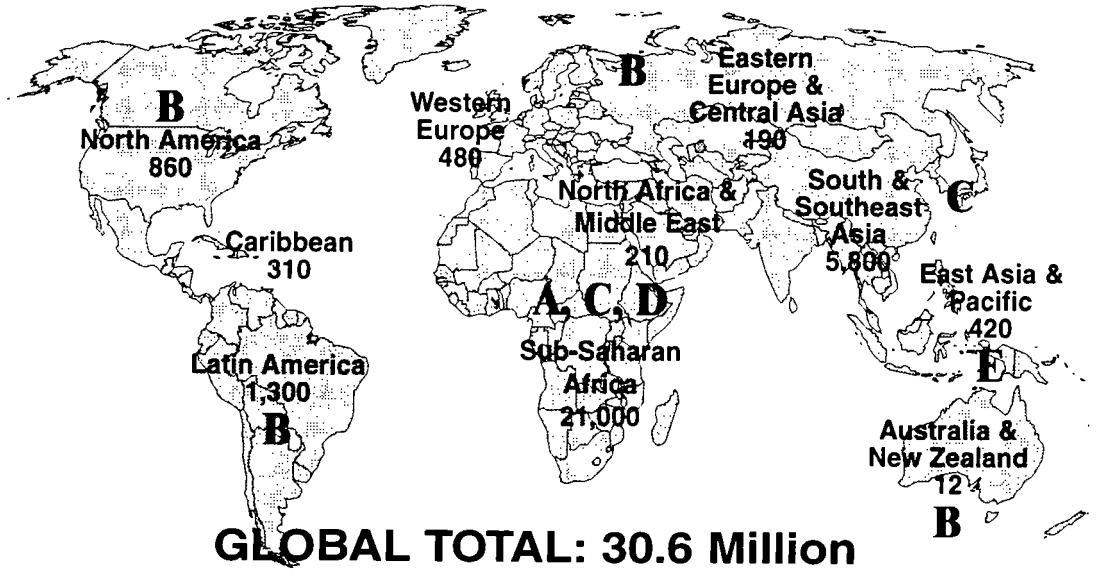
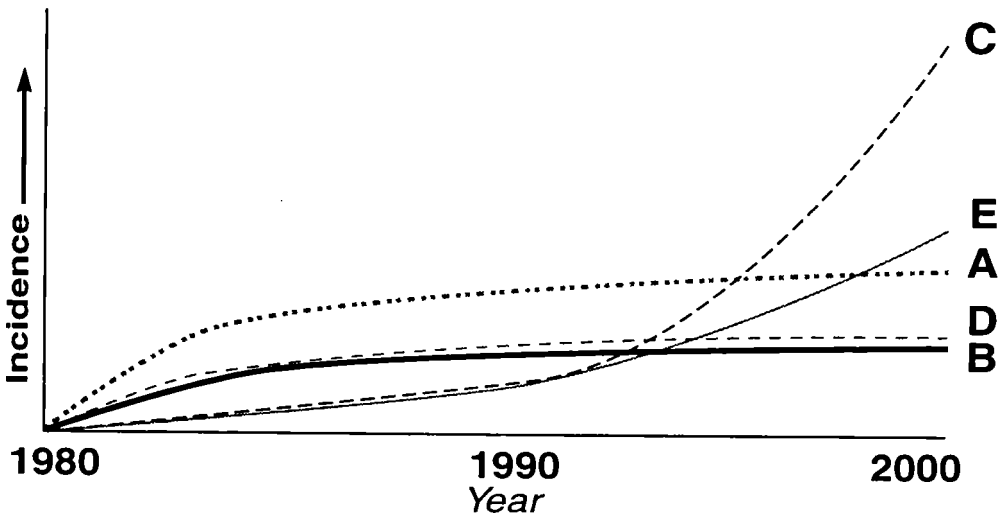


Figure 2. Incidence of HIV-1 Clades

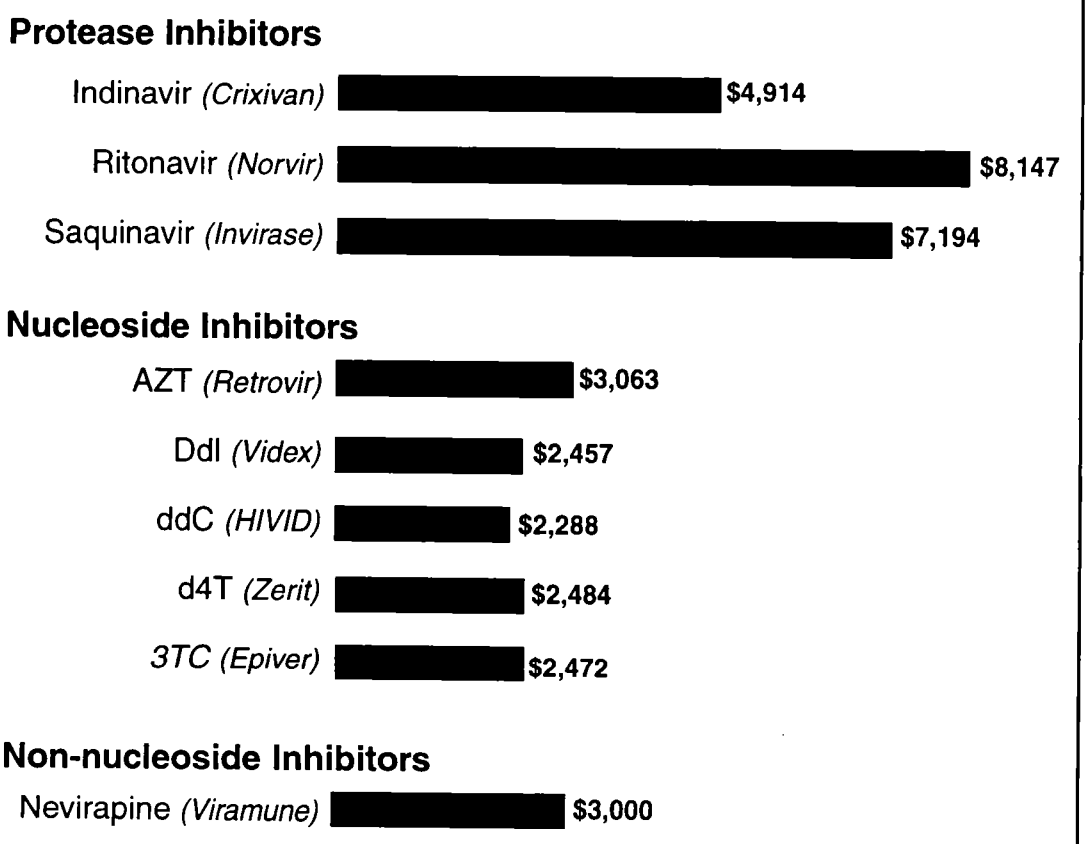


Rough IAVI projection of clade incidence, based on HIV incidence and estimates of clade distributions.

have improved the length and quality of life for individuals with HIV who have access to and can afford such therapies (Figure 3). However, global access to these expensive drugs will remain limited; few developing countries have the infrastructures to ensure appropriate use of these drugs; and development of resistance will limit their long-term effectiveness, even in locations where treatment decisions can be based on viral load monitoring.

Finally, there are no data available concerning the long-term effect of current therapies on health and on HIV transmission. Even when current treatment regimens are available, in the absence of an effective vaccine HIV infection most likely will remain an incurable, ultimately fatal disease. The best hope for preventing the spread of an infec-

Figure 3. Estimated Annual Cost of Anti-HIV Therapies



Adapted from *AIDS Treatment Data Network*. Source: Jerri Tolson, Ph.D., 2/18/97

tious agent such as HIV is the development, distribution, and use of a safe, accessible, affordable, effective preventive vaccine.

The Ideal Vaccine

A vaccine is a substance that teaches the immune system to recognize and protect against a disease caused by an infectious organism or virus. An effective HIV vaccine given before exposure will protect the vaccine recipient from HIV disease. If the virus is never detected, this would be referred to as "sterilizing" immunity. However, it is unlikely than an HIV vaccine, or any vaccine, would induce sterilizing immunity. Vaccine-induced immunity more probably would result in a transient infection, in which the virus replicates for some time and then becomes undetectable, with no signs of disease in the vaccine recipient and no transmission to others. Alternatively, a successful vaccine could induce a protective immunity that holds the virus in check for the person's lifetime. Thus, progression to AIDS would be prevented and the level of virus kept so low that it could not spread to others, including from pregnant mothers to their children.

A formidable challenge in vaccine development is the enormous genetic diversity of HIV found worldwide. There are now 10 or more genetic subtypes, or "clades," of HIV-1 that have been characterized. Only one of these subtypes, subtype B, predominates in industrialized countries (Figure 1). The ideal vaccine will protect immunized

individuals against AIDS if they become exposed to any subtype of HIV.

The ideal vaccine will be effective worldwide, regardless of the ethnicity and nutritional and health status of the target population. The ideal vaccine will also protect against any route of HIV infection (vaginal, rectal, or oral sex; intravenous exposure; perinatal transmission); be inexpensive to manufacture; easy to transport and administer, even in remote areas of developing countries; stable under field conditions; and require few if any follow-up inoculations.

The ideal vaccine will be effective worldwide, regardless of the ethnicity and nutritional and health status of the target population.

Further, the ideal vaccine will have the capability for production in adequate quantities at an affordable cost, and have physical characteristics that make it amenable to worldwide distribution.

Given the rate of spread of HIV worldwide, even a less-than-ideal vaccine could provide substantial public health value and help contain the epidemic. For example, while a vaccine that gives lifetime protection to only 50% of recipients might not be suitable for licensure in the United States or Europe, where the epidemic has slowed and drug treatments are available, such a vaccine could have significant value in populations in which the disease is spreading at a high rate and other interventions are not widely available. Similarly, a vaccine that only protected against one route of transmission (*e.g.*, maternal-child transmission) could be of public health value if targeted to those populations.

An HIV Vaccine Is Possible

There is now almost complete agreement among scientists that an effective HIV vaccine is possible. This confidence comes primarily from several observations. First, a small number of individuals appear to have been repeatedly exposed to HIV, yet remain uninfected. Their ability to resist infection does not seem to be linked with any genetic variation that impacts the ability of their cells to be infected with HIV. Rather, they appear to have HIV-specific immune responses, that is, cytotoxic T lymphocytes, which could explain their resistance to infection.

In addition, there are now several candidate vaccine designs that have shown some ability to protect monkeys from infection and/or disease caused by a virus very similar to HIV, the simian immunodeficiency virus (SIV). A few candidate HIV vaccines have protected chimpanzees from HIV infection.

The major reasons for confidence are listed in Table 1.

Table 1.
Why an HIV Vaccine Is Possible

- Vaccination has been successful in halting other viral diseases.
- Experimental vaccines have protected nonhuman primates from infection and/or AIDS-like illness.
- Some candidate vaccines have induced strong immune responses in almost all human volunteers and have proven safe to date.
- Some humans may have virus-induced immune responses that appear to have protected them from HIV infection (*e.g.*, highly exposed, uninfected individuals).
- All individuals infected with HIV control HIV infection for some period of time before becoming ill; a small percentage of infected individuals have no signs of disease even after 15 years (*e.g.*, long-term nonprogressors).
- Lowering viral load in infected individuals provides a clinical benefit. A vaccine that helps the individual control viral load for a long period of time, perhaps lifetime, may enable the recipient to remain healthy and prohibit transmission of the virus to others.
- Mucosal transmission of HIV is relatively inefficient compared with intravenous exposure; protection from mucosal exposure to HIV may not require as strong an immune response as protection from intravenous exposure.

III. Conventional Approaches to Vaccine Research and Development

For any successful vaccine R&D effort, basic research is necessary to isolate and characterize a disease-causing organism, to discover methods to effectively immunize and protect susceptible hosts, and to develop assays to measure immune responses and eventually identify immune correlates of protection. A wide variety of scientific disciplines, such as molecular and cell biology, virology, immunology, pathogenesis, natural history, and epidemiology all contribute to the groundwork necessary to produce vaccines.

The process of vaccine R&D itself, as opposed to basic research, can be divided into three critical steps:

1. Targeted research, including vaccine discovery and "proof-of-concept" animal model studies

2. Manufacturing and preclinical development

3. Clinical and field testing in humans

Although there is frequently partial overlap in the timing of these steps, each is summarized separately below.

Targeted Research

Vaccine R&D begins when a researcher combines existing knowledge about immunology, pathogen structure, epitopes for inducing immune response, and available viral stocks, reagents, assays, and animal models, to design or "discover" a new candidate vaccine. The researcher produces this candidate vaccine or its animal model equivalent and studies it to determine if it is safe and what immune responses it induces in small animals and primates. The researcher may also test the concept for protective efficacy in an animal model. Based on these results, the design might be modified to improve its safety, immunogenicity, or efficacy in the animal model. This research is usually done with experimental vaccines prepared in the laboratory. Most discovery and targeted research is supported by large national research programs in industrialized countries such as the United States, France, and Japan. Several companies also support small-scale efforts in this area.

Manufacturing and Preclinical Development

Based on results from targeted research, a vaccine sponsor, usually a private sector manufacturer, selects the "candidate vaccine" and moves it into a formal development program. This requires a significant commitment of people and resources.

The manufacturer must gather the necessary viruses, reagents, and animals; create and validate standardized assays for measuring immune responses and other biological and/or chemical characteristics of the product; decide how the vaccine will be constructed and formulated for delivery; construct and evaluate the vaccine product in animals; and explore the route, dose, and schedule of product administration in animals.

In addition, the manufacturer must demonstrate that the product

- is made in a consistent, cost-effective manner;

- can be produced to the necessary scale to meet supply;

- meets specifications using validated

assays, even after scale-up;

- is stable for known amount of time under field conditions;

- meets all regulatory requirements for testing in humans, particularly with respect to safety, purity, consistency, stability, and potency.

Clinical and Field Testing in Humans

Safe and immunogenic candidates are selected from the range of experimental vaccines that have been studied during targeted research and preclinical development processes. These candidates are tested in human volunteers to determine their safety, biological activity, and, eventually, efficacy in humans.

A preventive HIV vaccine will be effective in controlling the global epidemic only if it is distributed and used throughout the world.

The stages of clinical testing include:

- Phase I—testing in small numbers (15-100) of individuals at low risk for HIV infection to evaluate safety and biological activity (immunogenicity), typically in a dose-escalating fashion. In addition, manufacturers often use small clinical trials to demonstrate consistency in their ability to manufacture the product.

- Phase II—testing in larger numbers (hundreds) of individuals at high risk for HIV infection to evaluate safety and biological activity and/or to determine the optimal dose and schedule of administration. Phase II trials (sometimes called "intermediate" sized trials), appropriately designed and controlled, can provide a broadly defined estimate of efficacy.

- Phase III—testing in individuals at high risk for HIV infection to determine efficacy (usually in thousands of subjects). The size of the trial depends on the incidence, expected efficacy, and statistical considerations.

After the process of clinical development, if a vaccine is determined to be safe and at least partially effective, the sponsor will seek to manufacture, market, and distribute it or license it to another company for one or more of these purposes. A preventive HIV vaccine will be effective in controlling the global epidemic only if it is *distributed* and *used* throughout the world. The major incentive for any company to engage in preclinical and clinical development of an HIV vaccine is the potential for return on investment after the cost of development, licensure, manufacture, marketing, and distribution.

An adequate infrastructure is needed to conduct clinical trials of candidate vaccines. The preparation of clinical trial sites and potential volunteers requires considerable time and effort. HIV-related trials present even more challenges, particularly when there is a need to conduct vaccine trials in developing countries; where infected or at-risk individuals are stigmatized; or when a large number of volunteers is needed.

The infrastructure for conducting phase I vaccine trials is in place in many academic centers of industrialized countries and selected developing countries. For diseases such as AIDS, where there is no completely successful and available treatment, phase II and III trials require enrollment and retention of individuals at risk for infection. Depending on the at-risk population, enrollment in phase II and III trials can be relatively straightforward (*e.g.,* children, college students) or extremely complex (*e.g.,* commercial sex workers, injection drug users). Alternatively, trials that enroll and randomize entire communities in which the risk of HIV infection is high may also be feasible. In either case, infrastructure is key to ensuring that multiple HIV vaccine trials can be conducted. In most coun-

tries, infrastructure development will require considerable resources invested over many years (see Appendix D).

Vaccine development is typically a reiterative process, in which results from clinical studies of candidate vaccines help guide the design of potentially improved vaccines. In addition, results from clinical studies are necessary to validate whether a particular laboratory assay or animal model correlates with protection in humans. When candidate vaccines do not move forward in clinical trials and efficacy trials are not done, no definitive evidence of a vaccine's effectiveness is known. Nor can we make progress on understanding the correlates of immunity. Subsequent vaccine design is guided only by laboratory and animal studies, and can be potentially ill-informed, as the history of vaccine development has demonstrated.

IV. Current Global HIV Vaccine Research and Development Efforts

Since the discovery in 1984 that HIV is the cause of AIDS, there has been considerable scientific progress toward an HIV vaccine. Both public and private sector entities have made significant contributions to achievements thus far.

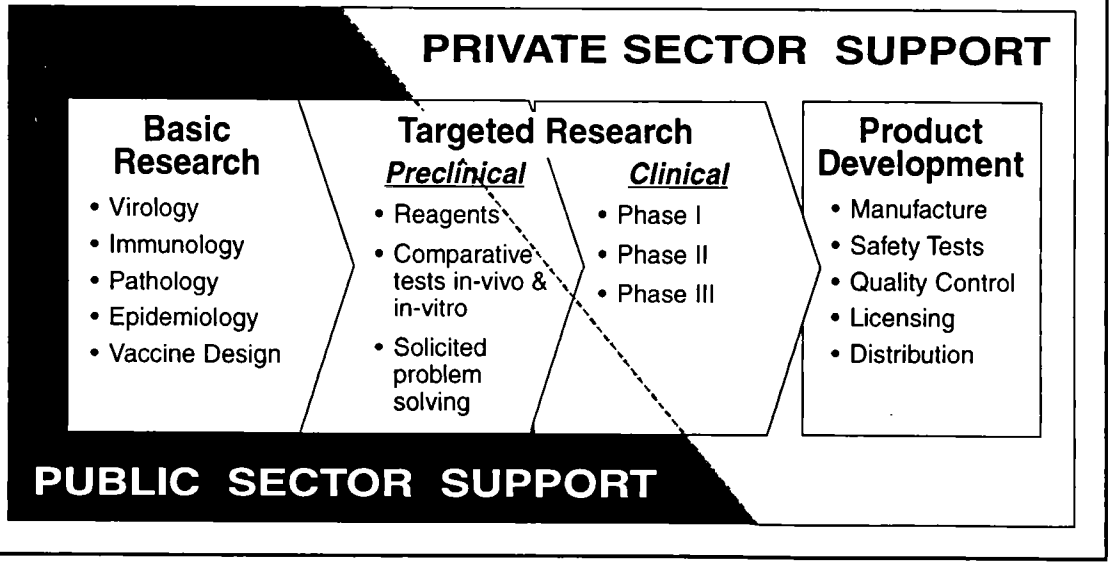
Role of Government Agencies

Government agencies play multiple roles in vaccine research and development. Most important, government agencies support both basic and targeted biomedical research on the disease in question, develop clinical-trial infrastructures, conduct clinical trials, and train researchers (Figure 4).

Simply stated, basic research provides information on the structure and activity of pathogens, the mechanisms of immune defenses in general, and the interaction between pathogens and the immune system. Targeted and clinical research seeks to develop tools and methods to evaluate vaccines, and provides detailed information on the biological activities of experimental vaccines in animals and human volunteers. Infrastructure development ensures that vaccine trials can be carried out in a manner that gives valid answers about vaccine safety, activity, and efficacy. Training activities help ensure that there are appropriate cadres of investi-

When candidate vaccines do not move forward in clinical trials and efficacy trials are not done, no definitive evidence of a vaccine's effectiveness is known.

Figure 4. Who Pays For Vaccine Development



gators capable in the diversity of functions necessary to conduct both preclinical and clinical research on experimental vaccines, including vaccine-related social and behavioral research.

Government programs in many industrialized countries, especially the United States, devote considerable resources to these activities. While the majority of funds go to investigator-initiated basic research grants, government officials can solicit grants or contracts to address specific research questions or needs that are not adequately addressed through investigator-initiated mechanisms.

In addition, government agencies regulate vaccine development. In most countries, government approval of the product and clinical protocols must be obtained prior to each clinical trial of experimental vaccines in human volunteers. Regulatory agencies also decide whether vaccine products are approved for marketing and export/import.

Role of the Private Sector

While government programs support laboratory, animal, and clinical studies of candidate vaccines, government and academic researchers generally do not have the expertise or resources to translate new ideas into material suitable for testing in humans (Figure 4). This is the case even when the desired product can be well defined in advance. In the words of one industry leader:

> *. . . It is generally recognized that much of the technical expertise and infrastructure required for HIV vaccine development is present only in industry.*
>
> (Gordon Douglas, M.D.
> President, Merck Vaccines
> Congressional Task Force
> May 1997)

Production of vaccines under Good Manufacturing Procedures (GMP)–manufacturing procedures and documentation required by regulatory authorities such as the U.S. Food and Drug Administration for human testing, licensure, and export/import of drugs and vaccines–requires specific technical know-how and considerable financial resources. Thus, clinical researchers generally depend on the private sector or specialized laboratories to carry out the steps in preclinical development (outlined in section III) before testing a vaccine in human volunteers.

Companies that elect to participate in vaccine development face two key decisions. The first is to select a clinical candidate and initiate preclinical development. Although different companies prefer different data prior to making this decision, moving a candidate into development demands a significant commitment of resources. The manufacturer creates a process for producing the vaccine consistently and to acceptable specifications for safety, purity, potency, and stability. Manufacturers must provide an accurate, detailed description of the manufacturing process for regulatory agencies. In addition, the assays used to evaluate the product must be validated.

These include assays for "in-process" testing as well as assays to evaluate the final product. Final product (final bulk and/or final container) testing should include safety, purity, potency, sterility, and identity. In addition, stability data must be obtained to demonstrate that the product is stable over a determined period of time in order to establish an expiration date.

The second key decision is to build a facility that will produce the vaccine in sufficient quantities to meet demand. Designing a facility can cost US$10 million to $15 million, and as much as

US$150 million can be required for construction. The process of design and construction typically takes four to five years and often must be initiated before efficacy trials begin so that sufficient product is available after approval. Indeed, regulatory agencies are unlikely to approve a product unless supply can meet demand.

Another difficulty in making the decision to build a manufacturing facility is that it is not possible to construct a plant to produce a particular vaccine until the manufacturer knows what the product is and how to make it. This is a particularly tough problem in the absence of a marker for efficacy that can help assure companies that the product they take into efficacy trials is likely to succeed.

Manufacturers may choose to use product made at full scale in the facility intended for licensure for their pivotal efficacy trial. Alternatively, the vaccine used during clinical development, including in the pivotal trials, may be manufactured at a smaller scale than that intended for licensure and/or at a different facility than that intended for licensure. In the case of scale-up, the manufacturer usually needs to demonstrate that the scale-up product is clinically equivalent to the material used in the efficacy trials. Typically, this is accomplished with a comparative clinical "bridging study" that has immunogenicity and safety as endpoints. Other manufacturing changes prior to licensure may also necessitate a clinical bridging study. In addition, clinical bridging data may be requested if there is a change in facility.

However, at least with regard to the U.S. Food and Drug Administration, the manufacturer is not precluded from seeking licensure for a smaller scale of production and/or at a "pilot" facility, if that facility will be used at least initially following approval. But the manufacturer must submit a supplement(s) to its approved license application with supporting data in order to request a change in manufacturing scale or for other changes.

It is more typical for companies, particularly large vaccine manufacturers, to move into manufacturing prior to the efficacy trial. This is usually an extremely costly gamble, but it can ensure that the product tested in the efficacy trial is identical to the product intended for market, and also that sufficient product will be available to meet demand post-licensure.

In general, industry claims that development of a new pharmaceutical product takes an average of 10 years at a total development cost of US$150 million-$250 million.

Activities of Specific Public Sector Agencies and Institutions

Aside from the pharmaceutical and biotechnology industry, the largest sources of funding for HIV vaccine research and development are the government-supported research programs of the United States, France, and other countries belonging to the Organization for Economic Cooperation and Development. The largest of these programs is the U.S. National Institutes of Health (NIH). The French National AIDS Research Agency (ANRS) and the U.S. Walter Reed Army Institute of Research (WRAIR) also fund significant HIV vaccine initiatives. Other programs include the European Commission's European Vaccine Against AIDS (EVA), Britain's Medical Research Council (MRC), and activities of the national research agencies of Japan and Canada.

The role of these national research agencies has historically been threefold: active research to develop baseline knowledge and technologies for public health; support of a public health infrastructure for clinical evaluation of new health products; and support for the training of clinicians and researchers. With regard to research for HIV vaccines, these government agencies have largely kept to their historic roles.

U.S. National Institutes of Health: In the United States, the NIH Office of AIDS Research has defined NIH's HIV vaccine research and development program as encompassing three components:

- Basic research related to HIV vaccines
- Targeted research on HIV vaccine concepts
- Support for clinical trials networks and the conduct of clinical trials

To date, the NIH has not funded preclinical vaccine development, as defined in section III, to any significant level.

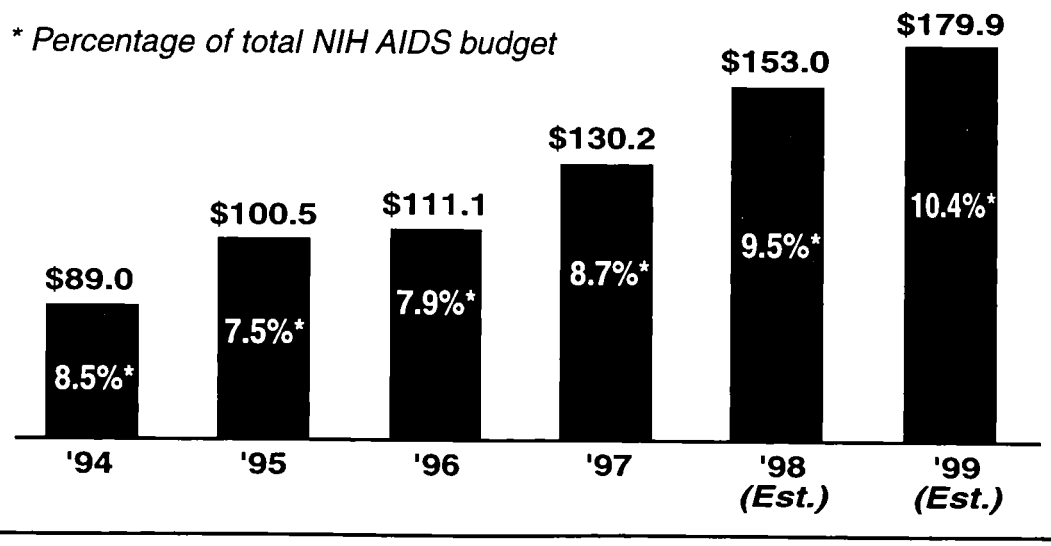
In part because of the advocacy of IAVI and others, the U.S. government has given increased attention to HIV vaccine research in the past two years.

Specifically, the NIH supports extensive academic research in the areas of HIV structure, molecular biology, immunology and virology; supplies research reagents and challenge virus stocks; and supports animal studies. The NIH also supports a network of vaccine clinical trial sites in 12 U.S. cities and in several African, Asian, Latin American, and Caribbean countries.

Perhaps in part because of the advocacy efforts of IAVI and others, the U.S. government has given increased attention to HIV vaccine research in the past one to two years. Expenditures for HIV vaccine research have increased and are estimated to exceed US$150 million in 1998 (Figure 5). This gain was possible primarily because of substantial increases in the overall NIH budget. The percentage of the total NIH AIDS budget coded as vaccine research remains under 10%, and the largest increases have gone to basic research on HIV vaccines.

The NIH has established a new AIDS Vaccine Research Committee (AVRC) under the direction of David Baltimore, a Nobel laureate. President Clinton has held up the NIH as the "discovery

Figure 5. U.S. NIH Spending on HIV Vaccine R&D, 1994-1998
(US$ Millions)



engine" of HIV vaccine research and development, and has set the goal of developing an HIV vaccine within the next decade. Toward that goal, NIH is creating a new vaccine center.

In addition, NIH is launching new programs to fund extramural investigators, including:

- Innovation Grant Program, designed by the AVRC to stimulate creation of new vaccine designs

- HIV Vaccine Research and Design Program (HIVRAD), a grant program to support vaccine ideas that have evolved from the initial stages

- The Integrated Preclinical/Clinical Program (IPCAVD)—a redesign of the National Cooperative Vaccine Development Groups (NCVDG)—a grant program to encourage academic investigators to further develop their vaccine concepts; the redesigned program includes the potential for small clinical trials, thus adding much-needed focus on human immune responses to experimental vaccines

- A new program (termed a Master Agreement Contract) designed to contract quickly for the production of novel vaccines for clinical trial

- Redesign and recompetition of the HIVNET program to support infrastructure development for conducting trials of HIV vaccines and other prevention measures in developing countries

The National Institute of Allergy and Infectious Diseases (NIAID), the lead institute at NIH responsible for HIV vaccine research and development, also supports other grant programs. These are more basic in nature (*e.g.*, mucosal immunity, HIV variation, AIDS pathogenesis) and are not listed here. Through contracts, NIAID also supports access to human specimens, reagents, and primates to further the efforts of vaccine investigators. All NIAID programs are described more fully on the Internet at the web site: http://www/niaid.nih.gov/daids/vaccine.

The NIH vaccine center under development will involve, at least initially, current NIH intramural investigators already working in fields related to HIV vaccine development. Only one candidate HIV vaccine, a peptide-based vaccine, has entered clinical trials in the NIH intramural program, and this candidate is being evaluated only in HIV-infected individuals. The focus of the new center is likely to be on discovery and targeted research, rather than product development, although the center may in the future develop the capacity to move designs into phase I trials. Despite statements that HIV vaccine development is among the highest priorities of the NIH, it has been more than one year since plans for the center were announced and a director has yet to be named.

With respect to NIH's extramural programs, innovative designs will almost certainly arise from the increased funding of academic laboratories under the Innovation Grant Program, HIVRAD, and other grant programs. NIH funding should be sufficient to evaluate these new designs in animal model studies so that promising vaccine candidates can be identified. Investigators successful in obtaining funding under IPCAVD could eventually see their designs move into clinical trial. However, even if fully successful in their intentions, these programs are not designed to contribute to the subsequent stages of HIV vaccine preclinical

development manufacturing. Nor are they likely to produce a design that will lead to an HIV vaccine by the year 2007.

The Small Business Innovative Research (SBIR) Program is a U.S. government effort that requires NIH (and other agencies) to set aside funds to support the study and evaluation of potential new products by small businesses (as defined by the government). These businesses must compete for the funds through a peer-review application process. It remains to be seen whether SBIR and the IPCAVD/NCVDG programs can attract the expertise of and provide funding to the private sector. While the NCVDG program has been in existence for over eight years, only one NCVDG-funded company, Therion, has brought a candidate HIV vaccine (vaccinia-env/gag/pol) into phase I trial. None of the SBIR-funded companies has done so.

Companies have tremendous uncertainty about whether they can evaluate their candidate HIV vaccines in developing countries.

It will be necessary to closely monitor these programs to determine if there is any shift in companies' willingness to participate, and if NIH will finance in-house development activities. To date, NIH support for company in-house HIV vaccine development activities has been virtually nonexistent. This, coupled with the fact that it is difficult for academic investigators to bring designs to clinical trial without a corporate partner, makes it unlikely that the number of vaccine products moving from these programs into human trials will increase in the next two to four years.

The new NIH Master Agreement mentioned before could help fill gaps in the preclinical development and the manufacture of candidate HIV vaccines. However, there are several reservations. A previous attempt by NIH to fund HIV vaccine manufacturing attracted only one offerer, precluding a competition among offerers. It is questionable to what extent private companies will respond to this new contract solicitation, given their concerns about government control of their in-house processes and decision making. Further, given the pace of government competitive processes and start-up time, this program is not likely to fill gaps for two to three years.

Finally, the redesigned HIVNET sites will be designated as "vaccine" sites or "prevention" sites and will merge domestic (U.S.-based) and international (non-U.S.-based) sites. This move appears to place less emphasis on HIV vaccine trials because apparently some sites will only conduct trials of other prevention measures. This is of particular concern for the conduct of vaccine trials in developing countries. It is unlikely that developing-country sites can compete with U.S. institutions for funding unless there is a mandated international mission that includes the conduct of all phases of clinical testing in developing-country settings. In addition, NIH has made no discernable effort to link test sites outside the United States with companies at the early stages of a product's development. Instead, NIH has opted to develop test sites independent of the product to be evaluated at that site. As a result, companies are left with tremendous uncertainty about whether they can evaluate their candidate HIV vaccines in developing countries, and where. It also becomes more difficult for companies to make decisions about which HIV subtypes to use.

WRAIR. The Walter Reed Army Institute of Research (WRAIR) has considerable experience in directing applied, highly focused vaccine development efforts, and has well-established laboratories and clinics in several overseas locations. In particular,

WRAIR's site in Thailand provides an opportunity to evaluate candidate vaccines in individuals at risk for HIV infection in a setting where a strong laboratory and clinical infrastructure already exists. WRAIR has contracts to produce vaccines under GMP conditions, though these contracts have not yet been used to prepare candidate HIV vaccines for human trials. Instead, WRAIR has relied on the private sector to provide candidate vaccines for clinical testing. WRAIR-supported researchers are conducting lab and animal studies on an oligomeric form of HIV envelope, which has not yet attracted company sponsorship. WRAIR does have a vaccine pilot production facility, which may be used to produce candidate oligomeric envelope vaccines.

Even with limited resources, WRAIR is conducting trials of bivalent preparations of rgp120 (B+E) made by Chiron. WRAIR plans to initiate trials of a recombinant canarypox vector and a DNA vaccine as part of a long-term strategy to initiate a three-or-four-arm phase III trial comparing a

- candidate that induces only antibody (envelope);
- candidate that induces CTL but little antibody (DNA);
- combination that produces both antibody and CTL (canarypox + envelope);
- placebo.

European Government Funded HIV Vaccine R&D. The European Vaccine Activity (EVA) program supports academic research in immunology and virology, and devotes resources to supply research reagents; develops challenge virus stocks; supports animal studies; characterizes virus in selected countries; and facilitates communication on new research concepts and advances. The British MRC and the French ANRS also support this range of activities, plus phase I clinical trials. MRC has backed a phase I trial of SmithKline Beecham's recombinant subunit vaccine. ANRS has supported clinical studies of Pasteur-Merieux Connaught's live recombinant canarypox vaccine and peptide/protein vaccines. In addition, ANRS has gone beyond the role of many national programs by providing financial support for the preclinical development activities of Pasteur-Merieux Connaught. The European Union (EU) and perhaps other European agencies and foundations may place increased emphasis on HIV vaccine research in the coming years. For example, the EU is planning to make HIV vaccine research a high priority in its next five-year plan, but will likely funnel its funds to more fundamental and vaccine targeted research rather than product development per se. The MRC no longer has an AIDS-directed program; its funding will continue to include investigator-initiated HIV vaccine targeted research only if it competes well with non-AIDS research applications.

The European Union is planning to make HIV vaccine research a high priority in its next five-year plan.

Other Public Sector HIV Vaccine Efforts. Thailand, with its history of vaccine development, has been involved in clinical trials of HIV vaccines for a number of years, and has evaluated several proteins and peptides in uninfected individuals. Two trials have been conducted in collaboration with U.S. WRAIR-supported programs. The other trials have been supported predominantly by private companies using infrastructure developed in part with funds from UNAIDS. Trials of a canarypox expressing HIV env, gag, and pro (protease portion of the pol gene of HIV) are planned. In addition, researchers in Thailand have

had discussions with a U.S. organization concerning transfer of technology to produce a candidate DNA vaccine and a candidate vaccine comprising soluble HIV proteins. However, funding for these projects has not yet been identified.

The most advanced preclinical development in Asia is being done at the National Institute of Infectious Diseases in Japan, where a group is preparing a recombinant BCG vector for clinical trials in Japan and Thailand. The first generation product expresses only the V3 loop region of the HIV envelope (B+E). Second generation products will express V3 as well as 2-3 T cell epitopes from internal HIV proteins.

India, which has vaccine manufacturing capabilities and a talented pool of researchers, has expressed interest in becoming involved in HIV vaccine development.

India, which has vaccine manufacturing capabilities and a talented pool of researchers, has expressed interest in becoming involved in HIV vaccine development. To date, however, only a small amount of preclinical research has been initiated.

Brazil has conducted a phase I trial of one candidate, a peptide-based vaccine, and has also been preparing to participate in large-scale efficacy trials.

China has experience in vaccine production and has conducted a successful efficacy trial of a lentiviral vaccine, a live-attenuated EIAV in horses. A small biotechology company has expressed interest in developing a DNA vaccine in China, but funding for this work has not yet been identified.

A nonprofit institution in Australia, Macfarlane Burnet Centre for Medical Research, has joined forces with a small biotechnology company, AMRAD, to explore development of a DNA-based, infectious but attenuated vaccine. The vaccine is based on an apparently attenuated form of HIV isolated from individuals who were infected through blood products from a single donor. This design is currently in preclinical development.

Uganda has been preparing to conduct an HIV vaccine trial in Africa, the first in several years. The product, a canarypox expressing HIV env, gag, and pro, is based on clade B HIV. The goal of the trial will be to determine if CTL that kill HIVs circulating in that population can be induced in that population by immunization with this clade B-based candidate vaccine.

South Africa is uniquely situated in Africa in that it has a strong clinical infrastructure, talented researchers, and access to high-risk populations. Two South African groups with access to high-risk populations have recently been named U.S. HIVNET sites. In addition, a centralized lab to evaluate clinical samples may be awarded. Although expertise in preclinical vaccine design and development is negligible in South Africa, there is experience in conducting clinical trials of other vaccines. Further, South Africa has vaccine manufacturing capabilities, although none in newer vaccine technologies.

UNAIDS is currently discussing the possibility of developing national AIDS vaccine plans in several other countries in Latin America, the Caribbean, Africa, and Asia.

Activities in the Private Sector

As discussed previously in this section, the private sector generally allocates resources and expertise where there is profit to be made from application of new technology and inventions that meet public needs or demands.

The world's four largest vaccine suppliers by revenue are SmithKline Beecham (SKB) and Pasteur-Merieux Connaught

(PMC), both based in Europe, and Merck and Wyeth-Lederle/American Home Products, both based in the United States. Other major world vaccine companies include CSL (Australia), Medeva and Swiss Serum and Vaccines Institute in Europe, and Chiron in the United States. Of these large companies, only PMC and Chiron appear to be making a substantial long-term investment in pursuing multiple HIV vaccine designs. Wyeth-Lederle recently purchased Apollon but has not yet indicated its level of commitment to Apollon's HIV vaccine programs. Glaxo Wellcome has entered the field of HIV vaccine development, but appears focused on vaccines as potential immunotherapeutics for HIV infected individuals. Merck is pursuing a program centered on DNA vaccines.

The motivations and capacity of biotechnology companies are often different from those of larger pharmaceutical companies. Biotechnology companies have less investment capital and are able to take greater risks, as long as some indication of success or failure is achieved in a relatively short (three-to-five-year) period. While a larger company may be able to invest tens of millions of dollars over a 10-year period before marketing a product, smaller biotechnology firms must quickly demonstrate the potential of the product so that additional funds can be raised or the rights sold to a larger company.

Smaller biotechnology companies involved in HIV vaccine development have included Apollon, now owned by Wyeth-Lederle (DNA vaccine); Therion Biologics (recombinant vaccinia); Virogenetics, now owned by PMC (recombinant viral vectors); Immune Response Corp. (whole-killed vaccine); United Biomedical, Inc. and CelSci, Inc. (peptide vaccine development); and VaxGen and Protein Sciences, formerly MicroGeneSys (recombinant protein vaccines). The long-term commitment and investment of any of these companies depends almost solely on their ability to raise private investment dollars, build bridges with larger companies, or be purchased by a larger company.

Table 2 lists the products known to have advanced to clinical studies in HIV-negative volunteers to date and their status in development. It is noteworthy that the more traditional vaccine designs (whole-killed and live-attenuated) are not on this list because of safety concerns. No company has been willing to develop a vaccine that is made from or that is live, infectious HIV, although this approach has proven to be the most successful for other viral diseases and has achieved the best protection in the SIV animal model. Recombinant hepatitis B and influenza vaccines stand out as the only recombinant vaccines licensed for human use. The HIV vaccines being pursued are produced by recombinant or synthetic technologies and have no possibility of causing HIV infection themselves. Except where these vaccines have been formulated in novel adjuvants, side effects have been minimal and have resolved without intervention.

While larger companies may be able to invest tens of millions of dollars over a 10-year period before marketing a product, smaller biotechnology firms must quickly demonstrate the potential for the product.

Activities of International Organizations and Philanthropic Groups

UNAIDS. This organization is involved in the following HIV vaccine R&D activities:

- Collection, exchange, analysis, and dissemination of information necessary to make decisions about HIV/AIDS vaccine research and clinical trials of candidate vaccines, especially in developing countries

- Promotion of collaborative networks

Table 2. Candidate Preventive HIV Vaccines[1]

Concept	Product	Clade	Producer	Status
Proteins	gp160	B	ImmunoAg	inactive
	B	MicroGeneSys	inactive	
		oligomeric	WRAIR	preclinical
	gp120	B	Chiron	PII
		B + *E*	Chiron	PI
		B	Genentech	PII
		B + *E*	VaxGen	PII/III
		B + *B*	VaxGen	PII/III
	p24	B	MicroGeneSys	inactive
	p24	B	Chrion	PI
	p55	B	NIH contractor	preclinical
Peptides	Lipopeptides	B	ANRS	PI
	HGP-30	B	CelSci	PI
	V3-MAPS	B	UBI	inactive
	V3-MAPS	multi B	UBI	inactive
	gag-lipopeptide	B	UBI	inactive
	C4-V3 peptides	multi B	Duke/Lederle	inactive
	V3	B	Cuban company	PI
	mixed env	B	(unknown-France)	inactive
	V3-PPD	B	SSI	inactive
	V3-PPD	multi	ID Vaccines	preclinical
Viral vectors	vaccinia-env	B	Bristol-Myers Squibb	inactive
	vaccinia-e/g/p	B	Therion	PI
	canarypox-e	B	PMC	PI
	canarypox-e/g/p	B	PMC	PII
	canarypox-e/g/p+	B	PMC	PI
	canarypox-e/g/p++	B	PMC	preclinical
	HBc-V3	B	KCST, Japan	preclinical

Table 2. Candidate Preventive HIV Vaccines[1] *(cont.)*

Concept	Product	Clade	Producer	Status
Bacterial vectors				
	Salmonella-env	B	U MD	PI
	BCG-V3	B (+E)	NIID, Japan	preclinical
Particles	Ty-VLP-p176/p24	B	British Biotech	inactive
	Ty-VLP-V3	B	British Biotech	inactive
	pseudovirions	B	PMC	preclinical
	p55	B, C, A, D	IMMH, Germany	preclinical
	p55 + env	B, C, A, D	IMMH, Germany	preclinical
DNA	env, rev	B	Apollon	PI
	gag, pol	B	Apollon	PI
	env, rev	non-B	Apollon	preclinical
	multi	B	Merck	preclinical

[1] Clades in italics designate primary HIV isolates
Abbreviations:
PI, phase I; PII, phase II; e, envelope; g, gag; p, protease; WRAIR, Walter Reed Army Institute of Research; UBI, United Biomedical Inc.; PMC, Pasteur-Merieux Connaught.

of scientists and institutions working on HIV/AIDS vaccine research in industrialized and developing countries, in order to foster better understanding of the challenges arising and their possible solutions

- Assistance in building capacity in developing countries to support HIV/AIDS vaccine research, including clinical trials

- Counseling developing countries on independent and authoritative scientific, technical, and ethical issues concerning the conduct of HIV/AIDS vaccine trials; identification of and action on ethical, regulatory, and legal barriers to international HIV/AIDS vaccine development and future availability

- Encouragement of worldwide commitment to accelerate the development and future availability of HIV/AIDS vaccines, especially in developing countries

This is an extensive list of activities, and UNAIDS has to balance this HIV vaccine work with all other responses to the epidemic globally. Its broad mandate puts UNAIDS in a unique and valuable position to appreciate the wide

context within which vaccine research and development activities are conducted. Nevertheless, the UNAIDS vaccine program remains small, with limited financial and human resources relative to its broad mandate.

UNAIDS has clearly stated that it will not engage in vaccine discovery or vaccine (product) development. It does, however, support a very small HIV vaccine research component, together with the Global Programme on Vaccines and Immunization, using earmarked funding from the Japanese government.

The broad mandate of UNAIDS puts it in a unique position to appreciate the wide context within which vaccine research and development are conducted.

Of the activities outlined above, infrastructure development (termed "capacity building" by UNAIDS) falls into the "critical path" of vaccine development, as defined in this document. UNAIDS currently supports infrastructure development in Thailand, Uganda, and Brazil, and is considering similar activities in South Africa and Kenya. Financial support for infrastructure development from UNAIDS remains small but contributes to capacity strengthening, training, and technical assistance.

UNAIDS also contributes to vaccine development indirectly through its HIV isolation and characterization network, which provides isolates that can be incorporated in candidate vaccines.

Perhaps most critical is the normative and advisory role that UNAIDS plays in international collaborative efforts to conduct HIV vaccine trials. UNAIDS conducts external, independent reviews of protocols; provides consultation and advice to governments and institutions; and is establishing ethical guidelines for the conduct of HIV vaccine trials. In addition, UNAIDS provides technical assistance to countries that elect to formulate national AIDS vaccine plans outlining goals and decision-making processes and procedures.

Foundations and Other Nonprofit organizations. The American Foundation for AIDS Research (AmFAR) has a long history of supporting basic and therapeutics research in the area of HIV/AIDS. In addition, it has supported community-based clinical trials of experimental HIV therapeutics. Recently AmFAR issued a solicitation to fund research on HIV vaccines and made 11 basic research grants totaling approximately US$1.1 million. The Rockefeller, Alfred P. Sloan, William H. Gates, Until There's A Cure, and Starr Foundations support HIV vaccine R&D through the International AIDS Vaccine Initiative.

Other nonprofit organizations and foundations have not directly supported HIV vaccine research or development. The Wellcome Trust, which has enormous resources, only recently began accepting grant applications in the field of HIV research, and is confining its support to fundamental research. The Sabin Foundation is working in policy areas related to HIV vaccine development, but does not currently plan to fund vaccine R&D activities. The Salk Foundation is supporting research on a whole-killed HIV stripped of its envelope, and plans to conduct animal studies of this design to determine if it might be suitable for testing in uninfected individuals.

Collaborations among Sectors

Existing systems for transferring technologies from government or academic labs to private industry work best when there are incentives for the private sector to engage in product development. Initially, companies had sufficient incentives to engage in development of safe, clade B-based HIV vaccine designs. NIH's decision in 1994 not to

proceed with phase III trials of rgp120 has often been cited as putting a damper on the private sector's commitment to HIV vaccine development. Since 1994, VaxGen and Chiron have continued to improve their rgp120 products and have produced rgp120 based on primary HIV isolates, including clade E HIV. VaxGen recently announced its decision to evaluate its bivalent rgp120 products in efficacy trials in the United States and Thailand.

HIV vaccine-related collaborations among government research programs, multinational pharmaceutical companies, and smaller biotechnology firms almost exclusively center on the clinical evaluation of candidate HIV vaccines. Two exceptions are the program at WRAIR, which conducts preclinical R&D on almost every product the program clinically evaluates, and the ANRS in France, which contributed to Pasteur-Merieux Connaught's preclinical HIV vaccine programs.

NIH has supported phase I trials of the following products through its U.S.-based AIDS Vaccine Evaluation Group (AVEG):

- Envelope vaccines produced by ImmunoAg, MicroGeneSys, Genentech and Chiron
- Peptide vaccines produced by UBI and Wyeth-Lederle
- Vaccinia vectors produced by Bristol Myers Squibb and Therion
- Canarypox vectored vaccines produced by Pasteur-Merieux Connaught
- Bacterial vector produced at the University of Maryland
- Ty-based particle produced by British Biotech
- "Naked DNA" vaccine produced by Apollon

WRAIR has supported phase I trials of Chiron gp120s and may initiate trials of canarypox-env/gag/pro and a DNA product in the United States and in Thailand.

Another company, Therion, received financial assistance in the form of a grant (National Cooperative Vaccine Development Group) to support preclinical work on its clade B-based recombinant vaccinia vector. Also, University of Maryland had financial support from NIH to prepare the recombinant Salmonella vector, now in phase I trial.

ANRS has supported phase I clinical trials of Pasteur-Merieux Connaught's envelope, peptide, and viral vectors and has also provided funds to catalyze production of candidate HIV vaccines.

With respect to larger trials, NIH supported a phase II trial of Chiron's rgp120(B) and Genentech's rgp120(B). A combination prime + boost, (canarypox-env,gag,pro + rgp120) recently entered phase II trials in the United States under NIH support. WRAIR is supporting a phase I/II trial of a bivalent (B plus E) gp120 vaccine in 380 healthy volunteers in Thailand. VaxGen will move into phase III trials of its bivalent rgp120 products in the United States and Thailand later this year, but the financial resources for these trials appear to be coming from the private/venture-capital sectors.

With few exceptions, trials supported by the U.S. and French agencies have evaluated products based on clade B HIV. Only two trials conducted outside the United States have used vaccines based on other than clade B HIV.

With few exceptions, trials supported by the U.S. and French research agencies have evaluated products based on clade B HIV.

Table 3. Candidate HIV Vaccines Evaluated in Developing Countries

Product	Producer	Location	Start
V3-MAPS, peptide (B)	UBI	China, Thailand, Brazil	1994
rgp120(B)	Chiron	Thailand	1995
rgp120(E+B)	Chiron	Thailand	1998
rgp120(B)	Genentech	Thailand	1995
rgp120(E+B)	VaxGen	Thailand	1998
V3 protein (B)	CIGB	Cuba	1996
canarypox-env,gag,pro (B)	PMC	Uganda	1998
canarypox-env,gag,pro (B)	PMC	Thailand	planned
BCG-env (B + E?)	NIID, Japan	Thailand	planned

Appropriately designed larger clinical trials in humans will be required to determine if and to what extent a vaccine works.

Candidate HIV vaccines being evaluated in developing countries are listed in Table 3.

V. Why Conventional Approaches Are Inadequate for an HIV Vaccine

Technical and Scientific Uncertainties

There are significant scientific and technical uncertainties that present barriers to development of an HIV vaccine. Foremost among these is the lack of correlates of immune protection that in other diseases have been determined from animal models, individuals who recover from infection, and/or passive transfer trials in humans. This means that researchers and manufacturers do not know what specific immune responses an HIV vaccine will need to induce in order to protect humans from HIV disease and transmission. Further, there is no validated animal model of HIV infection that can be used to predict in advance whether an HIV vaccine will be effective in people. The newly developed chimeric virus SIV/HIV, or SHIV, model shows promise, but it remains unknown if this will provide reliable information on how vaccines protect humans against natural HIV strains acquired through risky behaviors.

For these reasons, it will not be possible to definitively conclude from small clinical studies or animal studies whether any specific vaccine candidate is effective. Appropriately designed larger clinical trials in humans will be required to determine if and to what extent a vaccine works, and to gain information on correlate(s) of immuni-

ty and the validity of animal models for that immunization procedure. The process for getting definitive answers will therefore take years and millions of dollars for clinical studies on each specific HIV vaccine product. Taking a vaccine through efficacy trials is estimated to cost more than US$25 million, excluding infrastructure, building, and training costs.

Further, there is unprecedented diversity in HIV isolates around the world. Based on genetic sequencing techniques, HIV has been classified into at least 10 related families, known as subtypes or clades (Figures 1, 2). The significance of this diversity to vaccine development is not yet known. It may be that a single vaccine will prove effective against all subtypes, or it may be that a cocktail of vaccines will be required. Vaccines will need to be evaluated in populations where different HIV subtypes circulate to determine if the vaccine is effective against those subtypes. This will require years of preparing for and conducting efficacy trials in various countries.

Because of technical barriers and the resulting uncertainties about what a successful vaccine will look like, there is consensus that multiple-candidate vaccine designs need to be investigated in human studies within a goal-oriented, directed vaccine development approach. At the same time, these studies must provide data on the activity of various candidates in order to inform design of subsequent generations of vaccine candidates. Further, the urgency of the epidemic demands that multiple vaccine designs be evaluated as soon as possible so that answers can be found concerning which designs are effective. This will require multiple efficacy trials of multiple products in multiple locations, conducted within as short a time period as feasible. While this general philosophy has been promulgated by others, (e.g., UNAIDS, U.S. NIH), no organization has put forward a comprehensive plan for its accomplishment.

Considerations in Developing Countries

A number of factors need to be considered in the design and development of AIDS vaccines for use in developing countries. These include the clade on which the vaccine is based to help determine the relevance, if any, of HIV clade to vaccine efficacy. Simplicity of use is also important, as the administration of multiple doses over an extended period will not be feasible in most developing-country settings. Eventual cost is another consideration, although this is difficult to assess at early stages of development, when savings from scale-up in manufacturing are hard to estimate.

Ownership of intellectual property on which a vaccine is based is important.

In addition, ownership of intellectual property on which the vaccine is based is important; the number of licenses required, which impacts cost, and the willingness of the intellectual-property owner(s) to produce vaccine for developing-country markets will have a tremendous impact on the ultimate availability of a product in poorer populations. It is essential to create mechanisms to ensure that a successful vaccine is available to populations with the most need at the same time or shortly after that vaccine is available in industrialized countries. Many developing countries have production and/or vialing capabilities. In fact, 60% to 70% of the world's vaccines are produced and/or vialed in developing countries. Although these capabilities have not yet been drawn upon in AIDS vaccine development, doing so could help, at least in part, address downstream accessibility issues.

Efficacy trials can be conducted most expediently and efficiently in populations at high risk for HIV infection, most of which are now in developing countries. Multiple clinical trials will need to be conducted in different populations to ensure that vaccines have comparable safety, immunogenicity and/or efficacy in all major ethnic groups. More problematic will be the need to demonstrate efficacy against all the HIV clades.

The conduct of clinical trials in developing countries will require the full cooperation of their scientists, communities, and political leaders. To have less than a full partnership harbors the danger of paternalism or exploitation.

The conduct of clinical trials in developing countries will require the full collaboration of their scientists, communities, and political leaders. Further, the priorities of the developing country partner must be met to the same extent as are those of the outside collaborator. For example, this may require that scientists in developing countries assist in capacity building, technology transfer, and/or training. To have less than a full partnership harbors the danger of paternalism or exploitation.

Full partnership with developing country scientists will also help ensure that local risk-benefit issues are thoroughly considered in decisions about whether to advance a product through the pipeline. For example, a design that offers some calculated safety risk with a high probability of providing protection might be considered acceptable to a population where HIV is spreading rapidly. Also, a vaccine that is expected to be only partially effective, but is clearly very safe, could be considered useful and worthy of consideration by populations at highest risk. In the end, as noted above, simplicity of design, cost, and ease of administration will all be critical to widespread use in developing countries. These issues may need to be weighed against other considerations, such as vaccine efficacy and/or frequency of minor side effects.

From a global perspective, and given the global urgency for an HIV vaccine, it is desirable to test vaccines in populations where trials can be conducted easily, quickly, and ethically. In industrialized countries, if highly active anti-retroviral therapy (HAART) becomes standard of care, it will be difficult, if not impossible, to measure the impact of an HIV vaccine on viral load if the volunteer becomes HIV infected. Trials in countries where HAART is not available would make it potentially feasible to use viral load measurement as an endpoint in the clinical trial. In addition, trials to measure a vaccine's ability to block maternal-infant transmission might be more readily conducted in populations where anti-retroviral therapy during pregnancy is not available.

A key component in these difficult decisions is ensuring that developing countries are full partners, as they will have to decide if a proposed trial is ethical. For example, it must be up to the developing country to determine if, when, and to what extent infected vaccine recipients are offered anti-retroviral therapy; or whether mothers are routinely offered anti-retroviral therapy to prevent maternal-infant transmission. Such preparation will ensure that the trials are neither protectionist nor exploitative.

Value of a Multipronged Strategy

The urgency of the HIV epidemic demands that all reasonable avenues to a vaccine be explored. A conventional, linear, stepwise approach might arguably be the least expensive. But a more aggressive, multipronged strategy has better potential to solve scientific problems and identify promising approaches. Additional basic information must be obtained through laboratory and animal model studies at the same time that additional information

is obtained through human trials (Figure 6).

All reasonable candidate vaccine designs should enter phase I trials to evaluate safety and immunogenicity. The best designs that prove safe and that induce immune responses with reasonable protective potential should advance to phase II clinical studies in individuals at risk for HIV infection, and eventually to larger trials to determine efficacy.

In the absence of a validated animal model to evaluate the efficacy of candidate HIV vaccines, and in the absence of validated markers that predict protection from HIV disease in humans, it is essential to conduct human trials of sufficient size to determine whether a candidate vaccine has any efficacy. Anything less would be guesswork at a time when the urgency of the worldwide epidemic demands definitive answers. Because the goal is to develop candidate vaccines that protect at-risk people against all subtypes of HIV, vaccines should be tested in diverse populations where those subtypes are being transmitted.

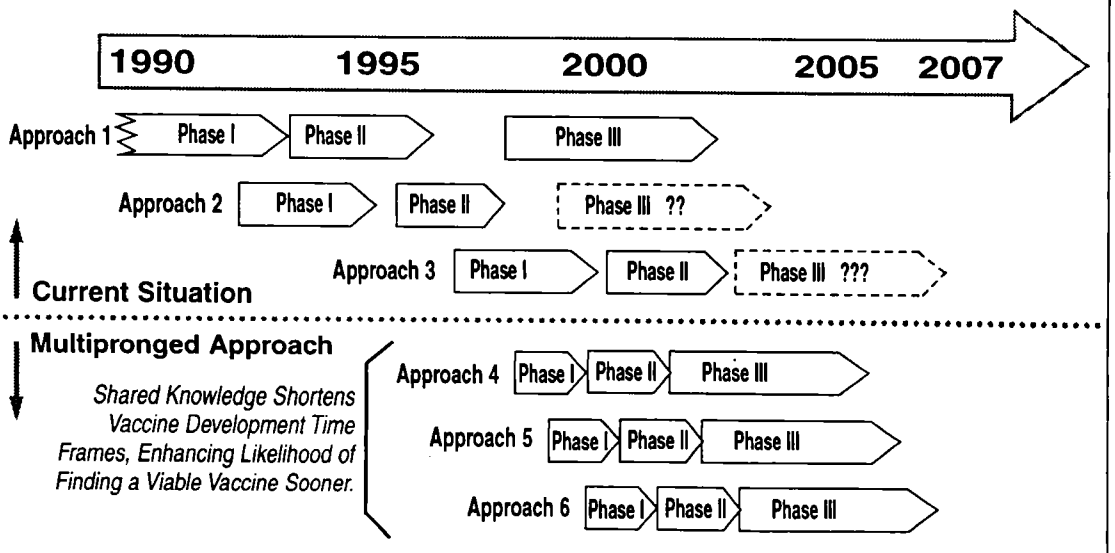
Without definitive knowledge about the immunologic significance of genetic subtypes or a clear definition of immunotypes on which a vaccine can be logically based, candidate vaccines tested in individuals at risk for HIV infection should be based on the HIV subtype(s) that predominate in the proposed trial population. Alternatively, there may be justification to advance to larger trials a "mismatched" vaccine that has been shown to induce strong immune responses against the spectrum of viruses that circulate in the proposed trial population. The "mismatched" approach, however, is risky and potentially too time consuming. For example, failure of the "mismatched" vaccine to show efficacy would raise the question of whether it failed because of the design, or because the design was not based on circulating virus isolates.

Pressures of a 10-Year Time Line

Unless there is an immediate, major breakthrough in vaccine design, it is highly unlikely that basic research findings will lead to an effective vaccine within a decade. It would take about two years to optimize and translate a

All reasonable candidate vaccine designs should enter phase 1 trials to evaluate safety and immunogenicity.

Figure 6. Why an Accelerated Multipronged Approach?



new design into material suitable for human studies and receive regulatory approval for a phase I trial. The phase I trial would take about one and a half years; phase II, about two years; phase III, at least three and a half years. That is a conservative total of nine years. So if a vaccine is to be developed in 10–or even more–years, considerable attention will have to be given to the current candidate vaccines.

A rational and thorough approach would be to continue the vigorous support for new, potentially improved designs, and at the same time evaluate the most promising of the known vaccine design options and combinations.

Unfortunately, the product pipeline is flowing slowly, if at all (Figure 7). There are few novel designs entering phase I trials, and fewer yet that have been designed for testing and use in developing countries. A rational and thorough approach would be to continue the vigorous support for new, potentially improved designs, and at the same time evaluate the most promising of the known vaccine design options and combinations. In addition, promising candidates already in clinical trial (rgp120, canarypox) should be particularly vigorously pushed toward efficacy trials at the earliest possible date.

Strategic Gaps

There are certain crucial research questions that, if answered, would undoubtedly accelerate HIV vaccine development. These questions (which are addressed in more detail in the Appendix) include:

- Which immune responses will provide protection from HIV disease and block transmission in humans?
- Which antigens and delivery methods induce these immune responses?
- Which animal model of HIV disease can be used to evaluate candidate HIV vaccines for efficacy?
- What is the immunological significance of genetically diverse HIV subtypes found around the world?

Clearly, the more that can be learned about these strategic questions, the more confident manufacturers will be that their candidate vaccines are worthy of vigorous development. While basic research alone may shed light on the unknowns, it is far more likely that clinical trials with a variety of different vaccine designs will provide definitive answers.

One compelling strategy for accelerat-

Figure 7. Ideal/Current Pipeline for HIV Vaccine Development

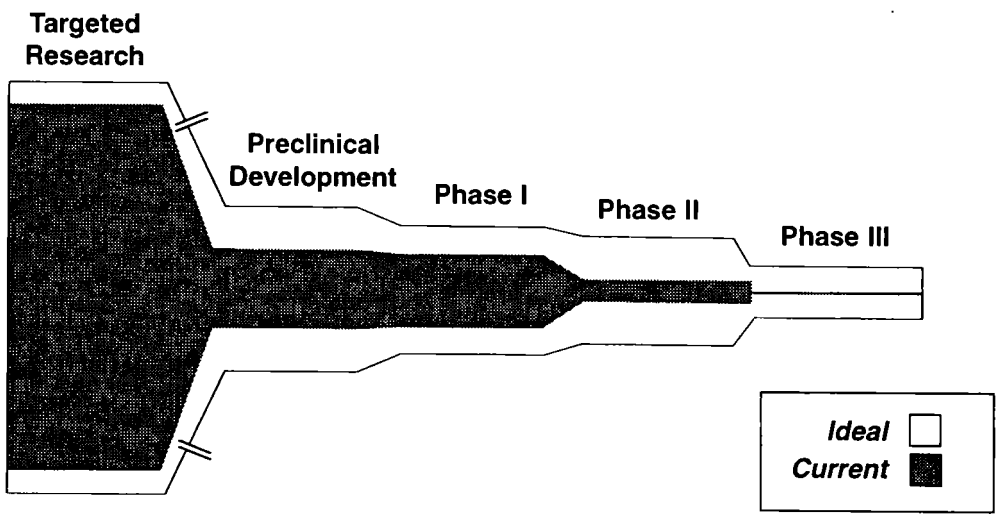
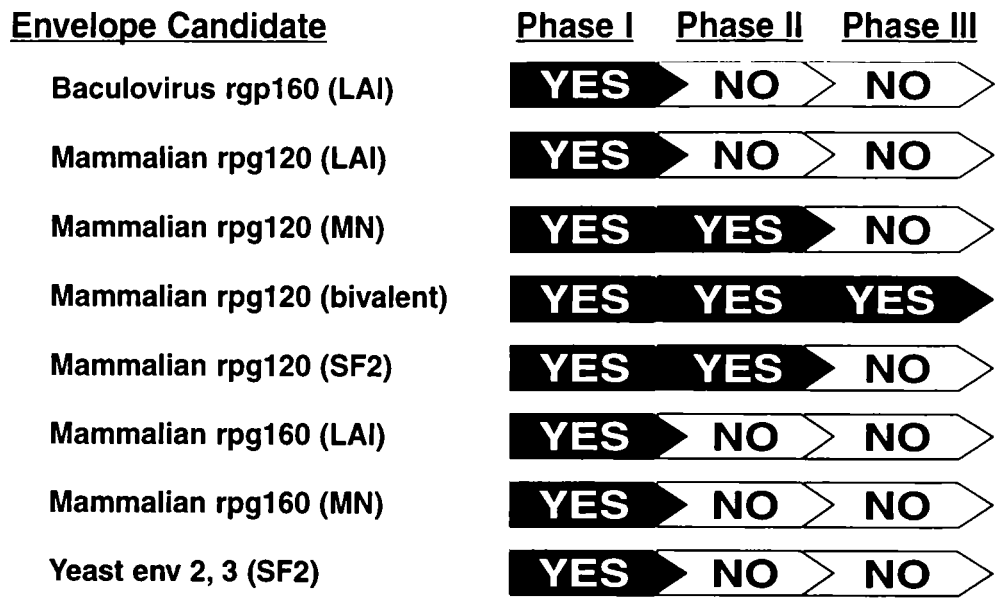


Figure 8. Evaluation of Candidate Subunit Envelope HIV Vaccine



ing HIV vaccine development is to advance candidate vaccines as rapidly as possible through clinical trials. In this strategy safety is paramount: as long as a candidate is proven immunogenic and safe, it is moved expeditiously to efficacy testing. Scientific data are gathered at each step. Multiple products of each vaccine design class are evaluated in phase I studies. The best one or two designs, based on safety, immunogenicity, and animal model data, advance to phase II trials. Candidates of each design that show the best characteristics in phase I and phase II trials are selected for evaluation in phase III field efficacy trials. This strategy of rapid testing and evaluation of candidate vaccines in human volunteers has been referred to as "thoughtful empiricism."

The empirical testing of vaccines–through phase I and phase II testing–has been an important part of all successful vaccine research and development programs. Figure 8 shows envelope-based candidate HIV vaccines evaluated in the different phases of clinical testing. However, to date no candidate vaccines have been advanced to the crucial phase III efficacy trials, although phase III trials of VaxGen's rgp120's will begin later this year. The lack of phase III trials has seriously hampered HIV vaccine research; scientifically sound data on correlates of protection, on the value of animal models, and on virus immunologic typing can only be achieved by knowing which vaccines protect humans.

Figure 7 outlines the ideal HIV vaccine development pipeline based on this *Scientific Blueprint*, and shows the number of designs or products that is reasonable to have at each stage of development at any point in time. This model contrasts markedly with the existing pipeline, where the number of vaccine designs advancing into preclinical development is small, resulting in a low flow in the stages of clinical evaluation. Revising the pipeline will have

The empirical testing of vaccines–through phase I and phase II testing–has been an important part of all successful vaccine research and development programs.

implications for the resources provided to vaccine development.

An Abundance of Good Ideas

Although downstream vaccine testing has slowed to a trickle, upstream vaccine discovery efforts have already led to a great number of novel vaccine concepts. Many of these have not been advanced to product development, and others have only been through phase I testing with a B genotype construct. To accelerate movement of products down the HIV vaccine development pipeline, more concepts must be taken to product development, and more products must be advanced through the phases of clinical testing, including the best of those products already in human trials (Table 4).

Although downstream vaccine testing has slowed to a trickle, upstream vaccine discovery efforts have already led to a number of novel vaccine concepts.

If a vaccine is going to be successfully developed in the next 10 years, development work must be intensified on the following HIV vaccine concepts.

DNA Vaccines. Several groups have experimented with "naked DNA" HIV vaccines. However, no company has produced and tested a non-clade B DNA vaccine. DNA vaccines are attractive because, if they prove to be effective at reasonable doses, they could be one of the more affordable and stable of designs and could be produced within one or more developing countries. A sensible way to address DNA vaccines would be to produce and evaluate two or three non-clade B candidate HIV DNA vaccines in populations where non-clade B HIV circulates, thus identifying the most promising designs for evaluation in human trials. Then the different approaches could be compared and the most desirable further evaluated.

Table 4. Vaccine Concepts

DNA vaccines: One of the newest technologies for vaccine design. 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 act against. Work on DNA vaccines is focusing on improving what is presented to the immune system, particularly to get a stronger antibody response to HIV.

Live-attentuated vaccines: 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 vector vaccines: HIV genetic material placed into harmless viruses or bacteria that then show pieces of HIV to the immune system. When HIV proteins are created in viruses (such as vaccinia, canarypox, or adenovirus) or bacterial vectors (such as BCG or attenuated salmonella), HIV epitopes expressed during vector replication can elicit HIV-specific immune responses.

Peptide vaccines: Small portions of HIV proteins. Extensive basic research on potential CTL and antibody epitopes of HIV have shown that the immune system will mount a response to very short peptide sections of an antigen when presented appropriately to the immune system.

Recombinant subunit vaccines: Single proteins of HIV, including structural envelope glycoproteins (such as gp120 and gp160) and also other proteins (such as p55 and p24). The recombinant subunit approach was first used against hepatitis B virus, where viral envelope produced in yeast cells proved effective in clinical trials.

Virus-like particles: Incomplete viruses produced by cells that are infected with parts of HIV DNA. Studies have shown that these incomplete viral particles can contain antibody and CTL epitopes, yet are safe and not infectious.

Whole-killed vaccines: Based on some of the oldest vaccine technologies. Whole-killed viral vaccines are used for such diseases as polio, influenza, mumps, and typhoid fever. With regard to HIV, the conceptual advantage of the whole-killed approach is that the entire viral particle is presented to the immune system, yet it cannot infect and replicate as live-attenuated viruses can.

Novel Envelope Designs. Several concepts have been explored regarding how to present the HIV envelope in order to induce more broadly reactive and functionally potent antibodies. These include various oligomeric envelope designs, as well as complexes between envelope and receptors or antibodies, to help "freeze" key conformational envelope structures. To date, novel viral envelope protein designs (other than rgp120 based on primary, CCR5-using HIV isolates) have not progressed beyond laboratory and animal experimentation.

Viral Vectors. Replicating viral vectors offer the hope of consistent, long-term protection. A wide variety of viral vector approaches have been reported. Vaccinia replicates in humans not previously exposed to vaccinia (e.g., smallpox vaccine). One recombinant vaccinia vector expressing multiple subtype B HIV proteins is currently in phase I trial in the United States. Canarypox vectors do not replicate in humans. Several recombinant canarypox vectors have been evaluated in phase I trials. One, in combination with rgp120, is currently in a phase II trial in the United States. A comparative phase I trial of three canarypox vectors is about to begin, also in the United States. Data from this trial will be used to select the best of these vectors for an efficacy trial slated for the year 2000. Another vaccinia-based vector, Modified Vaccinia Ankara (MVA), has been evaluated in thousands of individuals and found to be safe. However, so far no organization has moved recombinant MVA expressing HIV proteins into clinical trial. Similarly, other viral vectors, including VEE, polio, adenovirus, and various viral (noninfectious) replicons, have shown promise but are not being pursued in clinical trials. Nor are any recombinant viral vectors that express non-clade B HIV internal proteins being developed.

Particles. Particulate antigens are highly immunogenic, and several particulate HIV vaccine concepts have been explored. A clade B pseudovirion is being developed by Pasteur-Merieux Connaught but the technical difficulties of this approach are quite challenging. Further, the design will not be applicable to developing countries without significant improvements in the manufacturing process to lower costs. Evaluation is needed of pseudovirions based on other clades, as well as on primary HIV isolates, rather than laboratory strains. A research group in Germany is studying p55-based particles that do or do not contain the HIV envelope. The group will select a design based on animal model results, and then hope to obtain funds to prepare Good Manufacturing Procedures material based on clades A, B, C, and D for possible evaluation in China and Uganda. No commercial partner for these studies has been identified.

Bacterial Vectors. Live, replicating bacteria that carry HIV genes can be vigorously pursued. A large number of bacterial species have been proposed as vectors for HIV. Japan's National Institute of Infectious Diseases is pursuing a BCG vector toward possible phase I trials in Japan and Thailand. This first-generation vector contains only the V3 principal neutralizing determinant. Second-generation BCGs will contain V3 in addition to two to three CTL epitopes. There are other bacterial vectors that need to be evaluated to ensure that the best vectors move into efficacy trials. These include BCG vectors that express full-length HIV genes, rather than small pieces, so that the number of individuals able to respond to the vaccine might increase. A Salmonella vector produced at the University of Maryland will not move beyond phase I

trials without additional resources. No commercial entity is currently involved in development of recombinant bacterial vectors as HIV vaccines.

Whole-Killed HIV. Whole-killed (purified, inactivated) viruses are used in a great number of commonly used vaccines, such as hepatitis A and polio. The incomplete protection observed with whole-killed SIV in the monkey model has led to the judgment that development of a whole-killed HIV vaccine is not warranted. However, the IAVI Scientific Advisory Committee has reviewed this field and concluded that the correct experiments have not yet been done. For example, inactivation procedures that do not disrupt the conformational epitopes of the HIV envelope need to be developed, and then those inactivated candidates evaluated in animal models. Unfortunately, given the highly applied, labor-intensive nature of this work, it is unlikely to be funded through investigator-initiated research. And given the uncertainty for success, this approach is also unlikely to be funded by the private sector, particularly because of safety and liability issues associated with a product that originates with a live, infectious virus. Indeed, an intensive, multi-year effort by a small U.S. biotechnology company, Acrogen, to raise funds to develop a whole-killed HIV was unsuccessful.

Even the large vaccine manufacturers have made only relatively modest investments in HIV vaccine research and development.

Live-Attenuated HIV. Live-attenuated virus strains have been successfully used to protect against a great number of diseases. Live-attenuated SIV has proven to be the gold standard in protecting monkeys from SIV infection. Safety is a serious concern, however, because of well-documented instances of AIDS occurring in a few monkeys inoculated with live-attenuated SIV vaccines. Therion, a company that holds an intellectual property position on live-attenuated vaccines, is unable to move this concept forward without additional funds.

Whole-killed and live-attenuated vaccines for HIV, while universally considered viable strategies from a scientific point of view, have not been attractive to industry due to concerns about safety and their perceived high potential for liability.

Nontechnical Barriers

In addition to the scientific and technical issues discussed in this section, there are other obstacles to HIV vaccine development. These nontechnical barriers must also be addressed if industry is to be fully engaged in the HIV vaccine development effort.

For smaller companies with promising vaccine concepts, attracting investor resources to HIV vaccine development has been nearly impossible. The scientific uncertainties for success, the long time frame between concept development and efficacy trial results, and questions about market size make investing in HIV vaccine development very risky compared with other investment opportunities.

Even the large vaccine manufacturers have made only relatively modest investments in HIV vaccine research and development. This is particularly problematic because it is industry that has the capacity for product development.

There are also few incentives for companies to collaborate with one another. Most companies do not consider evaluating their candidate vaccine in combination with a vaccine from another company until later stages of clinical testing, if at all. Incentives for companies that have new adjuvants or delivery systems need to be developed. This would encourage them to apply these new technologies to

HIV vaccine development through collaborations with companies already working on HIV vaccine design.

To tackle the unique challenges afforded by HIV vaccine development, and in consideration of the suboptimal market forces, novel approaches to collaboration must be designed and attempted. One potential approach to combining the strengths of the public and private sectors is public funding of biotechnology and industrial development efforts in exchange for sharing of intellectual property that results from the funded activity. New technologies arising from the funded project could be used by industry to develop HIV vaccines and acquire profits from major markets, as well as provide valuable information for other projects. Public funding of private sector efforts would diminish financial barriers to a company's involvement in the HIV vaccine effort and facilitate access of final product to populations less able to pay. Tiered pricing, and acceptance of tiered pricing worldwide, would be a key component of this plan.

Concerns of larger vaccine developers go beyond funding and include inadequate protection of intellectual property by certain countries; parallel trade that brings low-cost vaccine back into higher-priced, industrialized-country markets; government price and profit controls that would limit incentives to invest in high-risk development; inadequate infrastructure to conduct trials in developing countries; and inadequate resources for developing countries to purchase effective vaccines. With sufficient leadership and international cooperation, these obstacles can be addressed.

VI. The IAVI Scientific Strategy to Accelerate the Global Effort

The International AIDS Vaccine Initiative (IAVI) was formed in 1996 after two years of international consultations with scientists, financial experts, philanthropists, policy makers, and members of HIV-affected communities. These consultations explored the need for, and the potential to create, effective HIV vaccines. The initial supporters–the Rockefeller Foundation, Alfred P. Sloan Foundation, Starr Foundation, World Bank, Until There's A Cure Foundation, UNAIDS, Fondation Marcel Mérieux, and other organizations–helped found IAVI on the conviction that current global environment and research efforts are insufficient to ensure development of safe, effective, preventive HIV vaccines for worldwide use.

It is now apparent that an increased technology push and an increased economic pull can act synergistically to accelerate progress.

It is now apparent that an increased technology push and an increased economic pull can act synergistically to accelerate progress. Consequently, IAVI is active in both areas. IAVI's efforts to ensure a global market for an HIV vaccine–to increase industry's economic pull in product development and ensure accessibility–show encouraging progress, but are not the subject of this report. Instead, strengths and weaknesses in global science and technology approaches are weighed, and a new strategic approach is presented based on these assessments.

Progress Toward an HIV Vaccine

Some aspects of HIV vaccine research and development have gone extremely well. Basic research on virology, immunology, and pathogenesis of HIV has led to an unprecedented understanding of the virus and how it causes disease. Immune responses to many

candidate vaccines have been examined in great detail, with extraordinarily fine mapping of the genetic structures of the virus and immune responses in infected individuals. Further, an international network of epidemiologists and molecular biologists has tracked and recorded the presence of viral genetic variants in almost every corner of the globe.

IAVI Assessments of the Current Global Effort

These accomplishments are impressive, but much more must be done to ensure that an HIV vaccine is developed as rapidly as humanly possible. Following are observations on deficiencies or problems in the global effort and IAVI's assessment of each.

At this stage, the success or failure of every specific vaccine candidate remains uncertain; multiple promising designs need to be pursued in parallel.

Observation 1: Although the global cost of HIV/AIDS is staggering, in excess of US$18 billion per year, global investment in prevention is only a fraction of this amount.

> ***IAVI Assessment:*** *The total global investment in HIV/AIDS prevention of all types is inadequate. Expenditures on prevention interventions, especially vaccines, should be increased.*

Observation 2: Vaccine-induced immunity has been successful in preventing virus infection and/or disease in several animal lentivirus (viruses related to HIV) models and in the chimpanzee model of HIV infection. Further, anti-HIV immunity is effective in slowing disease progression in naturally infected human patients.

> ***IAVI Assessment:*** *It is likely that a preventive HIV vaccine can be developed.*

Observation 3: Although the global investment in total HIV/AIDS research is large, only a fraction of this investment is targeted to HIV vaccines.

> ***IAVI Assessment:*** *HIV vaccines should be a top research and development priority, and this priority should be reflected in funding levels.*

Observation 4: Most current HIV vaccine research focuses on basic science and concept exploration.

> ***IAVI Assessment:*** *Greater emphasis should be placed on HIV vaccine product development and testing in human volunteers.*

Observation 5: In the absence of validated correlates of immunity, it is impossible to predict if any particular candidate vaccine will succeed or fail.

> ***IAVI Assessment:*** *At this stage, the success or failure of every specific candidate vaccine remains uncertain; multiple promising designs need to be pursued in parallel.*

Observation 6: The expected time line for successful development of an HIV vaccine, from preclinical testing to field trial proof of efficacy, is about 10 years.

> ***IAVI Assessment:*** *If the goal is to develop a safe and effective HIV vaccine within a decade, then only products that have already approached the preclinical stage or are already in clinical trials have any chance of fulfilling that goal.*

Observation 7: Only three HIV vaccine

products have progressed to phase II and none has progressed to phase III efficacy trial. (One product will advance to phase III testing later this year.)

IAVI Assessment: *Promising HIV candidate vaccines that pass phase I and phase II safety and immunogencity testing should be routinely evaluated in efficacy trials. This includes rgp120 and canarypox vectors.*

Observation 8: All else being equal, efficacy trials can best be done in high-incidence cohorts.

IAVI Assessment: *Plans should be made to conduct multiple efficacy trials in developing countries, where the epidemic is spreading most rapidly. Accurate predictions of incidence trends will be critical to these efforts.*

Observation 9: Studies of immune responses and breakthrough virus infections can yield important scientific data even in "failed" vaccine trials.

IAVI Assessment: *The "thoughtful empiricism" approach to HIV vaccine development–the rapid, definitive testing of candidate vaccines–has twofold value: first, to identify efficacious vaccines; and second, to generate immunologic data that can lead to improved vaccine designs. The only truly "failed" trials are those that yield no useful scientific information.*

Observation 10: Research needs of developing countries have often been overlooked.

IAVI Assessment: *HIV vaccine research and development efforts should be targeted to regions of the world and populations with the most severe epidemics–in developing countries.*

Observation 11: Instances of international cooperation in HIV vaccine research and development are rare, especially between the public sector and industry.

IAVI Assessment: *Mechanisms should be established to foster international cooperation in HIV vaccine research and development, especially between vaccine companies and developing countries.*

Observation 12: Excessive regulatory requirements may slow the process of new-product development. Regulatory officials often overlook the cost of lost time and financial consequences of their decisions.

IAVI Assessment: *Regulatory authorities should be called on to reduce their requirements to the minimum necessary to ensure the safety of vaccine recipients.*

These observations and assessments lead inevitably to the conclusion that more candidate vaccine products should be tested for efficacy in more trials in more countries. The risk of failure to find efficacy for any given vaccine may be great, but the probability that at least one candidate vaccine will be found to have some measure of efficacy increases with the number of promising candidates subjected to rigorous, statistically robust field efficacy trials.

Other risks and costs associated with the thoughtful empiricism approach to accelerated HIV vaccine development and testing must also be carefully weighed. The most serious of these

Plans should be made to conduct multiple efficacy trials in developing countries, where the epidemic is spreading most rapidly.

concerns is that volunteers may suffer adverse effects from the candidate vaccines. This risk can be minimized by ensuring that products be considered for phase III testing only after they have undergone rigorous safety testing in phase I and phase II trials. Another serious concern is that volunteers may increase their risk-taking behaviors as a result of trial participation. This danger can be minimized by repeated counseling throughout the trial. Indeed, data suggest that overall, risk taking by trial volunteers does not increase, at least with frequent, quality counseling. Other issues, such as financial, political, and legal risks, also merit sober consideration, but in most instances these are more than counterbalanced by the urgency of the pandemic.

The IAVI strategy is designed to complement, not compete with, existing HIV vaccine research and development programs.

Based on the assessments set forth here, IAVI has developed a distinctive scientific strategy. This strategy is specifically designed to complement, not compete with, existing HIV vaccine research and development programs at UNAIDS, the U.S. NIH, the French ANRS, and other national and international organizations. Further, the plan emphasizes cooperation with industry. Indeed, during the formulation of the IAVI scientific strategy, extensive consultations were held with leaders of national, international, and industry organizations.

IAVI's strategic plan is unique in that it focuses exclusively on accelerated product development and testing through international collaborations at all stages of research, development, and evaluation. Because our strategy carries obvious political and financial risks, other–more risk-averse–organizations have been reluctant to move decisively down this important path. IAVI is a new non-government entity whose sole purpose is to accelerate HIV vaccine development. Therefore, we are prepared to implement a very aggressive action plan, while more established organizations stick to other important–but more politically secure–traditional research avenues.

VII. The IAVI Scientific Action Plan

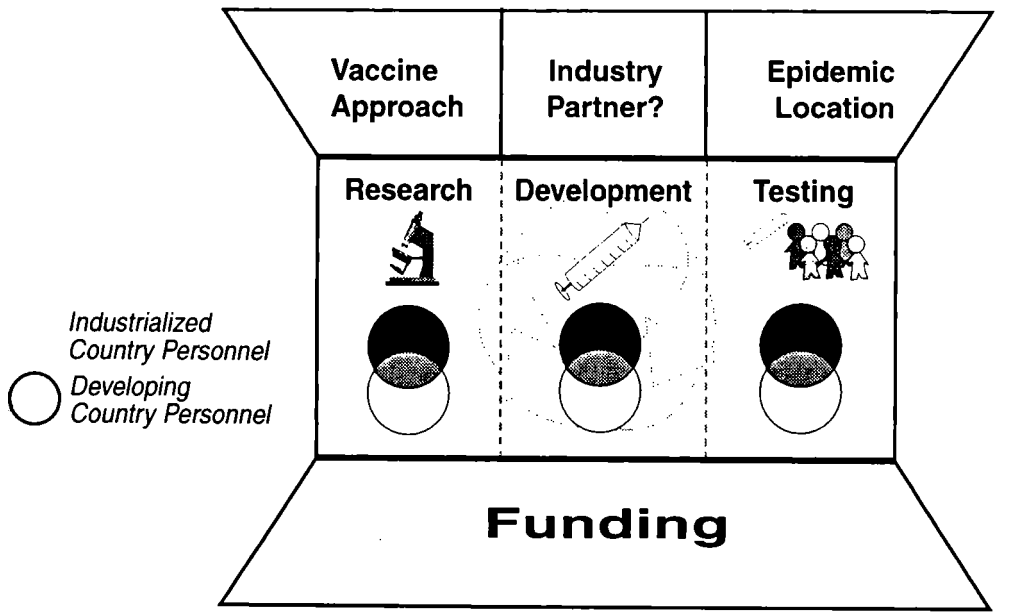
The foregoing sections have discussed the steps in HIV vaccine development, the current activities of key players, and–in general terms–what must be done if an HIV vaccine is to be identified in the next 10 years. While basic research on HIV immunology is well supported, and targeted research on vaccine concepts also receives considerable support, many vaccine designs are not progressing to phase I human trials. Most important, no HIV vaccine field efficacy trials have been initiated.

To meet the 10-year goal, promising designs must be expeditiously evaluated in clinical trials, preferably in populations with the most need for an HIV vaccine. Candidate vaccines with satisfactory safety and immunogenicity profiles can then be immediately moved into phase II trials, and the most promising candidates promptly tested in phase III field efficacy trials.

Product Development Teams

The challenge in executing such a fast-track HIV vaccine development strategy is to ensure that the most promising new candidate vaccines are tested in the best clinical and field study sites as rapidly as possible. While this may seem obvious, there is no ready mechanism whereby a researcher with an exciting new vaccine approach can identify and establish direct contact with clinical and field researchers, and with populations in epidemic locations. Vaccine researchers in industri-

Figure 9. IAVI Product Development Team



alized countries are often unaware of opportunities to work with trial-site researchers in developing countries, and vice versa. Indeed, almost all HIV vaccine pilot lots manufactured to date have been based on the HIV-1 B genotype, on the questionable assumption that trials would be done in North America or Europe, or that clade B vaccines will protect against other clades. The exceptions are the two gp120's based on clade E HIV produced by Chiron and VaxGen. Once a candidate vaccine has been manufactured, industry is understandably reluctant to fund production of a second candidate vaccine for a different genotype in a different location.

The need to match vaccine approaches with epidemic locations for testing can be solved by creation of international "product development teams" (Figure 9). The concept is simple: assemble a team of vaccine designers/researchers, manufacturers (initially pilot lot manufacturers), and clinical researchers around a candidate vaccine product before a candidate vaccine is produced.

The team then formulates and adheres to a comprehensive, seamless vaccine development plan. Most often such a team would have an international composition; many of the new technical approaches would derive from laboratory research in industrialized countries, while the epidemic locations with the highest incidences are typically in developing countries.

Team leadership would be established on a case-by-case basis, depending on the needs and constraints of each partner. The successful team will meet the most pressing needs of all its partners. These needs are likely to include generating high-quality data, ensuring that ethical standards are met or exceeded, infrastructure development, and technology transfer.

The exact institutional makeup of each team would vary according to the expertise of team members. Certain key elements would be constant within all product development teams:

1. Targeted laboratory research. These

The need to match vaccine approaches with epidemic locations for testing can be solved by creation of international product development teams.

activities would consist of construction of prototype vaccines, modified vaccines, analog vaccines (for testing in animal model systems), and measurement of immune responses. The work would be done in either the industrialized or the developing country. Many of the researchers would likely be drawn from academia.

2. Pilot lot manufacture. This would entail preparation of small lots of vaccine under Good Manufacturing Procedures. Appropriate GMP facilities are limited in many developing countries, so this step may need to be done in the industrialized country. If pilot lot manufacturing is done in an industrialized country, developing-country scientists should nonetheless participate in this process to ensure that the product has the confidence of all parties. Larger-scale manufacturing and other development tasks can best be conducted by industry. Industry talent and experience are key to the long-term success of any vaccine development project.

3. Clinical and field testing in human volunteers. Here developing-country scientists can be expected to take a lead role, although training and support from the industrialized partner may prove very important.

Three to six product development teams should be formed as soon as practicable.

The multidisciplinary technical professional staff and resources needed for each team are significant but attainable if vaccine development is given sufficient priority and long-term commitment. In addition, efficient and professional project management is critical to the teams' timely progress.

In all key elements of project development teams, scientists from the developing-country partner would be expected to work closely with industrialized-country scientists. "Twinning," or pairing of developing-country institutions with the industrialized-country counterpart, is encouraged as an excellent mechanism to help build trust, confidence, and sustainability (Figure 9).

In addition to putting forward this model of international collaboration in HIV vaccine development, IAVI intends to catalyze the formation and funding of several product development teams. We will use our own resources to launch at least one team in the coming year.

Parallel Evaluation of Multiple Vaccine Approaches

Given that no single vaccine approach is a sure thing, the fastest strategy to identify which, if any, approach is effective will be to test multiple products in multiple locations around the world. It is impossible to predict exactly how many product development teams will be optimal. But if the basic premise—that all promising approaches should be promptly tested—is accepted, then three to six product development teams should be formed as soon as practicable. In order to establish efficient procedures for formation and coordination of product development teams, one promising candidate vaccine should be identified as a lead product, with others following shortly thereafter.

Stable funding will be essential to the success of HIV vaccine product development teams. In some cases, these teams might be assembled from vaccine researchers, manufacturers, and field researchers who already have active support for HIV work through other funding mechanisms. Some product development teams could be built on pre-existing developing country/industrialized country collabora-

tions. Indeed, it is likely that each product development team can be supported by a variety of public and private sources. IAVI will seek to establish new collaborations and secure funding to ensure that these synergistic relationships are successful.

Possible Criteria for Selection of Vaccine Approaches

As noted in section V, a wide variety of new vaccine approaches are being explored worldwide. Key criteria for selection of a specific vaccine approach as the core for a product development team might include:

- Safety
- Immunogenicity in non-human primates
- Probable efficacy based on trials in animals, where possible
- Cooperation of the intellectual property holder

Other desirable product characteristics, such as ease of manufacture, low cost, and shelf life, would enter into the decision as secondary criteria. It is expected that if a difficult-to-manufacture or expensive vaccine were proven effective, the data on protective immune correlates will be instrumental in the design and manufacture of a second generation of more available and affordable vaccines.

Possible Criteria for Selection of Trial Sites

Key practical criteria for selection of a trial site might include:

- Well-characterized population with high incidence and good follow-up, so trials can be conducted easily, quickly, and affordably
- Circulating virus with minimal genetic and antigen variation, to minimize the potential impact of viral diversity on outcome
- Infrastructure and experience adequate for phase I, II, and III trials, so that reliable, high-quality data can be obtained

Expression of political support from authorities will also be important to ensuring the success of a team's vaccine development efforts.

Time Lines for Product Development

If an effective vaccine is to be identified, fully evaluated, and available within the next decade, a very tight set of time lines with milestones must be established and observed. The additional costs associated with this increased level of activity over nine years is roughly estimated to be US$350 million-$500 million (Table 5).

Legal and Ethical Issues

Establishment of HIV vaccine international product development teams will give rise to a host of complex legal and ethical issues. For example: protection of human research subjects; patents and intellectual property rights; distributive justice to ensure that benefits accrue to trial participants; provision of or referral to care for subjects who may become infected with HIV during clinical studies; pricing and accessibility of a vaccine if one is proven effective. If given sufficient forethought, however, all of these issues can be resolved, particularly if the partnerships strive to be fully collaborative. This is the vision for product development teams.

One valuable method for dealing with

If an effective vaccine is to be identified and available within the next decade, a very tight set of time lines and milestones must be established and observed.

Table 5. HIV Vaccine Product Development Teams ($M/YR)

(in US$ millions per year)

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Vaccine Manufacture, Testing, and Scale-up										
Product Development Team Assembly n = 6	3	3								
Pilot Manufacture and Preclinical Testing n = 6		9	12	12						
Phase I and II Clinical Trials n = 6		6	9	12	12	12				
Scale-up Engineering n = 3					9	15				
Phase III Field Trials n = 3					9	9	30	30	30	
Product Manufacture n = 1										N/A
Targeted Vaccine Research										
Laboratory Research n = 5	12	12	12	12	6	6	6	3	3	
Policy Research	3	3	3	3	3	3	3	6	6	6
SUBTOTALS	18	33	36	39	39	45	39	39	39	6

legal and ethical issues would be to build a targeted policy research program into the product development team structure, in parallel with the targeted laboratory research effort (Table 5). Reconciliation of differences as they arise–between academia and industry, developing country and industrialized country, researcher and patient–will be crucial to the success of any product development team, as well as the entire HIV vaccine research and development effort. Good will and trust are priceless ingredients in a team effort, and they must be vigilantly protected.

Conclusion

Even with the ongoing efforts and plans of the private and public sectors, critical gaps in HIV vaccine development must be filled if an effective vaccine is to be ready by 2007. Foremost among these is the need to clinically evaluate every promising new vaccine approach for safety, immunogenicity, and efficacy as rapidly as possible. The most efficient strategy to achieve this is to build international HIV vaccine product development teams that bring together research, manufacturing, and clinical trial expertise. At least six promising

approaches should be moved into clinical trials in developing countries hardest hit by HIV and AIDS. Planning should begin for at least two phase III efficacy trials by 2000, followed by at least three more by 2002.

Appendix

A. Fundamental and Targeted HIV Vaccine Research

Vaccines are products that teach the immune system to recognize and defend against diseases caused by microorganisms and viruses. From the beginning of our understanding of viral and bacterial causes of disease, development of new vaccines has always rested on both industry efforts and publicly supported research efforts. Basic research and targeted research focus on questions that might provide background knowledge and technologies for vaccine development.

- **Basic HIV vaccine research** focuses on the structure and activity of HIV, the mechanisms of immune defenses in general, and the interaction between HIV and the immune system.

- **Targeted HIV vaccine research** is more specific to questions directly relevant to HIV vaccine design and development, and includes development of laboratory assays and animal models, and evaluation of candidate vaccines in animal models for their ability to alter the interaction of HIV or a comparable retrovirus within the animal's immune system.

The ultimate goal of both basic and targeted research is to provide the underpinnings for development of vaccine candidates that can be tested for use in the populations where they are needed.

The world's major funders of basic and targeted research in health science are the national agencies of the United States, France, Britain, Japan, and other countries. The U.S. effort is the largest of these. The U.S. National Institutes of Health (NIH) spends US$1.5 billion annually for HIV/AIDS research out of a total of US$13 billion for all medical research at NIH. The U.S. budget for all government-sponsored scientific research and development is approximately US$65 billion. This public spending has an enormous influence on the private sector; although private industry spending on research surpasses government spending, most new industry patents rest on at least some discoveries made in publicly funded research at universities, government laboratories, and other public agencies.

B. Directions in HIV Vaccine-Related Basic Research

Basic research in HIV vaccines can be defined as seeking to further understand the HIV virus, the human immune system, and the interaction between the two. Following are examples of goals in basic research critical to HIV vaccine development.

Understanding Key Structures of HIV

HIV vaccine research seeks designs that mimic the natural shapes of HIV as the body's immune system sees them, and thereby induce immune responses. In order to do that, basic researchers work to understand the detailed structures of external HIV envelope protein and how those structures may vary across HIV isolates. Classifying and mapping HIV by serotype (the shapes of HIV proteins as seen by the human immune system) may be more useful for HIV vaccine development than classifying HIV by clade (subtype) or genotype (genetic sequence). This work needs to be done on a global scale to ensure that the true range of immunogenic "faces" of HIV are understood, and to

determine if all HIVs share a common "face" to which all people's immune-system defenses can be directed.

Understanding the Mechanisms of the Human Immune System

- Researchers are investigating how immunologic memory is induced and activated. This understanding can help them design vaccine-induced protection that is long lasting and requires few follow-up inoculations.

- Researchers are trying to understand which mucosal immune responses might be effective against viruses, so that vaccines can be designed to induce this type of response.

- Researchers are working to develop new animal models that use identical macaque (monkey) twins, so that immune cells can be transferred from one animal to the other. This will help determine which cells are critical for protection against retrovirus infection.

- Additional information is being sought about how genetic differences influence an individual's response to foreign invaders such as HIV, so that researchers can tailor vaccines to all populations worldwide.

- Additional research is needed on the impact of vaccine adjuvants. Adjuvants are substances that modulate the force, speed, and direction of overall immune system responses. When used with HIV vaccines, adjuvants might help direct vaccine-induced immune responses where they are most needed to protect against infection or disease.

Understanding the Virus-Host Interaction

- To determine which parts of the immune system might be useful in protecting against HIV infection and/or disease, additional work is needed to determine possible correlates of protection. This includes the study of animals with vaccine-induced protection from infection or disease, long-term nonprogressors, and adults and newborns who may have been exposed to HIV but who have no signs of a chronic HIV infection.

- Work is being done to understand the pathways of HIV infection through the mucosa, and mechanisms for mucosal protection. Determining which cells HIV first targets, and how this early infection might be prevented or cleared, may lead to important guidelines on how to block the sexual transmission of HIV.

- Animals and newly infected people are being studied to learn how HIV spreads after entry into the body, evades immune defenses, and rapidly establishes itself in lymphoid tissue despite a strong immune response. This knowledge may help in designing candidate HIV vaccines, and contribute to an understanding of why various candidate vaccines may or may not work. In addition, the natural history of HIV infection and disease in people may be different in different parts of the world, and should be better defined.

- Vaccine development would benefit from having an animal model of HIV infection that more closely mirrors the process of HIV infection and disease in people. Animals susceptible to HIV infection and disease could

serve as models for testing the activity of candidate vaccines.

C. Directions in HIV Vaccine-Related Targeted Research

Following are some of the critical directions in developing tools, evaluating methods for altering and measuring immune responses against HIV, and determining the potential significance of those immune responses.

- Develop and improve standardized, accurate, reproducible, quantitative measures of neutralizing antibody, cytotoxic T lymphocyte (CTL), and other immune responses, particularly for use in developing countries.

- Further define specific antibody and CTL epitopes of HIV that circulate in different parts of the world. Successful HIV vaccines may have to elicit very broadly cross-reactive immune responses in many genetically diverse populations and against many variants of HIV. Vaccine development will be aided by classifying which HIV structures provoke which types of immune responses.

- Evaluate candidate vaccine concepts in animal models of HIV infection in a comparative, systematic way, to determine which candidates show the most promise.

- Develop the capacity for standardized animal studies of candidate vaccines, including animal models and corresponding challenge viruses that most clearly mimic the dynamics of human/HIV infection and disease. This includes developing a pathogenic SHIV virus that is a hybrid of an SIV core with HIV envelope that can mirror the human/HIV infection and disease dynamic in macaques.

D. Infrastructure Development Needs

An adequate infrastructure must exist to conduct clinical trials of candidate HIV vaccines. The preparation of clinical trial sites and potential volunteers requires a great deal of time and effort. There are also unique challenges because of the need to conduct vaccine trials in developing countries, the stigma of HIV, the large number of volunteers that will ultimately be needed, and the complexity of the laboratory work.

The components of infrastructure include:

- *Training researchers and staff.* Clinical trials of HIV vaccines require teams of researchers who have training and experience with the target population and in clinical trial design and implementation, epidemiological research, laboratory procedures specific to HIV, data collection methods and analysis, informed consent processes and ethical review boards, HIV risk-reduction interventions and services, and clinical care referrals.

- *Community preparedness.* Community education and participation are needed to prepare people for large-scale recruitment campaigns for HIV vaccine efficacy trials, and to address any issues of mistrust and political ambivalence.

- *Recruitment of study participants.* A key infrastructure question is whether a site can quickly recruit a cohort of participants who are eligible for the study; willing and able to take part in the study over time;

capable of informed consent; and, for phase II and phase III trials, at a certain level of risk for HIV infection even when participating in a study involving quality risk-reduction counseling and services.

- *Informed consent process and institutional review boards.* Each research site must establish protocols and infrastructure to ensure ethical standards of trial design and conduct.

- *Counseling.* To be ethical, research to evaluate methods to prevent HIV infection must also provide what is known to be effective in preventing HIV infection.

- *Vaccine administration and clinical monitoring.* The evaluation of a candidate vaccine in a placebo-controlled trial requires careful dose preparation, randomization, administration of vaccine or placebo such that the participant and clinician do not know which has been given, and careful monitoring of the participant for clinical symptoms or side effects.

- *Participant retention.* The proportion of participants who remain in the trial and make every appointment within the desired window of time is crucial to the design and outcome of clinical trials.

- *Laboratory capacity and specimen collection, transport, processing, and analysis.* Laboratory infrastructure needs to include the ability to assess the incidence of HIV and other infections; monitor the magnitude, specificity, and kinetics of antibody, cellular, and other immune responses; and, in breakthrough infections (individuals who become infected after immunization), to monitor viral load and disease progression.

- *Data collection, processing, and analysis.* To gather valid, reliable information on trial participants at enrollment and throughout the study, research sites require standardized questionnaires, skilled interviewers, and an ability to track visits, immunizations, and test results.

- *Health services and service referrals.* Based on the ethical mandate to maximize benefits and minimize harms, clinical trial sites usually establish standard protocols to go beyond trial-related activities in provision of health services and referrals.

E. Vaccine Concepts

The effort to research and test HIV vaccines has included the following vaccine technologies.

- **DNA vaccines** use one of the newest technologies for vaccine design, in which parts of the genetic structure of HIV (specifically, pieces of HIV DNA) are incorporated in harmless plasmid DNA from bacteria. This is used to make the body's cells produce HIV proteins for the immune system to recognize and act against. Work on DNA vaccines is focusing on improving what is presented to the immune system, particularly to get a stronger antibody response to HIV. Two clade B HIV DNA vaccines are now in phase I clinical trials in the United States. Other DNA vaccines are in development.

- **Live-attenuated vaccines** consist of weakened (attenuated) live virus that is unable to cause disease, but is still able to infect cells and replicate within the body. This attenuated virus

can present itself through multiple rounds of replication in cells, and can elicit strong, persistent antibody and cellular immune responses. The immune system is then potentially prepared to protect against future infection by pathogenic strains. Studies of live-attenuated SIV in macaques have shown unparalleled protection against wild-type SIV. However, further research is needed to determine what level of attenuation is needed so that live-attenuated HIV is non-pathogenic, yet still able to infect and elicit protective immune responses. Because of safety concerns, no private sector company is developing this approach for testing in humans, despite success of naturally attenuated EIAV vaccine in China and data in a handful of humans naturally infected with an apparently attenuated HIV.

- **Live vector vaccines** use HIV genetic material placed in harmless viruses or bacteria that then show pieces of HIV to the immune system. When HIV proteins are created in viruses (such as vaccinia, canarypox, or adenovirus) or bacterial vectors (such as BCG or attenuated salmonella), HIV epitopes expressed during vector replication can elicit HIV-specific immune responses. Vaccinia vectors for HIV have been tested in animal models for more than 10 years. Current efforts focus on attenuated strains of vaccinia that would be expected to be non-pathogenic in immunocompromised people, yet able to infect and be broadly immunogenic. While some strains may retain their ability to replicate in individuals not previously exposed to vaccinia (e.g., smallpox vaccine), others, such as Modified Vaccinia Ankara (MVA), replicate little if at all.

  Canarypox virus differs from vaccinia in that canarypox undergoes only one incomplete round of cell infection, which may increase its safety without diminishing immunogenicity. Several generations of canarypox vector vaccines have been tested in clinical trials by Pasteur-Merieux Connaught, with substantial support from the U.S. National Institute of Allergy and Infectious Diseases as well as the French government. A recombinant canarypox virus vector is now being tested in the United States in a phase II clinical trial in combination with a recombinant gp120 product. Further trials will be needed to determine efficacy, and to evaluate the magnitude and duration of immune responses over time.

  Other vectors, such as MVA, adenovirus, poliovirus, VEE, and BCG, have undergone promising preclinical studies and could offer safety or efficacy advantages over vaccinia. However, due to a lack of funding, private sector companies are not developing these alternative strategies.

- **Peptide vaccines** are small portions of HIV proteins. Extensive basic research on potential CTL and antibody epitopes of HIV have shown that the immune system will mount a response to very short peptide sections of an antigen when presented appropriately to the immune system. Researchers have attempted to improve the shape of recombinant peptides by linking them together in multimeric sequences, or by attaching them to a carrier protein. However, with respect to antibody recognition, the linear sequence of a peptide may matter less than the three-dimensional structure of the peptide. Several peptide vaccine candidates have been evaluated in phase I clinical trials, where some

were shown to induce antibody responses but were not highly immunogenic in general. Private industry has shown dwindling interest in developing newer generations of these products, even though their potential has not been ruled out and they are relatively inexpensive and easy to produce.

- **Recombinant subunit vaccines** are single proteins of HIV, including structural envelope glycoproteins (such as gp120 and gp160) and other proteins (such as p55 and p24). The recombinant subunit approach was first used against hepatitis B virus, where viral envelope produced in yeast cells proved effective in clinical trials. Various HIV subunit vaccine candidates are currently being tested in clinical trials and efforts continue toward designing subunit structures that can induce broad and strong immune responses. Some evidence indicates that the way proteins are "folded," or assembled, into multimeric structures may be important. Researchers are experimenting with several ways of producing and assembling subunits to achieve more immunogenic structures. A monomeric, monovalent gp120 is being tested in the United States in a phase II trial in combination with a canarypox vector vaccine. A monomeric, bivalent gp120 will be evaluated in phase III trials in the United States and Thailand later this year. Multimeric and other innovative envelope vaccines are not currently being developed by any company, and need to be produced for evaluation in humans.

- **Virus-like particles** are another vaccine approach, consisting of incomplete viruses produced by cells that are infected with parts of HIV DNA. Studies have shown that these incomplete viral particles can contain antibody and CTL epitopes, yet are safe and not infectious in animals. Further work is being done to engineer virus-like particles from primary isolates from different clades, and test these in animal models for immunogenicity and protection. Only two companies have engaged in an effort to develop this type of product for clinical trials; one has been dropped from development and the other has not yet entered human trials.

- **Whole-killed vaccines** are based on some of the oldest vaccine technologies. Whole-killed viral vaccines are used for such diseases as polio, influenza, and typhoid fever. With regard to HIV, the conceptual advantage of the whole-killed approach is that the entire viral particle is presented to the immune system, yet it cannot infect and replicate as live-attenuated viruses can. Many licensed human whole-killed vaccines are safe, non-infectious, non-toxic, and non-oncogenic. However, before assessing the immunogenicity of whole-killed HIV vaccines in human volunteers, further research is needed on these vaccines to demonstrate that inactivation techniques can retain the viral structures and provide protection in animal models. No private sector company is developing whole-killed HIV vaccines for preventive trials, despite data demonstrating that HIV can be safely inactivated and despite the success of these vaccines in feline retroviral diseases.

About the International AIDS Vaccine Initiative

The International AIDS Vaccine Initiative (IAVI) is a non-profit, scientific organization committed to ensuring the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI is forging global collaborations to accelerate the development and testing of HIV vaccines–the most promising solution to end the AIDS pandemic. IAVI fosters cooperation among private industry, national governments, regulatory agencies, academic institutions, non-governmental organizations, and scientists, leaders, and communities throughout the world.

IAVI was founded in 1996 with the initial support of the Rockefeller and Alfred P. Sloan Foundations, Until There's A Cure Foundation, UNAIDS, and the World Bank, all of which provide ongoing support. The Starr Foundation has since become a founding partner. IAVI also gratefully acknowledges the support of the William H. Gates Foundation, Glaxo Wellcome's Positive Action Program, Fondation Marcel Mérieux, the U.K. National AIDS Trust, and the U.K. Department for International Development.

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