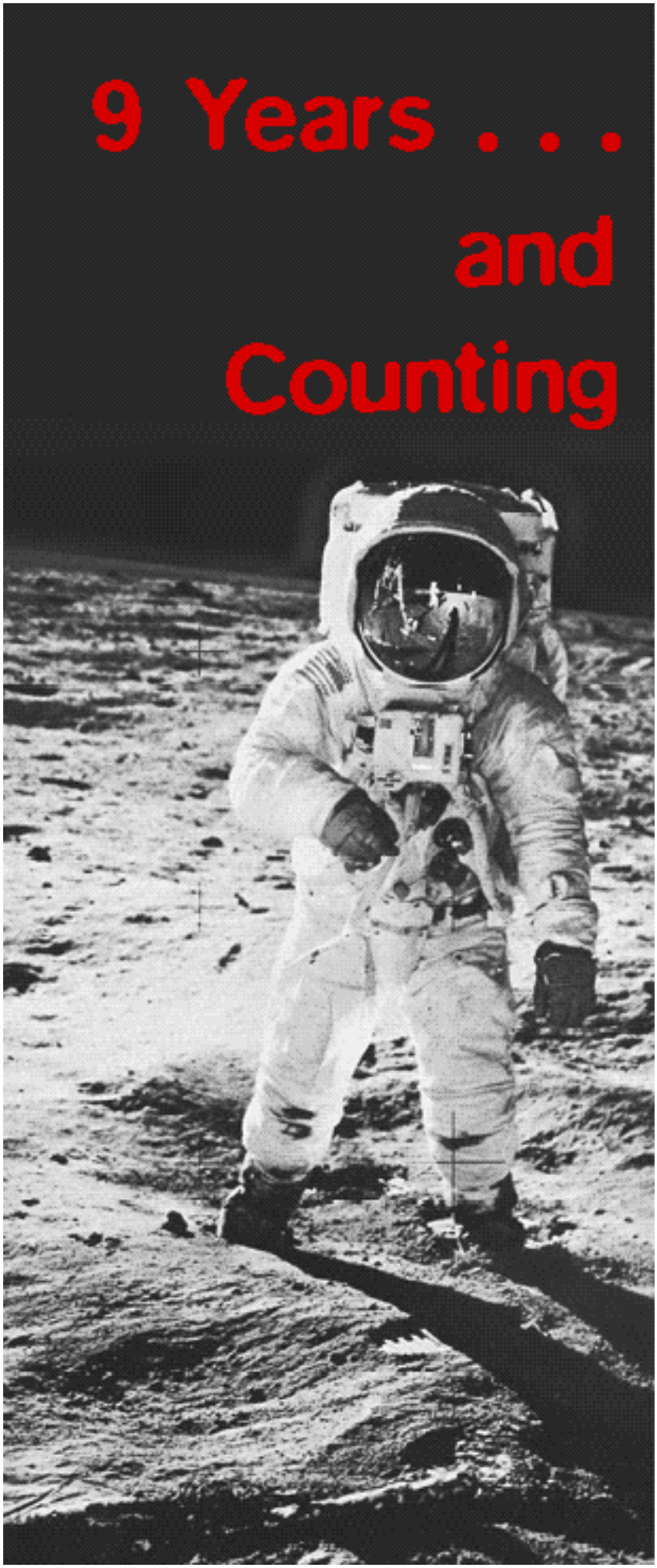

Will we have an HIV vaccine by 2007?

An Agenda for Action
for an HIV Vaccine

By the AIDS Vaccine Advocacy Coalition,
May 1998

"Thirty-six years ago, President Kennedy looked to the heavens and proclaimed that the flag of peace and democracy, not war and tyranny, must be the first to be planted on the moon. He gave us a goal of reaching the moon, and we achieved it-ahead of time . . .

"Let us today set a new national goal for science in the age of biology. Today, let us commit ourselves to developing an AIDS vaccine within the next decade . ..

If America commits to find an AIDS vaccine and we enlist others in our cause, we will do it. I am prepared to do all I can to make it happen.

"Today, I am pleased to announce the National Institutes of Health will establish a new AIDS vaccine research center dedicated to this crusade. And next month at the Summit of the Industrialized Nations in Denver, I will enlist other nations to join us in a worldwide effort to find a vaccine to stop one of the world's greatest killers. We will challenge America's pharmaceutical industry, which leads the world in innovative research and development to work with us and to make the successful development of an AIDS vaccine part of its basic mission. My fellow Americans, if the 21st century is to be the century of biology, let us make an AIDS vaccine its first great triumph."

-President Bill Clinton
Commencement Address, Morgan State

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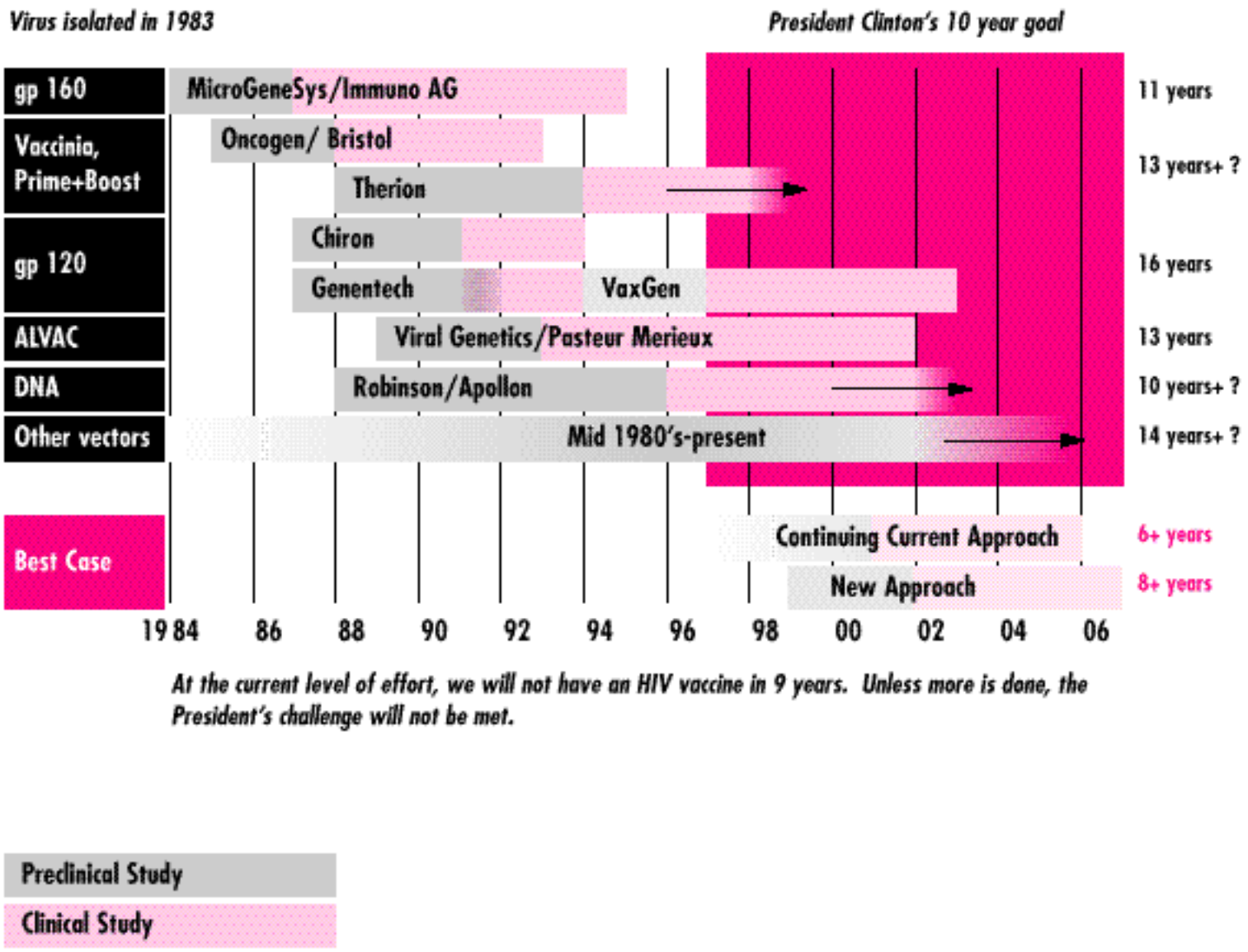
Can We Get There in Nine More Years?



One year ago, the President of the United States invoked America's mission to the moon in challenging this country and the world to develop an HIV vaccine within a decade. That ten years is now nine.

At the current level of effort, we will not have an HIV vaccine in 9 years. Unless more is done, the President's challenge will not be met.

Like the race to the moon, overcoming any scientific and technological challenge requires both discovery and a methodical development process. The science of HIV vaccines is complex, yet that is not the only barrier before us. The obstacles that prevent us from reaching an HIV vaccine by the year 2007 include a pervasive unwillingness to risk failure and continued inadequacy in governmental and industry efforts toward systematic vaccine development.

This report surveys the public and private sector efforts on HIV vaccine research and development in the past year, with a focus on the U.S. government agencies and pharmaceutical companies that are most likely to make a difference. It finds that, despite an impressive array of dedicated researchers and increasing funding for HIV vaccines, the world will fall far short of President Clinton's deadline. U.S. government research efforts are not focused on results, leaders err on the side of caution rather than on moving forward, responsibility is diffuse, and the nation has stood silent as pharmaceutical companies, including the world's largest vaccine producer, make little or no investment in one of the greatest public health challenges of our century.

To address these obstacles, the AIDS Vaccine Advocacy Coalition (AVAC) recommends the following agenda for action:

Agencies funded to conduct HIV vaccine research and development must establish clearer plans and goals to expand the HIV vaccine pipeline.

The ultimate goal is a safe, effective, preventive HIV vaccine that can be used to protect people throughout the world. Interim goals must also be set, against which the success and failure of the vaccine effort can be judged. These interim goals should include:

- increasing the annual number of targeted research projects that are applicable to new and improved vaccine concepts;
- increasing the annual number of vaccine concepts evaluated in primate models;
- increasing the annual number of vaccine products that should be evaluated in Phase I trials;
- increasing the number of industry partners involved in developing HIV vaccines; and
- increasing the annual number of products developed that can move into Phase II, proof-of-concept, and Phase III efficacy trials.

Without interim goals, the ultimate goal of an HIV vaccine will not be met.

Global efforts toward a vaccine are scattered and uncoordinated. At this time, only a handful of vaccine products are sufficiently far along in the process to have any chance of being developed into effective vaccines by 2007. The pipeline is a pipette. This must be changed. AVAC calls upon all organizations involved in vaccine research to assess their efforts in the context of clearly articulated plans for rapid development of HIV vaccines.

The U.S. Government must be clear about who should take responsibility and accountability to achieve these goals.

In the United States government, the Directors of the National Institute of Allergy and Infectious Diseases (NIAID) and the Walter Reed Army Institute of Research (WRAIR) should be adequately funded and held accountable for progress toward a vaccine. Other agencies, institutes, and committees who wish to claim a role in developing HIV vaccines should be clear about how they work with these major players. In 1998, responsibility is scattered. Industry spends miniscule amounts on HIV vaccine development. NIAID is increasingly well-funded for HIV vaccine work, but is plagued by a bureaucratic paralysis of committee reviews, second-guessing, lack of leadership, and fear of failure. WRAIR is better structured, but is inadequately funded.

The leaders of NIAID, WRAIR, and industry must be held accountable for the adequate funding, structuring and staffing of their organizations to achieve progress toward an HIV vaccine. The CEOs and directors of Merck, American Home Products/Wyeth-Ayerst, Pasteur Merieux Connaught, SmithKline Beecham, Chiron and other major vaccine companies should be publicly questioned and also encouraged by the U.S. President to invest in developing an HIV vaccine.

Increased commitment, funding, and courage is required from all sectors.

So far in many parts of government and industry, having no progress in HIV vaccine development is seen as a better alternative than staking dollars and scientific reputations against the unknowns of preclinical and clinical research. This must change. It is a failure to take a year to hire a director of the NIH Vaccine Research Center. It is a failure that no candidate HIV vaccine has moved into an efficacy study. It is a failure that the G-8 nations, despite their commitment to boost HIV vaccine development, have taken no significant coordinated action. It is a failure that companies like SmithKline Beecham, the world's largest vaccine manufacturer, have remained largely on the sidelines of HIV vaccine development.

This annual report chronicles events during the past year, and seeks to provide an independent, honest, well-informed critique of current efforts toward an HIV vaccine. AVAC is a United States advocacy group and this report focuses largely on the efforts of our government. This is not to ignore the fact that the challenge and effort are international in scope, and that advocacy must focus on the efforts by industry, governments, and international agencies throughout the world. Toward that goal, we hope that this report furthers dialogue and progress in the many organizations whose missions relate to combating the HIV epidemic.

Introduction

During the past twelve months, the world has begun to rise in earnest to the challenges of developing a vaccine to prevent HIV, a deadly virus now infecting one new person every six seconds-5.8 million people each year. In May 1997, the U.S. President issued a bold challenge to the nation to develop an HIV vaccine within a decade. More federal money was allocated to the vaccine effort. A distinguished oversight committee was convened. New funding mechanisms were created and new grants awarded. Phase II trials began in the United States and Thailand, and a U.S. NIH Vaccine Research Center was announced. A group of physicians demanded human trials of a risky but promising vaccine approach.

For communities in the United States and around the world devastated by HIV, was this an embarrassment of riches? Not exactly. An ambitious challenge has been issued, but the mobilization necessary to meet that challenge is not yet complete. The truth is, many essential elements necessary to address one of the most important and difficult scientific goals of the century are still not in place. Advances in HIV vaccine funding and research remain cautious, while the pandemic rages out of control.

One year ago, AVAC identified several gaps in the effort toward a truly comprehensive and accelerated HIV vaccine research program. Many of the recommendations from the December 1996 AVAC report Industry Investment in HIV Vaccine Research have been implemented: the President set a national goal for developing an HIV vaccine, U.S. government funding increased and is slated for continued increase, and a grant-funded targeted research program aimed at stimulating new approaches and enticing new investigators was initiated. Other AVAC recommendations met with less success. Last year, the focus of our report was on private industry, where much of the expertise to develop and test products is found. We talked to representatives of 23 pharmaceutical and biotech companies about the need for government to provide scientific and political leadership and increase direct financial support for industry efforts. Of those 23, only 6 are still in the business of HIV vaccines in any significant way.

In 1996, there was virtual silence on the need for an HIV vaccine. In 1997, a goal was established by the President, but without a coordinated plan to achieve it. In 1998 so far, it's pretty quiet again. Whether or not we reach the ambitious ten-year deadline for an HIV vaccine, it is critical in 1998 that we move quickly to expand the breadth and timeliness of HIV vaccine research, so that we can reach the goal as soon as possible. Pretending to fill the leadership gap, marginally increasing public funds, and improving part of the grant evaluation and awards process does not add up to the full mobilization we need to develop a vaccine for HIV.

In this report, AVAC attempts a comprehensive and up-to-date assessment of government HIV vaccine research efforts by an independent community-based group. We have compiled a summary of positive and negative events over the year, analyzed government actions and spending, and briefly reported noteworthy events in private industry involvement. Historical data brought together for the first time demonstrates the urgency to move rapidly on research and testing. Key issues in vaccine trials and research are analyzed and discussed. What follows is an agenda for action to galvanize the strengths of all stakeholders in the HIV vaccine effort.

Agenda for Action

Any agenda for action in HIV vaccine development must take into account the very long lag time between a scientist's promising idea for a vaccine and the delivery of that product to the millions of people at risk for HIV in the world. Preclinical research, animal testing, preparation of the vaccine for use in humans, Phase I and II human trials to measure safety, delivery schedule, dose, and immune response and large-scale Phase III efficacy trials are all part of the process. Dozens of Phase I and II trials, and several Phase III trials may be necessary. And once a vaccine is proven effective, global access will be needed, particularly in poorer countries where 95% of new infections are occurring. Ten years is not a lot of time.

1. The logical answer to meeting a ten-year goal is to do many things at once in a clearly planned effort.

Agencies funded to conduct HIV vaccine research and development must establish clearer plans and goals to expand the HIV vaccine research and development pipeline. Basic and targeted research must be funded with a focus on applicability to new and better vaccine candidates. Development of new vaccine approaches must be pursued with the goal of comparative testing in primate models. New vaccine products need to be moved into Phase I clinical trials. Existing vaccine products must continue to be evaluated in clinical trials and improved based on clinical data. Proof-of-concept and Phase III trials must be considered with an eye toward what can be learned from them. And, finally, mechanisms such as international purchase funds must be developed to guarantee eventual global access to vaccines. What exists today is only a shell of that effort.

2. A far greater number of clinical trials must be initiated if there is to be any chance of reaching a ten-year goal for an HIV vaccine.

Basic research and targeted research to develop new vaccine concepts are important, but if a ten-year goal is to be met, it will probably be met with one of the vaccine concepts now in or close to Phase I clinical trials. Two or three products currently in Phase I and Phase II trials may show enough immunogenicity to warrant Phase III efficacy trials. Only three Phase II trials have ever been initiated, and only one or two efficacy studies are currently being discussed. This must change.

AVAC supports the evaluation of vaccine products in clinical trials when the products and trial designs are likely to help researchers learn more about vaccines and protection from HIV, even if the product proves ineffective. We believe that the NIH domestic clinical trials networks have made substantial progress in ensuring a thorough informed consent process, sustained and high quality behavioral interventions for all trial participants, compensation for physical harm, an infrastructure to address discrimination against volunteers, and ongoing monitoring of the risk behavior of participants. Communities should be supportive of clinical trials as an essential part of the HIV vaccine development process.

3. Within the U.S. government, clearer lines of responsibility and accountability must be defined to achieve progress.

An HIV vaccine will be developed only through the combined, coordinated efforts of industry, community and governments throughout the world. Each sector of the international community is needed to achieve the outcomes necessary for an HIV vaccine. Among the largest industrialized countries (the G-8), the United States government provides the greatest share of resources toward HIV vaccine research and testing. Public funding for HIV vaccine research increased in the United States this year, but in all other industrialized countries, funding remained constant or declined. The United States government bears a special responsibility for the success or failure of the international HIV vaccine effort.

However, while the United States National Institutes of Health (NIH) are increasingly well-funded for the work, the institutes are mired in bureaucratic process and delay. A new and tangible leadership gap has emerged with the loss of several forceful and outspoken scientific leaders at NIH, and filling these positions is nearly impossible due to the perception that these positions do not provide the authority or freedom to accomplish anything really meaningful.

The United States Army's Walter Reed Army Institute of Research (WRAIR) is better structured, but works with so little funding and staffing that it is limited in the number of company products, countries, and trial sites with which it can partner. Other U.S. government agencies and offices, such as the Centers for Disease Control and Prevention (CDC) and the United States Agency for International Development (USAID), are not clearly linked to an all-out vaccine effort. The answer is not the creation of committees, but stronger actions and accountability.

4. The Director of the NIH should take ultimate responsibility in adequately managing the HIV vaccine effort. He should submit an annual report to the President and Congress on progress in meeting the ten-year goal.

The "trans-NIH" coordination of HIV vaccine research recommended by the Levine Report several years ago has been partly addressed through stronger communication links among the directors of the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), the Office of AIDS Research (OAR), and now David Baltimore's AIDS Vaccine Research Committee (AVRC), and soon the Vaccine Research Center. Yet the $150 million in HIV vaccine funding at the many NIH institutes, centers, programs and funding mechanisms should be spent with a central vision and coordinated agenda. Although there are many chiefs at the NIH, none seem to have the clear authority and responsibility for making sure something will come out of the pipeline. The OAR is not, in fact, coordinating the vaccine effort, nor is the AVRC. Beyond the directors of NIAID and NCI, the Director of the NIH has an opportunity to hire and cultivate such a leader through the now vacant positions of OAR Director and Vaccine Research Center Director. The Director of the NIH should make these positions more attractive to qualified candidates by streamlining the reporting and decision-making processes for these jobs, and increasing the autonomy and responsibility of these positions.

5. The Director of the NIH must ensure that the new intramural NCI-NIAID Vaccine Research Center is a driving force in vaccine development, and not merely a reorganization of researchers already on the payroll placed in a new building.

To be truly additive, the new Vaccine Research Center needs a talented leader and a unified team of researchers working with the goal of transforming knowledge into useable products. As noted above, the search for a director of this lab has already taken nearly a year. The NIH will probably not gain a strong leader in this position while the position reports to three directors and has little or no autonomous budget or staffing authority. This must change.

6. The NIH must continue to create new and innovative mechanisms to fund targeted HIV vaccine research.

In 1997, new targeted grant programs and contract mechanisms were established, such as NIAID Innovation Grants. A new vaccine-oriented study section was created. Vaccine-related investigator initiated grants increased in 1997 in number and total amount. However, the normal operational constraints imposed on government agencies often make it hard to respond quickly to new funding needs, or to work in a meaningful way with industry. There has been a continued drift of funding into understanding immune responses and away from work with direct applications to vaccine development. The NIH directors have publicly acknowledged the need for bolder, more innovative funding to address these issues. Continued strides in this direction are urgently required.

7. The Directors of NIAID and NCI must ensure that well-designed, comparative studies of promising vaccines are conducted in primates on a systematic basis.

Large comparative SIV-macaque trials of leading products are needed. The NIH should work toward new ways to evaluate the newer envelope vaccines, vaccinia and MVA vectors, poxvirus vectors, and DNA vaccines in a comparative way so that efforts and resources can be focused toward the most immunogenic products. A review of the Regional Primate Research Centers and their ability to conduct large-scale comparative testing of products was recommended by the Levine committee but has yet to be initiated.

8. The Director of NIAID must challenge his division directors to make funding more available for product development.

It is costly and complex to turn a novel vaccine concept at the research bench into a new vaccine product that can be evaluated in animals and people. The NIH should continue to create new funding for pharmaceutical and biotech companies, and for researchers such as those at St. Jude's and the University of Maryland, who want to move vaccine ideas into clinical trials. In the past year, the NIH created a Master Contract for Product Development, and Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) funding. These new funding programs are a first step, but the Director of NIAID, with the support of the directors of the NIH and the OAR, must continue to challenge the constraints of the NIH to make vaccine development funding more available to industry partners.

9. The Director of NIAID and the clinical trial investigators should be more assertive in recommending clinical evaluation of vaccine concepts.

NIAID should continue to integrate and support the U.S. HIVNET and AIDS Vaccine Evaluation Group (AVEG) clinical trial networks for evaluation of multiple products. NIAID should also continue to assist other countries in developing HIVNET clinical trial sites. Capacity for several simultaneous Phase II and proof-of-concept trials is needed.

10. The Director of NIAID should outline a clear process for deciding whether and when to move into Phase III efficacy trials.

Preparing for a Phase III clinical trial of a promising HIV vaccine candidate has been part of the OAR strategic plan since 1994. There is an urgent need for such a process, since multiple Phase III trials are likely to be needed, and there is the downside potential for very public, agonizing and confusing decisions on each. With the support of NIH Director Varmus, NIAID should state clearly who will make Phase III decisions for government so that scientists, community members and others will know how to give input into this process, and be able to accept and support its outcome. Phase III testing should not be seen as an end in itself, but a critical part of product development and testing.

11. U.S. agencies such as the CDC, USAID, the State Department, and leaders of the G-8 countries, the World Bank, and UNAIDS should increase support for international clinical trial activities.

At least twelve countries in Asia, Africa, South America and the Caribbean are trying to develop an ability to evaluate HIV vaccines for their populations. The NIH's NIAID and Fogarty international training programs have provided extensive support to most of these countries. UNAIDS and WRAIR should also be commended for their past efforts in supporting the leaders of Thailand, Uganda and other countries in developing plans and capability for HIV vaccine development. More funding of UNAIDS and WRAIR is needed for this effort.

12. The CEOs of the world's major vaccine companies must be publicly called upon to invest in HIV vaccine development. Companies like SmithKline Beecham must begin to play a significant role in the effort.

The true expertise to develop vaccine products and move them through clinical trials and FDA licensing exists in the private sector. Due largely to economies of scale, where profits on many vaccines can be made only at millions of doses, the world's entire private sector vaccine research and development effort is concentrated at about eight to ten companies, the largest being SmithKline Beecham, Merck, Pasteur Merieux Connaught and American Home Products/Wyeth-Ayerst Laboratories. During the past year, the interest by these large companies in HIV vaccines has remained minimal. SmithKline Beecham, for example, with $1.2 billion in annual revenues from global vaccine sales, has essentially no active HIV vaccine development program. Some of the large vaccine companies justify their "wait-and-see" hesitancy on the ambiguity of the science. That reasoning could absolve industry from their social responsibility to invest in HIV vaccines for many years to come. AVAC believes that industry has a responsibility to play an expanded role in addressing the AIDS public health catastrophe. The major pharmaceutical companies should be pursuing multiple HIV vaccine approaches, and/or investing in smaller biotech companies which have promising products. Both PhRMA and BIO, the industry trade associations, could play an expanded role by highlighting the importance of HIV vaccine work, identifying the impediments to increased investment in HIV vaccines, and lobbying for public and private funding for HIV vaccine projects.

13. The President must take a direct, personal role in encouraging private and public HIV vaccine development efforts. The directors of the NIH and the Office of National AIDS Policy should use their influence to enlist President Clinton and Vice President Gore in these efforts.

A few inspiring speeches do not constitute leadership. President Clinton's May 1997 speech was not enough. In his two final years in office, President Clinton should request large sustained funding increases for the NIH and WRAIR from Congress. Vice President Gore should follow up on his meeting last year with pharmaceutical industry representatives by convening a series of high profile working meetings with the pharmaceutical and biotech industries to develop potential policy and financial incentives for HIV vaccine research. The White House should go to Congress with proposals to address the fundamental market disincentives for industry investment, such as proposals for extensions of patent and intellectual property rights, tax incentives, and liability legislation. At the G-8 Summit in May of this year, the United States should work hard to encourage leadership and investment by the G-8 countries. In order to achieve a vaccine in the foreseeable future, our political leaders need to keep this issue on the world's calendar.

14. Non-government-sponsored research efforts need to move more quickly in certain areas of HIV-vaccine development. Such efforts must be encouraged and provided with broad-based support.

The International AIDS Vaccine Initiative (IAVI), the American Foundation for AIDS Research (AmFAR) and other organizations have made funding available for HIV vaccine research and development during the past year, but these groups will need substantial new resources to fill gaps in research and product development. AVAC applauds the direct funding for HIV vaccine research provided by IAVI and AmFAR in 1997. IAVI has done a good job at identifying research gaps. Their funding of product development in conjunction with securing patent rights to assure widespread vaccine access should be a model for others. UNAIDS is making important efforts to explore ethical issues in a meaningful and inclusive way. The major foundations and individuals who are or should be involved in AIDS and health research funding, including the Ford, Kaiser, and Rockefeller Foundations and individuals such as William Gates, David Geffen, and George Soros should increase their giving to these organizations and directly to HIV vaccine research.

15. AIDS-related conferences must provide increased opportunities for exchange of scientific information among vaccine researchers, developers and affected communities.

The NIAID Division of AIDS has in the past supported a regular conference of its National Cooperative Vaccine Development Groups (NCVDG), but may discontinue this conference. Researchers in the HIV vaccine field need continued opportunities for exchange of information. The organizers of the annual Conference on Retroviruses and Opportunistic Infections, the frequent Keystone Symposia, and the World AIDS Conference can create separate tracks in their regular meetings for HIV vaccine research and development that would stimulate research and information sharing.

16. An International HIV vaccine purchase fund must be created. IAVI's proposal to launch the fund, which would be managed by an international agency such as the World Bank, should be actively supported.

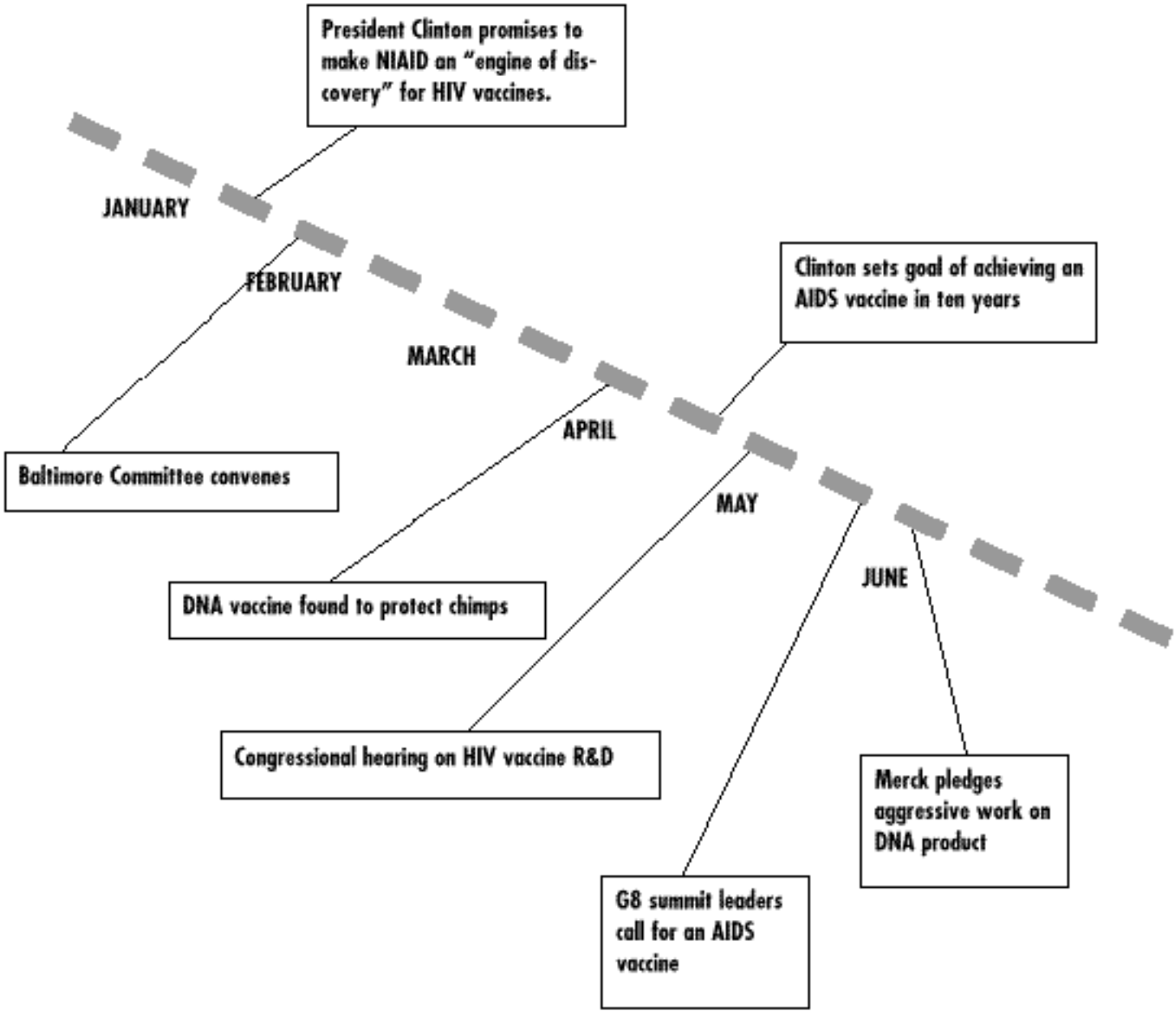
The International AIDS Vaccine Initiative has proposed an international HIV vaccine fund to purchase or provide lines of credit for poorer countries for purchase of HIV vaccines. We strongly support this concept and believe that such a fund could help encourage private investment in HIV vaccines and assure wider access to a product when it becomes available.

17. Community advocates and not-for-profit organizations must increase their commitment to HIV vaccines.

Affected communities can choose to participate in trials, demand ethical research, and work toward equitable delivery of a vaccine. AIDS prevention and service organizations largely supported the President's challenge this year, but vaccines are not yet prominent on the advocacy agenda. More is needed to build informed and passionate public advocacy for HIV vaccine research and clinical trials. During the past year, AmFAR directly funded research and published a directory of HIV vaccine trials. The National Minority AIDS Council (NMAC) and AVAC co-sponsored a national vaccine advocates forum. The Treatment Action Group (TAG) began speaking out on vaccines. IAVI published a newsletter, the IAVI Report, and created a web site on vaccines (www.iavi.org). Vaccine Advocates also created an excellent web site (www.vaccineadvocates.org) offering a wide variety of information and documents. Other advocacy organizations, community members and members of the press and public should seek greater involvement in learning about and debating issues such as which products should be in clinical trials, international trial ethics and readiness, participant rights and safety, and eventual global access to vaccines.

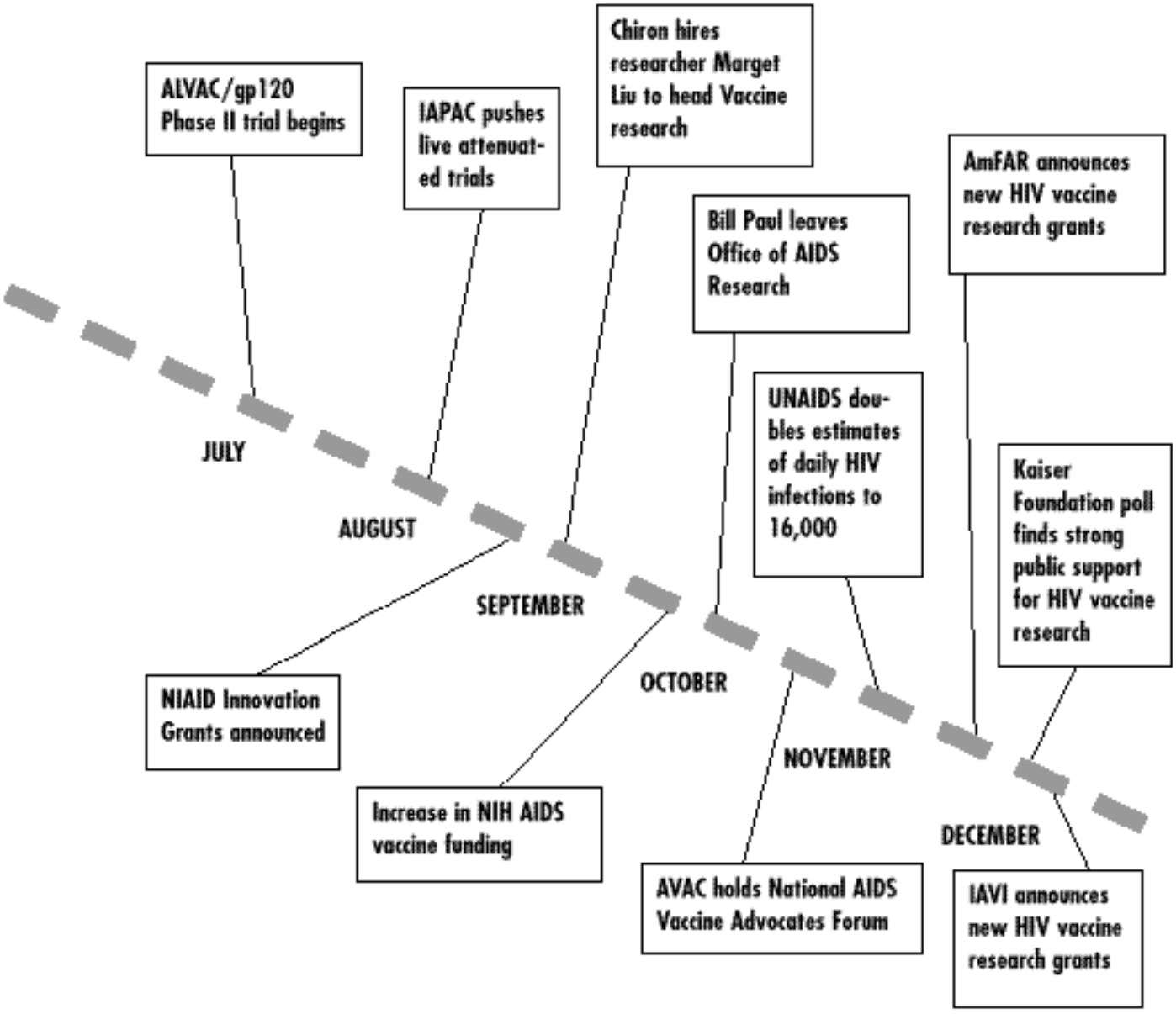
18. Community members should continue to push for resolution of several participant's rights issues as Phase III trials are being considered and planned.

These issues include compensation for medical expenses required as a result of physical harm caused by a vaccine, guaranteed low-cost access to any HIV vaccine which is licensed, and ability to continue full participation in a vaccine study in the event the volunteer is incarcerated. VaxGen and other private companies may be sponsoring their own large-scale HIV vaccine trials in the near future. Participants in these trials are entitled to the same rights and protections afforded to those in government-sponsored trials. These include (as noted above) a thorough informed consent process, sustained and high quality behavioral interventions for all trial participants, compensation for medical expenses necessitated by physical harm, an infrastructure to address discrimination against volunteers, and ongoing monitoring of the risk behavior of participants.



A year of good words...

...and *gradual* advances



19. Affected communities continually need to address justified fears that vaccine research may siphon off funding from HIV drug development and other prevention efforts.

Funding for vaccines must not come at the expense of investment in HIV therapies or other prevention approaches. For at least the next decade or two, treatments, behavioral interventions, condoms, clean needles and, maybe, microbicides will be our only means of fighting AIDS. Even when an effective vaccine is developed, the HIV epidemic is likely to be solved through a combination of behavior change, vaccination, treatment and care. The NIH role in supporting basic HIV research, and research on HIV treatments, microbicides and biomedical interventions to reduce perinatal transmission must continue and not be compromised. AVAC calls for a greater NIH vaccine effort within the context of aggressive research efforts in other HIV prevention interventions and treatment options.

Vaccine access issues

A vaccine for HIV can only control the global epidemic if it is available in the developing world where 95% of new infections are occurring. It is tempting to put aside the difficult and complex issues of vaccine access and pricing, particularly because advocates and governments are seeking to increase private industry interest in HIV vaccine research, and pharmaceuticals are wary of efforts to limit their ability to recoup investment costs and make profits. Yet without advance planning for vaccine purchasing and access, it is likely that delivery of the first useful vaccine would be delayed for years in the developing world.

The World Health Organization has reported that the lag time between development of a vaccine and its delivery in the developing world was 15 years for the polio vaccine and 15 to 20 years for the measles vaccines. The hepatitis B vaccine is another example. Originally marketed over a decade ago, this highly effective vaccine only recently became available in the developing world where prevalence rates are highest. Hepatitis B vaccine followed a classic drug development path that resulted in a vaccine far too expensive for most of those at risk and with no immediate plan to expand access beyond populations in industrialized countries. Planning for global access to HIV vaccines should begin now.

The International AIDS Vaccine Initiative has begun exploring options to maximize access to an HIV vaccine. These include a proposal to create an internationally financed purchasing pool administered by an agency such as the World Bank. The pool would be used to purchase HIV vaccines for developing countries. As part of its funding agreements with companies, IAVI is also attempting to retain limited patent rights for vaccine product development in developing countries.

AVAC applauds this effort to focus not just on the scientific developments of HIV vaccine research, but also on the issues of access: payment schemes, pricing agreements and patent negotiations. There was a time when far-sighted access arrangements should have been developed for new drugs called protease inhibitors in the same way.

Overview of U.S. HIV Vaccine Research

"The President has set a difficult goal for the research community, but NIH is ready to bring its scientific expertise and resources into play."
-NIH Director Harold Varmus
May 23, 1997

THE NATIONAL INSTITUTES OF HEALTH

The road to an HIV vaccine is likely to run through the 300 acres of the National Institutes of Health (NIH). In 1997, the NIH awarded 544 contracts and grants totaling more than $130 million for HIV vaccine research. Even before the recent industry drop-outs and increases in funding by the U.S. government, this was estimated to be 70% of all worldwide spending on HIV vaccine research and development conducted by private industry, governmental agencies and non-governmental organizations. In other words, in worldwide investment in HIV vaccine research and development, the NIH allocates twice the funding of all other sources.

The NIH is made up of 24 independent institutes, centers, and divisions (ICDs), most of which are located in Bethesda, MD. Eight of these received some HIV vaccine funding in 1997.

The National Institute of Allergy and Infectious Diseases (NIAID) received a larger share than any other institute, garnering more than three-quarters of all NIH HIV vaccine research funds (76.1%).

The Office of AIDS Research (OAR), under the Office of the Director of the NIH, received the second-largest disbursement of vaccine funding in 1997. The OAR, which oversees the distribution of all NIH AIDS research funds, also has direct control over a discretionary fund. In 1997, 9.4% ($12.1 million) of HIV vaccine spending went into the OAR discretionary fund, a three-fold increase over spending in 1996 ($3.4 million).

The National Cancer Institute (NCI) was the third leading recipient in 1997, with 6% of the funding for HIV vaccine work. Five other NIH institutes disbursed the remaining 8.5%: National Center for Research Resources, $6.5 million; Fogarty International Center (training), $1.8 million; Institute of Dental Research, $1.2 million; Environmental Health Sciences, $300,000; and Heart, Lung & Blood Institute, $200,000. Significant changes have occurred in the past year in the distribution of funds between institutes and centers. In 1997, NIAID and OAR made the biggest gains. As mentioned previously, discretionary funding at OAR increased from $3.4 million to $12.1 million. Funding at NIAID increased by $20.6 million, or 26%. Money for the National Center for Research Resources (NCRR) rose more modestly, while funds for the NCI and the Fogarty International Center were cut substantially in real and percentage terms.

Battling the Bureaucracy

NIAID, the OAR, the NCI and the other institutes and centers of the NIH fund a broad range of HIV/AIDS research. The vast amount and quality of the research funded makes NIH a true "discovery engine" for worldwide scientific advances. Furthermore, the NIH funds more than just the basic research that private industry is either unable or unwilling to do; its capabilities also extend into the domain of product development and clinical evaluation. As the recent development of the rotavirus vaccine against childhood diarrhea illustrates, NIH is, in many ways, uniquely positioned to generate new vaccine concepts, assess their viability, incorporate them into product designs, and conduct clinical trials when industry falls short.

However, as an enormous U.S. government agency, the NIH faces challenges of internal coordination and operational constraints imposed on U.S. government agencies which limit flexibility and retard timely shifts in resources in response to changing scientific knowledge and opportunities. As discovered by early AIDS treatment activists, the sheer size and structures of the NIH can be a hindrance as well as a help in overcoming the unprecedented scientific challenges posed by HIV/AIDS. For research and development of HIV vaccines, the relatively uncoordinated, Balkanized structure of the institutes and centers of the NIH has been criticized by many as an impediment to progress. Any HIV vaccine spending must be competitive and public, and most advisory meetings must be public as well. Although these are genuinely good rules, they can increase bureaucracy, slow things down, and stimulate political dissent.

Some of these constraints are an unavoidable part of government research funding. However, many constraints of large bureaucratic systems can be overcome by strong leadership and a change in organizational culture toward allowing bold creative decision-making. The U.S. corporate world is rife with examples of success.

One attempt to review the funding of HIV/AIDS research at the NIH was a congressionally mandated, year-long outside review of the entire $1.4 billion NIH AIDS research program, commissioned by the OAR in 1994. A blue-ribbon panel, headed by Dr. Arnold Levine of Princeton University, divided the AIDS research program into six areas, one of which was Vaccine Research and Development. In February 1996, the panel published a report that included a series of formal recommendations, which is commonly referred to as the Levine Report.

One of the fundamental recommendations of the Levine Report was that the "the entire AIDS vaccine research effort of the NIH should be restructured." It asked that "a trans-NIH vaccine program be established with leadership and oversight provided by distinguished, non-Government scientists." This recommendation has been partially addressed by creation of the AIDS Vaccine Research Committee (AVRC) as an oversight and advisory committee.

It is unclear, however, whether the Levine Report's call for greater centralization and coordination could ever be adequately met by either the OAR or the AVRC. While the NIH has given an oversight and advisory role to the AVRC, it has done so while maintaining the traditional autonomy of its institutes. And although the OAR sets goals and priorities for AIDS-related research funded through the institutes, the final decisions as to exactly who and what gets funded, according to these priorities, are made by the separate institute directors.

The responsibility for leadership and coordination of the NIH bureaucracy remains squarely on the shoulders of the Director of the NIH, and the Directors of NIAID, NCI and the other institutes. It cannot be delegated to the OAR or the AVRC advisory committee. Thus AVAC calls upon the Directors of the NIH, NIAID and NCI to take primary responsibility for focusing NIH efforts toward expanding the HIV vaccine pipeline. We recognize that directing the HIV vaccine effort within the NIH is a large task, and that only recently has NIH begun to give HIV vaccine research the resources and priority it warrants. Newer vaccine technologies present unique scientific and economic challenges. HIV vaccines present unique legal and ethical challenges. Progress has been made in terms of focus, strategies and recognition of previous shortcomings in the HIV vaccine program. But in light of President Clinton's challenge to develop an HIV vaccine within a decade, more is needed at the NIH to overcome bureaucratic constraints.

NIH HIV Vaccine Funding Across the Institutes

The call for substantially increased HIV vaccine research funding, a key recommendation of the Levine Report echoed by many others, has been visibly embraced by the NIH leadership. After remaining relatively flat from 1994-96, with a decrease in 1995 reflecting more accurate coding, funding for HIV vaccine research increased substantially in 1997 (17%), and will rise an additional 17% in 1998. Although funding remains less than 10% of total AIDS spending (see Table 1), it has clearly increased.

Table 1. Total NIH spending on HIV vaccine research, 1994-1998 (in millions of dollars).

	Total AIDS	HIV vaccine	% total
FY1994	1,296.5	110.6	8.5%
FY1995	1,333.9	89.0	6.7%
FY1996	1,410.9	111.1	7.9%
FY1997	1,501.1	130.2	8.7%
FY1998 est.	1,607.1	153.0	9.5%

The increase in HIV vaccine funding is important, but it should be noted that there are many different ways to spend money at NIH. The relative size of these various investments requires clear and consistent oversight on the part of the NIH administration. Proper structure and staffing at the NIH is imperative in providing this oversight.

Vaccine development involves four steps. The first is basic and targeted research involving laboratory and animal studies. The second is production of candidate HIV vaccines for testing in people. The final two steps are called clinical research, and involve testing candidate vaccines in human volunteers, initially for safety and immunogenicity (Phase I and II trials), then for efficacy (Phase III trials) (see Appendix A).

Preclinical vs. Clinical Research

From 1994-1996 a little more than one-third of all NIH HIV vaccine funding went to support clinical trials and the development of clinical trial infrastructure. The remaining two-thirds were devoted to preclinical research (See Table 2). In recent years, spending on clinical trials has declined in absolute and percentage terms. This shift is partly a reflection of no increase of testable products in the pipeline (and no efficacy trials), but also reflects a shift in the use and coding of the vaccine trial site dollars into trials of other prevention interventions. Vaccine spending in 1997 was thus largely directed into basic and targeted research on host defense mechanisms, vaccine design and animal testing.

Table 2. NIH HIV vaccine research, 1994-1997, by type of research (in millions of dollars).

	FY1994	FY1995	FY1996	FY1997
Preclinical	66.2	63.6	78.0	99.2
	59%	*63%*	*72%*	*76%*
Clinical	46.7	37.0	29.7	31.1
	41%	*37%*	*28%*	*24%*
Total (100%)	112.9	100.6	107.8	130.3

Intramural vs. Extramural Research

One recommendation of the Levine committee (made up largely of extramural researchers) was to increase the percentage of HIV vaccine research spending awarded to extramural research (conducted outside the NIH) compared to intramural research (conducted within the institutes). NIH intramural funding for HIV vaccine research did in fact decrease in total dollars and as a proportion of all HIV vaccine spending, from 14% to 9%. Extramural funding increased as a percentage of HIV vaccine research spending from 67% to 73%.The balance of extramural vs. intramural funding differs by institute; for example, NCI has had a greater intramural focus to its HIV vaccine effort than NIAID. It remains to be seen what the impact of the NCI-NIAID Vaccine Research Center will be on the level and distribution of intramural research, since at least part of the research of the large intramural labs will be coordinated there. It also remains to be seen whether the balance of extramural vs. intramural funding makes any difference in the quality and progress of research toward development of an HIV vaccine.

Grants vs. Contracts

Despite the creation of the Innovation Grants and increased investigator-initiated extramural funding (awarded as R01 grants), both extramural and intramural HIV vaccine funding at NIH remains heavily contracted. Since fiscal year 1994, for all AIDS-related research funding, the OAR states that the volume of investigator-initiated project grants has increased from 23% to an estimated 52% in FY1998. By comparison, in FY1997, HIV vaccine investigator initiated project grants accounted for only about 29% of total HIV vaccine funding, compared with 45% for extramural contracts. This probably reflects the need for large-scale systematic work in HIV vaccine research in areas of immunology, reagents, animal studies, and clinical trial networks. Rather than focusing on analyzing different contracting and granting mechanisms, it seems that the actual funding mechanism may matter less than the way that funding is used to speed progress toward HIV vaccine development.

National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases (NIAID), primarily through its Division of AIDS (DAIDS), is the primary agent in NIH's effort to develop an HIV vaccine, receiving three-quarters of the NIH's spending on HIV vaccine work. In 1997, NIAID spent $98 million on HIV vaccine research, 15% of its $648 million AIDS budget and about 7.8% of its overall institute budget.

For the last several years, the NIAID organizational structure has grouped HIV vaccine research funding in DAIDS under the Vaccine and Prevention Research Program (VPRP), one of three major areas of DAIDS, the others being Basic Sciences and Therapeutics. The VPRP vaccine program is, in turn, divided into three Branches: Preclinical Research, Clinical Development, and Efficacy Trials. VPRP has a professional staff of about twenty, managing virtually all of NIAID's vaccine-related contracts and grants (see Appendix B, Funding mechanisms: The way money gets spent at NIAID).

The Preclinical Research program of the VPRP oversees Innovation Grants for early concept research, standard investigator-initiated R01/N01/P01 grants now called HIV Research and Design (HIVRAD) funding, and targeted research funding called the Integrated Preclinical/Clinical AIDS Vaccine Development Program (IPCAVD, formerly the NCVDG). The Preclinical Program also supports contracts to fund research on HIV genetic and antigenic variation, mucosal immunology, adjuvant development, and utilization of animal models through Preclinical Master Agreements, Simian Vaccine Evaluation Units, and a Chimpanzee Unit.

The Clinical Development Branch of the VPRP manages the AIDS Vaccine Evaluation Group (AVEG), which conducts Phase I and Phase II human trials. The Efficacy Trials Branch of the VPRP manages the HIV Vaccine Efficacy Trials Network (HIVNET), which has domestic and international master contractors. In late 1997, the Associate Director of the Vaccine and Prevention Research Program left the NIH, and a search has been underway to replace her. There have also been discussions about reorganizing this program internally and adding new projects to fill out the program and make it as complete and "seamless" as possible. Three stated goals at present are: 1) filling the pipeline with new vaccine concepts; 2) identifying and improving assays and expanding access to reagents; and 3) designing a vaccine clinical infrastructure coordinated with at-risk communities and basic scientists involved in concept development. These changes are very much in progress and in flux, and it may take as long as two years for the DAIDS program to be restructured and complete.

NIAID enjoyed a $20.1 million rise in vaccine spending in 1997, an increase of 26% over 1996. A little over half of the increase, $11.1 million, went to studying Host Defense Mechanisms. The second largest increase went to Phase III Infrastructure Development in the amount of $3.4 million, a 61% increase. Active and Passive Pediatric Vaccine spending was up 33%, by $2 million. Vaccine Design and Animal Testing and

Phase I/II Vaccine trials received more modest increases of 9.5% ($2.5 million) and 7.0% ($1.1 million). In 1998, DAIDS announced a Master Contract to provide the capability to develop and evaluate specific products. For 1999, DAIDS has also proposed funding three to four Targeted AIDS Vaccine Research Centers, not unlike the planned internal NIH Vaccine Research Center. These centers would be multi-disciplinary, highly focused collaborations of corporate or academic scientists who would plan and execute a targeted HIV vaccine research effort, focusing on a particular vaccine concept. NIAID and DAIDS are also likely to propose more targeted grant initiatives, like the Innovation Grants, that would fill in the stages for vaccine development over the next few years as more funds become available and innovative concepts move forward.

Despite this progress, continued attention is needed to making the funding programs meet the challenges of HIV vaccine research and development. With 75% of NIH HIV vaccine funding, the Director of NIAID has a commensurate responsibility for ensuring that his institute moves products into trials, engages industry partners, supports international trial sites, and defines criteria for the multiple Phase III trials that will be needed for development of an HIV vaccine.

National Cancer Institute

The National Cancer Institute (NCI) is the largest of the 17 biomedical research institutes and centers at the NIH, but HIV vaccine work constitutes a small portion of its total funding ($7.7 million, which is 3.4% of NCI's $225 million in AIDS research and 0.3% of its total research budget of $2.39 billion). Vaccine research at NCI is conducted on the central NIH campus and at the Frederick Cancer Research and Development Center (FCRDC).

In recent years, NCI had been much criticized for the management of its HIV vaccine research program. The Bishop/Calabresi Report, which was issued in May 1995, identified a number of problems in the Institute's overall intramural research program. Richard Klausner, the current NCI Director, was appointed shortly thereafter. The 1996 Levine Report concluded that in FY1994 up to half of the money classified by NCI for HIV vaccine research had been unrelated to HIV. Judging from 1997 project summaries and recent decreases in the amounts allocated, this problem seems to have been corrected.

A second criticism by the Levine Committee (composed largely of extramural researchers) was NCI's heavy preference for in-house, intramural research over peer-reviewed, investigator-initiated external grants. For example, in FY1997, the ratio of HIV vaccine spending between intramural research and extramural R01 grants at NCI was thirteen to one (39% of total HIV vaccine spending versus only 3% for a single R01 grant). By contrast, at NIAID, two dollars were allocated for external grants for every dollar of intramural research. In addition, NCI spends more than twice as much in percentage terms for overhead charges (RMS) as NIAID, 8.4% versus 3% of total vaccine funding. NCI's intramural vaccine funding has been reduced since then, partly from recoding and partly from a true shift of dollars to external research institutions. A further shift of this intramural funding may occur in 1998 with the formation of the joint NCI-NIAID Vaccine Research Center.

There is no doubt that NCI supports a number of top-quality HIV vaccine researchers, and this support should continue. However, the Director of the NCI should continue to work closely with the Directors of the NIH and NIAID to coordinate research efforts and maximize the use of both institutes' particular resources.

National Center for Research Resources

HIV vaccine funding at the National Center for Research Resources (NCRR) was virtually unchanged in FY1997 with a decline of 1% (versus the increase in overall vaccine spending of 21%). There were, however, significant shifts in how the money was allocated. Spending in the largest category, Vaccine Design and Animal Testing through the Regional Primate Research Centers, rose 24%, and now constitutes 87% of NCRR's HIV vaccine funding. At the same time, there were corresponding decreases for clinical research activities. In 1996, the Levine Report asked the NCRR to review the primate centers. This has not yet been done.

Office of AIDS Research

The Office of AIDS Research (OAR), as mentioned previously, has the dual role of setting goals and priorities for AIDS-related research funding, and managing its own discretionary funds. In both roles, the OAR has been very supportive of HIV vaccine research, and hopefully will continue to be supportive under a new director.

Half of the OAR's 1997 discretionary spending for HIV vaccine research, $6 million, was channeled to NIAID to launch the Innovation Grant program. After a stronger than expected response from the scientific community, OAR added an additional $3.2 million from its discretionary fund to augment the amount available for the grants and NIAID came up with additional money. In addition, approximately $2 million was spent on supplemental funding for promising vaccine research supported by NIAID. In a departure from the prior year's spending pattern, OAR also spent $1.9 million on special projects categorized as Phase III infrastructure development. Even though a second round of Innovation Grant awards is currently underway, vaccine work is not expected to receive the same, disproportionate share of OAR resources that it enjoyed in 1997.

When William Paul resigned as director of the OAR last year, the cause of HIV vaccine research lost a strong advocate in a highly visible position. Over the last several years, OAR has played a key role in providing leadership and funding for HIV vaccine research, and it will be imperative that it continue to provide such leadership under its new director.

AIDS Vaccine Research Committee

Created on the heels of the Levine Report, and chaired by one of America's most influential scientists, Nobel laureate David Baltimore, the AVRC (also known as "the Baltimore Committee") has as its domain all HIV vaccine related spending throughout the NIH. The AVRC has also had the credibility with NIH leadership to informally influence spending decisions. Working in consultation with the Director of NIH, Harold Varmus, and the institute directors, the committee has had a substantial impact on the distribution of vaccine-related resources, in particular towards more support of immune mechanisms and preclinical product development.

AVRC's authority, however, is purely advisory in nature. It has no power over funding decisions. Despite being named by the NIH in its formal response to the Levine Report as the primary agent charged with implementing recommended changes in over a dozen places, the AVRC must rely on its powers of persuasion, public and private. The AVRC is staffed by Carole Heilman, Deputy Director of DAIDS, who is also acting VPRP Director. It meets three times a year and has been conducting regional science meetings to examine scientific challenges and involve new scientists into the vaccine effort. To date, the AVRC has focused only on scientific discussions and NIAID programs, the only exception being the Vaccine Research Center, which is a joint project with NCI.

AVRC has had its most significant impact to date through its role in the Innovation Grant Program for Approaches in HIV Vaccine Research that was created by NIAID. The Innovation Grants are designed to achieve three goals: provide funding support for new people and ideas that had been bypassed by NIH's regular funding patterns, allow NIH to respond more quickly to new concepts and changing science, and solicit targeted research aimed at solving specific scientific bottlenecks.

To achieve the first goal, the program and the application process was oriented specifically towards researchers who had not received prior NIH funding. As a result, of the 49 grants awarded last fall, over half (57%) went to researchers who had not previously received extramural research support from NIAID. These awards have the potential to leverage NIH's resources by attracting additional funding to grant recipients. In the words of one new recipient, the imprimatur of an NIH grant enhances a research team's credibility and can make it easier to attract additional funding.

To achieve the second goal, a new, streamlined review process was put in place that reduced the interval from application to final selection to less than six months, substantially quicker than the norm. The third goal was achieved by identifying three specific areas for the two-year grants: understanding the structure and function of the HIV envelope protein, improved animal models for vaccine and pathogenesis studies, and understanding how vaccines are processed in the body and evoke the immune response.

The Innovation Grants represent a substantial increase in the amount of funds devoted to early-phase HIV vaccine research and development. When the number of grant applications exceeded expectations, the level of funding was almost doubled from an initial budget of $6 million to more than $11.8 million. Based on an encouraging response from researchers, second and third rounds of Innovation Grants are planned for 1998, with scientific areas determined by the AVRC. The focus of the second round of Innovation Grants will be heavily skewed to immunology, soliciting applications to investigate the immunogenicity of HIV envelope proteins, and to investigate mechanisms that elicit cytotoxic T lymphocyte (CTL) responses.

Launching the Innovation Grants Program and awarding funding within six months of the announcement was an extraordinary accomplishment. The program is a clear example of what creative leadership and working together with the full support of the Directors of the NIH and NIAID can accomplish. Plans to expand the program deserve full support. The launching of the Innovation Grants also vividly highlights what NIH has not been able to do in other critical areas of HIV vaccine research, described below.

NIH Vaccine Research Center

A second major initiative of the AVRC has been the creation of a Vaccine Research Center (VRC) within NIH, announced by President Clinton last May. To be jointly overseen by NIAID and NCI, the VRC is designed to promote multidisciplinary research from basic and clinical immunology and virology through to vaccine design and production. Congress has appropriated $26 million of NIH's 1998 funding for construction of the new lab. After President Clinton set a goal of developing an HIV vaccine within the decade, NIH Director Varmus stated that "NIH's new Vaccine Research Center will be a vital part of the effort" (NIH Press Release, May 23, 1997). At the time, the NIH reported that "a search committee will be named before the end of May to seek a scientist with specific expertise in vaccine development to be Director of the new VRC. There will be a broad, national search."

As of April 1998, ten months after the lab was first announced, there has still been no announcement as to who will lead the VRC. NIH officials had confidently predicted that a leader would be found by Autumn 1997. This is a serious delay to the NIH's efforts in the area of HIV vaccine development. Of course, with

the dual reporting structure it is difficult to tell whose responsibility it is to choose a director of the Vaccine Center. Is it the NIAID Director, the NCI Director, the NIH Director, or all three? The confusion of clear accountability is a troubling sign. Moreover, there have been conflicting messages coming from NIH about the actual responsibilities of the VRC. Questions have also been raised as to whether the lab's director will wield sufficient power to be able to bring about real changes in the NIH's HIV vaccine program. If the NIH is serious about meeting President Clinton's ten-year goal, it had better move quickly in hiring a capable director for the center who can articulate a vision of what it will do. From the outside, in terms of the VRC, there appears to be little sense of urgency at the NIH.

Special Vaccine Study Section at NIH

One structural change recommended by the Levine Report that NIH has begun to implement is the creation of a special study section for vaccines. Study sections form the basis of the grant application screening process at NIH. Vaccine researchers have been at a competitive disadvantage for funding because their "applied research" proposals are poorly rated by traditional peer-review committees. Creation of a vaccine-oriented study section is designed to raise the visibility of vaccine research and carve out a domain with more supportive peer review.

The study section is focused on the review of development activities for vaccines against infectious diseases. The applications reviewed in this study section should be clearly distinguished from basic pathogenesis and immunology-oriented research designed to increase understanding of a specific pathogen or mechanisms of immune response, a necessary process that precedes the development of a vaccine. Guidelines are available for comment via a notice on the Center for Science Review (CSR) home page (http://www.csr.nih.gov) and applicants are encouraged to self-refer to this study section beginning this summer.

The new vaccine study section will not focus solely on HIV/AIDS, but will incorporate research related to the development of vaccines for a range of pathogens. It is designed to level the playing field for vaccine researchers and promote funding for multidisciplinary vaccine research. Part of a broader reorganization of the grant review process underway at the CSR, and a complete restructuring of the old AIDS study sections, the pilot vaccine study section is expected to become active in 1998.

NIH's Role in Industry Investment

The NIH has, to date, been less successful in another area highlighted by the Levine Report, the necessity of fostering greater industry involvement in the search for an HIV vaccine. According to a report issued by the Rockefeller Foundation, the private sector accounts for roughly 40% of general medical research but only about 15% of spending on HIV vaccine research. This estimate was made before several large pharmaceutical companies dropped or scaled back their HIV vaccine programs. Although the President and OAR have both set increased cooperation with industry and collaboration between companies as an explicit objective, it remains unclear how this will be accomplished. During 1997, the OAR spent a good amount of time discussing the possibility of initiating a joint meeting with leaders of the vaccine manufacturers and the executive branch, with the Vice President's office also involved in these discussions. In November, a meeting was held between executives of four major vaccine manufacturers and the NIH leadership. However, this meeting was held at the suggestion of PhRMA (Pharmaceutical Research Manufacturers of America), not OAR, and there has been little action in the area since Dr. Paul's departure. If the goal of an HIV vaccine within a decade is to be met, it will only happen with industry involvement. The Director of the NIH and the White House must make this happen.

Moving Towards Efficacy Studies

1997 looked like the year of preparation for efficacy trials by NIH. The Efficacy Trials branch and the Clinical Trials Branch of VPRP designed and enrolled a 420-participant Phase II trial of the best pox vector and envelope boost available at that time, Pasteur Merieux Connaught's (PMC) vCP205 and Chiron's gp120 SF-2 with MF59 adjuvant. Since the decision three years ago not to proceed with government trials of envelope-only vaccines, this has been the approach of choice by NIH. The PMC canarypox vector vaccines stimulate some cellular immunity measured by CTL and the envelope boost consistently stimulates strong antibody (though it is antibody to lab strains of virus only). It was assumed that if similar immunogenicity and safety were found in higher-risk participants in the larger Phase II study, government would be ready to move ahead with at least a proof-of-concept efficacy trial with several thousand at-risk participants at a dozen HIVNET sites in the U.S. This intermediate sized trial could have started early in 1999.

To be sure, this decision would not be a simple one. Fault can be found with each element of this combination vaccine. The CTL response is weak and variable; the antibodies aren't effective against wild viruses. Other approaches may ultimately hold more promise. On the other hand, this is the best we've been able to do in over ten years of human testing and we have no idea how hard it will be to stimulate some protection or improve disease course. Maybe we could get a clue from trials about correlates of immunity, how to design better products, or at least what doesn't work.

But in 1998, the problem of moving ahead has become more than just political. The successful launch of a Phase III efficacy trial depends on a NIAID decision, FDA approval, and community support for enrollment of thousands of people, but it also depends on the willingness of industry to provide products to be tested. Chiron researchers have recently suggested that they may not provide gp120 for such a trial without being paid for it, since it does not have prospects to become a licensed product in light of other wild-type envelopes in development. Meanwhile, PMC is developing its own boost, but has delayed use of its canarypox vector vaccine until Phase I trials have evaluated more complex canarypox constructs that may be more immunogenic. Data from these trials will be available in late 1998 or early 1999, leading to efficacy trials no sooner than the year 2000. Meanwhile, VaxGen claims to have an envelope vaccine.

The impact of early treatment on design of vaccine trials

As if things were not already complex enough, HIV vaccine efficacy trials will likely be complicated by the use of early treatment and post exposure prophylaxis (PEP) by trial participants in the United States and elsewhere. Early treatment uses antivirals within days or weeks after infection has been diagnosed in an attempt to reduce damage done early in the infection process and improve the course of HIV disease. PEP therapy is a combination of antivirals taken soon after possible exposure to HIV, with the goal of preventing infection from taking hold in the body.

If early treatment or PEP do become widely used by vaccine trial participants-and if they prove to be effective-then disease course could be improved for many and infections could be prevented in communities that can afford to implement PEP therapy. But the implication for vaccine trials is that measurement of vaccine effects on disease course would become far more difficult.

There are several ways in which an HIV vaccine might be effective. A vaccine might not succeed in preventing infection but instead prevent progression to disease or reduce infectivity of the vaccinated person. Viral load measures, which have been correlated with HIV disease progression, might be used as a test of vaccine effects. But because of the immediate and profound effects of combination antiviral drugs on viral load, it is not clear that viral load measurements would be a valid surrogate of vaccine effects on disease course or infectivity in a setting with widespread use of PEP and/or early treatment.

In addition, widespread use of early treatment would reduce the ability to even take viral load measurements in that there would typically be only one or two opportunities to test viral load prior to the immediate initiation of antiviral treatment. If PEP or other HIV prevention strategies succeed in reducing HIV incidence in a vaccine trial cohort, then larger sample sizes would be required to assess vaccine effects.

At a September 1997 conference sponsored by NIAID, Dr. Steve Self of the HIVNET Statistical Center at the University of Washington and Fred Hutchinson Cancer Center reported that trials could have sufficient statistical power to demonstrate vaccine impact on viral load measured shortly after infection and before initiation of therapy, but that interpretation of such a difference would be a challenge.

Annual Meetings on HIV Vaccine Research

In May 1997, NIAID sponsored the Ninth Annual Conference on Advances in AIDS Vaccine Development (also known as the NCVDG, National Cooperative Vaccine Development Group) at the NIH campus. For ten years this meeting has attracted leading AIDS researchers, vaccinologists, basic researchers, immunologists, industry scientists and animal researchers from around the world. The meeting was extraordinarily useful, particularly since vaccine research and development had usually been relegated to a minor place in the biannual World AIDS Conference and the annual Conference on Retroviruses and Opportunistic Infections.

However, at this point, no annual vaccine meeting is scheduled for 1998. NIAID, which was criticized for controlling the content of the previous meeting, is looking for an outside association sponsor. Organizing the conference takes an extraordinary amount of staff time away from existing responsibilities. This appears to be a legitimate concern.

AVAC recommends that the organizers of the annual Conference on Retroviruses and Opportunistic Infections, the many Keystone Symposia, and the World AIDS Conferences create a separate conference track for HIV vaccines within their conferences. At these meetings, there should be time allotted to the Director of the NIH or NIAID to issue a State of the President's Challenge report on the status of NIH efforts to develop a safe and effective HIV vaccine. This report and conference proceedings should be published on the newly developed DAIDS Vaccine Website (www.niaid.nih.gov/daids/vaccine).

Trial participant issues

It takes a special kind of person to volunteer for an HIV vaccine trial. It is very possible the product being tested will not work at all. Even if it does, one may get a placebo rather than the real thing. On top of all that, volunteers in HIV vaccine trials may have to confront discrimination, stigma, and other adverse events due to their participation.

Discrimination in application for health and life insurance, housing, immigration, military employment, and even child custody may result if participants develop an antibody response to the vaccine and test positive on standard ELISA HIV antibody tests. Family, friends, employers and others may make assumptions about individuals in HIV vaccine trials simply because they are enrolled in the trial. For example, it may be presumed that participants are homosexual, drugs users or "promiscuous". People may also falsely assume participants have HIV infection.

Though human trials of HIV vaccines are preceded by animal testing and other measures to determine the safety of products, participants in HIV vaccine trials are at some risk of physical harm from the vaccine. This is particularly true for individuals in Phase I and II trials.

In summary, trial volunteers receive no benefit from participation, other than access to health services and HIV prevention interventions. Thus the decision to volunteer often rests on the relative weight of individual risk vs. altruism and the potential benefits of the research. How informed are clinical trial participants to adequately evaluate either of these? How empowered are trial volunteers to challenge the system, either to reduce individual risks or to demand better research products and protocols?

In 1997, U.S. HIVNET Community Advisory Board members did challenge the system, and were able to convince NIAID and two vaccine manufacturers to agree to guarantee compensation for medical costs incurred by participants in the event of physiological harm caused by the ALVAC/gp120 vaccine that entered a Phase II trial that year. The community-based group Vaccine Advocates requested, and received, a public letter from NIAID pledging ongoing assistance to address issues of discrimination and social harm which may be experienced by trial participants.
HIVNET Community Advisory Board members and community groups such as Vaccine Advocates continue to pursue issues of importance to trial participants, including assuring the highest quality behavioral interventions for volunteers, a valid and thorough informed consent process, the right to continue trial participation if incarcerated, and other issues. Discussion about the various HIV vaccine products that may be tested is an on-going topic, and compensation for medical expenses for upcoming Phase III trials is also on the advocacy agenda.

NIH Leadership With Accountability Can Make a Difference

Developing an effective HIV vaccine requires the NIH to do more than just allocate funds and invite researchers to "come and get it." It has been said a hundred times by every constituency: to overcome the unprecedented challenge of developing an HIV vaccine, government, and particularly NIH, needs to provide leadership. Critical areas identified by the Levine Report include: placing greater emphasis on and promoting vaccine work, fostering more multi-disciplinary research, creating mechanisms for increasing the diversity of scientific approaches explored and the speed with which new ideas are funded, and increasing government-private industry cooperation.

For example, one area where the NIH can continue to make a difference is in increasing interest in and attention to vaccine work. The lack of focus on vaccine research in the first fifteen years of the AIDS epidemic has meant that talented, ambitious scientists have often looked elsewhere. The NIH, through its funding priorities and the specialties and sub-specialties it targets, can create strong incentives for investigators, especially young scientists, thereby increasing the intellectual capital invested in HIV vaccine research.

In our December 1996 report, one of our key recommendations was a call for accountability by our political and scientific leadership. In spite of commendable progress, accountability among the leadership of NIH in the efforts to develop an HIV vaccine is no less necessary today.

Although the President's call for an HIV vaccine within ten years has raised the public profile of the vaccine effort, of greater substantive importance has been the leadership provided by departing OAR Director William Paul and the Baltimore Committee. Positive changes have occurred that give some hope that the next few years will see the development of new candidate vaccines created through the resources and leadership provided by the NIH, OAR, NIAID, and NCI. But many obstacles remain before the road through NIH is transformed from a construction site to a thruway. The pace of reform has quickened somewhat, yet it is still not fast enough.

Despite its apparent influence and its charge by the NIH, AVRC does not wield the power envisioned by the Levine Report. The NIH values its input, but is unwilling to cede substantive control. Responding to the recommendation that a trans-NIH vaccine program be established with non-government leadership, NIH set

sharp limits on the substantive power of what became AVRC, stating, "While the NIH sees a value in the visibility, advice and perspective...it does not see the necessity of establishing an independent NIH center." More to the point, responding to a recommendation that vaccine research conducted under the auspices of NCI be coordinated through OAR, NIH reiterated the traditional, parochial, status quo, that "NCI's vaccine research... should remain under the administrative and scientific direction and authority of NCI."

Dr. Paul has been deeply committed to revitalizing the government's vaccine effort resulting in substantial increases in the funding for vaccines. His departure, as well as the recent resignation of Dr. Pat Fast (formerly Associate Director of the Vaccine and Prevention Research Program at NIAID) casts a shadow that will only be gone when as yet unnamed successors make similar commitments in the form of action as well as rhetoric.

THE WALTER REED ARMY INSTITUTE OF RESEARCH

The second most important agent in U.S. government's effort to develop an HIV vaccine is the Defense Department's Walter Reed Army Institute of Research (WRAIR).This unit is charged with the responsibility of producing the vaccines necessary to protect American service personnel deployed overseas. In contrast to the basic science approach that predominates at NIH, WRAIR engages primarily in applied research, and has a century-long history of close, successful collaboration with industry and foreign governments. WRAIR currently spends $25 million on HIV/AIDS, approximately half of which is devoted to vaccine development. It is important to note that approximately 70% of the WRAIR's AIDS vaccine program goes for clinical trials and cohort development. The remaining 30% of funding goes for preclinical HIV vaccine work. The other half of WRAIR's overall AIDS budget is earmarked for epidemiology (threat assessment and tracking the movement of different strains), prevention education, new treatment strategies and patient follow-up.

With comparatively limited funding, WRAIR has been able to initiate a number of human studies of candidate vaccines, negotiate production of vaccine constructs and move toward a Phase III trial. In the absence of predictive animal models or reliable correlates of immunity, the WRAIR is pursuing a multi-armed strategy of employing the best available candidate vaccine components in clinical trials. To this end, WRAIR has spent six years supporting the Thai government and the Royal Thai Army in their efforts to develop a clinical trial infrastructure in Thailand. This project, which is currently budgeted at approximately $5 million annually, has been used to conduct Phase I and Phase II trials and is scheduled to begin a Phase III study by the year 2000. WRAIR is currently conducting four clinical trials, two in the U.S. (with products from Apollon and PMC) and two in Thailand (against clade B and clade E). WRAIR is the only U.S. government agency with a primary focus on non-clade B strains of HIV. But WRAIR's comparatively low level of funding limits the number of projects that it can take on, both in terms of partnerships with trial site countries to develop clinical trial cohorts and collaborations with industry to develop non-clade B vaccine candidates for those countries.

The WRAIR program functions with a minimum of bureaucracy and administrative overhead. It more closely resembles a objective-driven private company than any other government program currently involved in HIV vaccine research. The current administration and Congress should increase funding for WRAIR's HIV vaccine research program to allow it to expand the number of countries and company products with which it can work.

"With new resources, NIH will now become the most powerful discovery engine for an AIDS vaccine, working with other scientists to finally end the threat of AIDS. Remember that every year we move up the discovery of an AIDS vaccine, we'll save millions of lives around the world."

-President Bill Clinton
State of the Union Address
February 4, 1997

THE WHITE HOUSE, PACHA, AND THE U.S. CONGRESS

In 1997, President Clinton referred to the importance of HIV vaccine development in his State of the Union address, and several months later called for a ten-year goal, an NIH vaccine center, and mobilization of the pharmaceutical industry and the G-8 governments. In 1998, although the President has not mentioned HIV vaccines, he has spoken about the importance of biomedical research and increased NIH funding.

One of the motivating forces for President Clinton came from a call for action on HIV vaccines from his own Presidential Advisory Council on HIV/AIDS (PACHA) and Office of National AIDS Policy (ONAP). In the spring of 1997, under new director Sandra Thurman, ONAP declared HIV vaccine development to be one of its highest priorities. In April 1997, PACHA issued a set of targeted recommendations for HIV vaccine research and development, calling for the President to declare the ten-year goal, support sustained increases in vaccine research funding, and provide greater coordination of national and international efforts. In March 1998, PACHA reiterated its recommendations for greater coordination of national and international efforts.

These words are encouraging, but if the President's ten-year goal is to be met, more than words are needed. The Presidential Advisory Council provides a useful voice on the needs of HIV vaccine research at a national and international level, but PACHA has only two members who have an active interest in HIV vaccines and has surprisingly limited clout with the President. The Director of the Office of National AIDS Policy is supportive of HIV vaccines but also complains of limited influence with the President. More effort will be needed by grassroots advocates to get the attention of the White House and to direct President Clinton's focus in his two final years to following up on his own words.

AVAC believes that President Clinton and NIH Director Varmus must have regularly scheduled high-level discussions with the CEOs and Board Chairs of Merck, PMC, American Home Products/Wyeth-Ayerst Laboratories, and SmithKline Beecham to emphasize the importance of these companies making a significant investment in HIV vaccine research. Incentives, such as U.S. patent extensions on other products, should be seriously explored.

The key role of the U.S. Congress in terms of HIV vaccine research is to ensure that sufficient funds are allocated to the NIH and the WRAIR for vaccine research and development efforts. In doing so, Congress must provide significant increases in funds for overall U.S. government-supported biomedical research and not just HIV vaccine research. The allocation of $26 million to the NIH for construction of the Vaccine Research Center is a clear indication of congressional support for HIV vaccine research. A number of representatives have been particularly vocal in supporting HIV vaccine research. These include Representatives James McDermott, Nancy Pelosi, and John Porter, Senator Arlen Specter and others.

The Not-For-Profit Sector

In general, not-for-profit AIDS advocacy and research organizations have not gotten involved in HIV vaccine research issues. With no product yet in Phase III efficacy trials, HIV vaccine research issues are often considered too abstract and intractable for most AIDS funders, advocates, and policy types. Research advocates focus on treatments, prevention advocates focus on condoms and needle exchange, and international advocates focus on poverty and access issues. HIV vaccines are often not on their agendas. Three organizations, however, are noteworthy for their impact in the past year.

International AIDS Vaccine Initiative

In 1997, the International AIDS Vaccine Initiative (IAVI) contributed significantly to raising the volume and quality of discourse about HIV vaccines. IAVI's work behind the scenes with G-8 countries, the World Bank, PACHA, international conference organizers and the NIH, all helped to steer resources toward HIV vaccine development. Ideas including a global vaccine purchase fund, mobilization of the G-8 process, and innovative NIH funding strategies all received a significant boost from IAVI's efforts. IAVI's quarterly newsletter, IAVI Report, is also becoming an important source of international perspectives on HIV vaccine research for scientists and non-scientists alike.

Despite a first round of funding of about $1 million for vaccine development in 1997, IAVI has yet to reach its potential to become a significant alternate system for development of HIV vaccines. Yet the organization continues to have good fundraising prospects and the advantage of being able to move quickly and strategically in developing vaccines for clinical trials, and thus has potential to become a major funder of HIV vaccine development.

American Foundation for AIDS Research

The American Foundation for AIDS Research (AmFAR) jumped into the HIV vaccine research effort in a major way in 1997. With its grassroots funding base, AmFAR was able to raise and distribute $1 million in HIV vaccine awards to sixteen research teams. The ability for AmFAR to fund innovative research, conduct broad-based public education campaigns, and incorporate vaccines into its AIDS research lobbying makes AmFAR an important presence in U.S. philanthropy and advocacy for HIV vaccines.

Until There's A Cure Foundation

Until There's A Cure (UTAC) is noteworthy for the proportion of funding that they devote specifically to HIV vaccine research and advocacy. There are a large number of funders who have supported AIDS research and research advocacy, including the Cummings, Dana, Ford, Kaiser, Monell, and Rockefeller foundations. But UTAC is the first to devote a substantial portion (as much as 20%) of its funding to the topic of HIV vaccines. Before the NIH was established, private philanthropy in the United States (especially from the Rockefeller Foundation) supported the bulk of public health research. Even now, organizations such as IAVI, AmFAR, and UTAC have shown that foundations and not-for-profit AIDS organizations can continue to act as important adjuncts to government-funded research programs.

Overview of Industry-Supported Research

Despite the President's call for a vaccine within ten years and an ever stronger scientific base of knowledge about HIV, no new pharmaceutical companies or biotechnology firms have announced any intention of entering into HIV vaccine development during the past few years, and several existing HIV vaccine programs have been scaled back or canceled. Among the firms no longer conducting active research are Bristol-Myers Squibb, British Biotech (a subsidiary of British Bio-Technology Group, PLC) and Immuno AG (following its sale to Baxter International). In addition, after taking its gp120 envelope vaccine through Phase I and II clinical trials, Genentech has halted further spending by spinning its product off into an independent company, VaxGen.

1997 was a banner year for the pharmaceutical industry. Earnings rose sharply, stock prices soared and, as one analyst reported "the prospects of new-drug launches promised to keep profits ascending steeply through 1998."

Vaccines as a subset of industry earnings also had an excellent year and prospects for the large vaccine producers' future seem brighter than ever. In December 1997, Forbes Magazine reported that vaccines are now a "thriving enterprise" and advised investors to "bet on heavily capitalized pharmaceuticals" within the vaccine field.

Yet these good times have not translated into real private sector interest in HIV vaccine development. The number of companies with active research programs has continued to decline. This erosion is critical because it impacts not only the number of firms actively involved in the search for an HIV vaccine, but also, more importantly, the range of strategies being pursued.

Of the major possible vaccine approaches, only three approaches are being actively pursued with significant industrial funding: a live recombinant poxvector vaccine (developed by Pasteur Merieux Connaught with support from the French Government), recombinant subunit vaccines and DNA. One prime-boost combination entered Phase II trials in 1997. DNA vaccines have shown promise in animal tests, but only one company has launched human trials of HIV DNA vaccines. Moreover, for the companies pursuing this approach, the commitment is as much to the DNA technology platform as it is to an HIV vaccine. If early results prove disappointing, these companies will be tempted to move on to less problematic pathogens.

The vaccine industry consists of two, very different types of firms: large, integrated drug companies, and the much smaller biotechnology firms. The trend among larger companies has been away from basic research and towards more focused, product-oriented work. This has led to diminished support for HIV vaccine work. The goal of many biotechnology companies, particularly the smaller ones, is to create a product sufficiently promising to attract either capital or some other form of relationship with one of the major, integrated pharmaceutical concerns. In fact, two of the largest biotechnology firms engaged in vaccine work, Chiron and Genentech, are themselves closely tied to industry giants. Novartis, the world's largest drug company, owns 49.9% of Chiron and Switzerland's Roche Holding, the world's seventh largest, owns 66% of Genentech.

For most biotechnology companies, venture capital is increasingly unwilling to underwrite investment in HIV vaccine research. Officials at a number of these firms have acknowledged that their vaccine programs are being kept alive entirely by government support from NIH or the Department of Defense and will have to remain so until the prospects of substantial revenues are more clear. In fact, in early 1998, the only company to have launched human studies of an HIV DNA vaccine, Apollon, was forced to withdraw its plans to sell stock through a public offering. One of the company's underwriters cited "market conditions" (which usually means lack of investor interest) for the withdrawal of the public offering.

Below is a review of the companies currently playing a key role in HIV vaccine research, and one with the potential to do so.

SmithKline Beecham

SmithKline Beecham (SKB) is the world's largest vaccine manufacturer and one of the largest pharmaceutical companies in the world. The company currently generates annual revenues of more than $1.2 billion from vaccines and expects this figure to increase dramatically over the next four years. SKB's recombinant hepatitis B vaccine is a key revenue generator, and the company recently introduced a combined hepatitis A and B vaccine. However, SKB's HIV vaccine program is quite limited, having once focused on a gp120 vaccine, but now largely geared toward adjuvant development. The program is funded, in part, by grants from the U.K.'s Medical Research Council. In 1997, the company did not report any new developments or changes in its HIV vaccine program.

Even if SmithKline Beecham revived its envelope vaccine effort, their commitment to HIV vaccine research would accurately be called miniscule relative to the company's size and influence. The world's largest vaccine manufacturer has, in reality, watched the epidemic from the sidelines. Investment decisions are understandably driven primarily by financial calculations. However, multi-national pharmaceutical companies, particularly the large vaccine manufacturers, must not ignore global health concerns.

In 1998, SmithKline Beecham should agree to contribute its impressive scientific and financial resources to the overall effort to develop an HIV vaccine. The company should, without delay, create or substantially invest in a broad-based HIV vaccine research program. President Clinton and NIH Director Varmus should invite the CEO and Board Chair of SmithKline Beecham to the White House to emphasize the importance of this company in making a significant investment in HIV vaccine research, and to explore incentives, such as U.S. patent extensions on other company products.

Pasteur Merieux Connaught

Pasteur Merieux Connaught (PMC), a subsidiary of the French pharmaceutical company Rhone-Poulenc, is also among the world's largest vaccine producers. The company is pursuing a number of different approaches and has what must be considered the broadest HIV vaccine program of any company in the world. PMC's program, which is supported largely by funding from the French government's Agence Nationale de Recherches sur le SIDA (ANRS), includes envelope subunit vaccines, HIV peptides, pseudovirions, poxvirus vector vaccines, and DNA vaccines.

In 1997, the company's vCP205 canarypox vaccine, in combination with Chiron's gp120 construct, entered Phase II study in the U.S. The company has hopes to launch a Phase III study of a canarypox vector with U.S. government funding, but recently indicated that they will be conducting a new study in 1998 to compare three canarypox vector vaccines (vCP205, vCP1433, and vCP1452) to assess which may be best for evaluation in larger trials. The company is also developing a combination clade B and clade E gp160 product to be tested as a boost with its canarypox and DNA products.

PMC and the French government have established a close working relationship in the area of HIV vaccine research. To their credit, both parties have made a strong commitment to developing an HIV vaccine. Their collaborative effort is a model for the U.S. government in designing public-private partnership in the area. The NIH appears to be working closely with PMC in preparing for an efficacy study of the canarypox prime/envelope boost combination. These efforts must continue.

Merck

Merck is also one of the largest pharmaceutical companies in the world and a major vaccine producer. In 1997, the company apparently decided to devote additional resources and attention to its HIV vaccine program and appointed Emilio Emini, head of the company's successful HIV protease inhibitor program, to oversee vaccine research at Merck.

Although Merck officials are tight-lipped about their HIV vaccine program, their strategy appears to be to vaccinate with DNA and then boost with an HIV envelope protein that can induce high levels of neutralizing antibodies. Merck is developing DNA vaccines for a broad range of pathogens, including influenza, tuberculosis and HIV. The company's DNA effort is based on a licensing agreement with Vical, a San Diego-based biotechnology company. In August 1997, Norman Letvin and Merck published data about the company's preclinical efforts to develop an HIV vaccine in the Proceedings of the National Academy of Sciences.

Merck's new emphasis on HIV vaccine research is a significant boost for the overall research effort. The company has a wealth of scientific and financial resources. Gordon Douglas, the president of Merck Vaccines, is one of the most respected leaders in vaccine development. Douglas maintains close relationships within industry and with the NIH leadership. Jerry Sadoff, who oversees Merck's clinical program for vaccines, is another highly-respected figure in vaccine development. At this time, Merck does not appear interested in obtaining assistance from the U.S. government in its research efforts. However, government officials should maintain regular contact with the company and President Clinton should communicate to the company's leadership the importance of the HIV vaccine effort.

Chiron / Novartis

Chiron, one of the world's leading biotechnology companies, has a significant vaccine research program. The company is developing vaccines for hepatitis A, herpes, influenza, CMV, whooping cough, HIV, and meningitis. Chiron's HIV vaccine research to has been focused on gp120 envelope subunit vaccines. The company is also developing a p24 vaccine, improved adjuvants and DNA-based vaccines. Chiron's SF-2 gp120 vaccine is being tested in Phase II studies with PMC's ALVAC vaccine. The company is also developing a bivalent gp120 vaccine based on HIV subtypes E and B. In 1997, a Phase I study of this vaccine was initiated in Thailand, in cooperation with the Thai government and the U.S. Army. Chiron also launched a Phase I trial of its recombinant p24 vaccine at Creighton University in Omaha, Nebraska, and may be developing an oligomeric envelope vaccine based on primary isolate for testing in primates.

In recent years, Chiron has reduced its investment in HIV vaccine development. The company's stock price has failed to keep pace with the overall market, creating pressures to invest in more potentially lucrative areas. However, in 1997, the company hired Margaret Liu, former head of Merck's DNA vaccine program, to lead its overall vaccine research program. Prior to the hiring of Liu, some observers had been unsure about Chiron's continued willingness to invest significant research capital in HIV vaccine development.

Chiron is an important company in terms of HIV vaccine research. While observers believe that the appointment of Margaret Liu could bode well for HIV vaccine development at the company, doubts remain about Chiron's overall commitment. The U.S. government should do whatever is reasonably necessary to support Chiron's HIV vaccine research program.

Apollon / Wyeth-Ayerst Laboratories

Apollon is a Pennsylvania-based biotechnology company that is developing a wide range of DNA products for use as preventive vaccines and as therapeutics. Wyeth- Lederle Vaccine and Pediatrics, a division of Wyeth-Ayerst Laboratories, a large vaccine producer that is owned by American Home Products, has made a significant investment in Apollon and is likely to increase this investment. While Wyeth-Ayerst Laboratories' efforts toward an HIV vaccine have been limited to declining efforts on an adenovirus vector and a peptide concept, Apollon has launched a wide range of human studies of HIV DNA vaccines.
In 1997, Apollon researchers, working with David Weiner of the University of Pennsylvania, reported that chimpanzees vaccinated with one of the company's HIV DNA constructs remained free of infection at least two years after challenge.

Apollon continues to move forward with human trials of preventive HIV DNA vaccines. Company officials believe that a final product will combine envelope-directed and core-directed components. To date, the trials have emphasized safety and immune response. The first Phase I trial of DNA (with env and rev components) in HIV-negative volunteers began in March 1996 at Bethesda. In February 1997, a second trial of the same product was initiated using needle-less injection. In July 1997, a Phase I trial of DNA (with gag) began in the AVEG network at four sites. The company appears to be interested in moving towards trials of a DNA (env/rev/gag) product in AVEG, and clade E and clade C DNA constructs with envelope and core components internationally.

As was noted, Apollon recently withdrew its public offering. But the company continues to develop its underlying technological platform (the ability to develop and produce DNA vaccines) and remains optimistic about prospects for generating future revenue streams with herpes, hepatitis B, and papilloma products.

Apollon has demonstrated that a company can initiate a series of human studies of HIV DNA vaccines in a short time with relatively limited resources. To its credit, NIAID has provided Apollon with substantial support. Apollon's strong relationship with NIH has also been a source of credibility within the banking community. WRAIR's plans to initiate a larger trial with Apollon are another example of effective U.S. government efforts in stimulating private sector research in HIV vaccines.

VaxGen / Genentech

VaxGen was created as a spin-off from Genentech, one of the world's largest biotechnology companies. Genentech provided the company with $2 million in capital to develop its HIV gp120 vaccine. VaxGen, which is headed by Donald Francis, has developed a bivalent clade B gp120, combining a gp120 derived from a lab strain and one from a primary isolate, and a clades B and E bivalent gp120 with the clade E gp120 derived from a primary isolate. VaxGen began a Phase I/II trial in the United States in late 1997, and is also testing its gp120 construct with a new vaccinia construct from another company, Therion. VaxGen is hoping to initiate Phase III studies in the U.S. and Thailand, and reports that it has raised $18 million in the private markets to test its newly reformatted gp120 products.

While some scientists are skeptical that VaxGen's gp120 vaccine used alone can protect against HIV, the company appears set to launch Phase III studies of the construct. Ideally, the studies will be designed so that even a negative result can yield important immunological data for future product developments and efficacy studies. In the meantime, VaxGen and Francis deserve credit and support for pursuing the testing of this product and obtaining private funding for its development.

Therion Biologics

Therion Biologics Corporation is a small Massachusetts biotechnology company engaged primarily on cancer vaccines and immunotherapies. Therion's HIV vaccine program has focused on developing recombinant viral vectors to express multiple HIV proteins. In 1997, a Phase I trial in the United States AVEG network began evaluating Therion's major HIV vaccine product - a vaccinia vector expressing gag, pol, and env - in combination with a VaxGen rgp120 boost.

Although Therion Biologics is a small company, it receives more funding from the NIH for HIV vaccine research than any other company. In 1997, Therion received more than $1 million from the NIH in HIV vaccine-coded funding for research and product development. Therion also holds the rights to genetically engineered live-attenuated HIV vaccines developed at the New England Regional Primate Research Center. These live-attenuated vaccines are being tested in primates and have not advanced into clinical trials, and Therion says that it has no plans to manufacture a live-attenuated vaccine for human studies. However in the past year, Therion was involved in several discussions with the NIH and FDA about FDA guidelines for the manufacture and development of these vaccines.

Therion's effort in moving ahead in developing its vaccinia vector product should be commended. The funding relationship between the NIH and Therion may be a good example of effective U.S. government support of private sector vaccine development. Therion, and other small biotech companies with the capability to develop novel products and severely limited access to resources, need and deserve greater government, corporate, and private support.

Overview of International Research

International Clinical Trials

Outside of the United States, the world's clinical trials of candidate HIV vaccines have largely occurred in France and Thailand, with other limited Phase I trials in Cuba and China and trial site preparation in Uganda, South Africa, Zambia, Zimbabwe, Malawi, India, Haiti, Trinidad and Brazil.

In France, through the ANRS and Pasteur Merieux Connaught, Phase I trials have evaluated the vCP125, vCP 205 and vCP300 canarypox vector vaccines, gp160, and lipopeptides (with gag, nef and V3). Phase I clinical trials in France are planned to begin in 1998-99 to evaluate vCP1433 (containing env, gag, pol and nef) and vCP1452 (essentially vCP1433 with two vaccinia regulatory genes to improve expression), newer formulations of the 6 lipopeptide combination, pseudovirions and a DNA vaccine.

In Thailand, trials are conducted through the Thai Ministry of Public Health and the Royal Thai Army. Phase I trials in Chaing Mai and Bangkok have evaluated clade B gp120 products produced by Genentech/VaxGen and Biocine/Chiron, and in January 1998 a Phase II trial was begun of a Chiron clade E gp120 vaccine candidate based on a primary isolate of HIV. Given the strong Thai infrastructure and political will for HIV vaccine trials, it is likely that Thailand will be the site for trials of several clade E envelope, vector, and DNA vaccines in the next few years.

In most of the countries where HIV vaccine clinical trials are being planned, resources for this research are scarce. Countries are eager to build the capacity to research, produce, and even export vaccines, but often need international assistance in building clinics and labs, training staff, and supporting a clinical trial infrastructure. The wealthier industrialized countries and international agencies, such as UNAIDS and the World Bank, often subsidize international clinical research.This support should be increased and better coordinated. United States agencies, such as the CDC, USAID, and FDA, often work with their counterpart

agencies in other countries on projects for HIV surveillance, prevention research, and regulatory review processes. These projects are valuable and need to be continued, but also need to be coordinated with HIV vaccine trial efforts to be sure that the best possible research is being conducted.

Community advocacy is needed on HIV vaccine research in each country where vaccine trials might take place. Channeling public and political mistrust of clinical research, particularly mistrust of research funded by foreign governments and industry, into a dialogue about research intent and design is an important part of minimizing risks to research participants and maximizing benefits. In the case of Uganda, Thailand and Brazil, where community involvement has been sought for several years, the input of political leaders and potential trial participants has led to increased efforts for broad public education, the incorporation of counseling, STD and other medical services in trial designs and the strengthening of systems for stringent ethical review of trial designs and plans.

Basic and Targeted Research in Europe and Japan

HIV vaccine research has had strongest support from the governments of France (ANRS), Sweden (Karolinska), the U.K. (MRC), and Holland (the Health Ministry). The governments of Japan, Germany, Canada, Italy, Russia, and other countries have had limited, if any involvement. The Japanese government's effort has been limited to a BCG-vector approach. The Canadian government has supported preclinical work only, and at continually decreasing funding levels. Recently the British MRC and Germany's Bundesministerium fur Bildung, Wissenschaft, Forschung und Technologie (BMBF-Federal Ministry of Education, Science, Research and Technology) ended specific funding lines for their AIDS-related research.

The European Union, under the Science, Research and Development directorate (DG XII), continued its programs to support SIV-focused primate research, an FIV research network, and the European Vaccine against AIDS (EVA) program. The EVA, launched in 1989, provides vaccine-related reagents, virus stocks, and antigens, and in collaboration with the WHO, has supported production of various reagents covering the majority of the world's known clades of HIV.

European governments and the European Union could do far more in supporting HIV vaccine researchers in their own countries and internationally. European AIDS activists, HIV prevention agencies, and international development organizations should do more to mobilize public sector support for this work.

"Preventing the transmission of HIV infection and the development of AIDS is an urgent global public health imperative. While other prevention and treatment methods must be pursued, in the long term the development of safe, accessible and effective vaccines against AIDS holds the best chance of limiting, and eventually eliminating, the threat of this disease. We will work to provide the resources necessary to accelerate AIDS vaccine research, and together will enhance international scientific cooperation and collaboration. Cooperation among scientists and governments in the developed and developing world and international agencies will be critical. We call upon other states to join us in this endeavor."

-Denver Summit of the Eight

Final Communique

Denver, Colorado, June 22 1997

The Need for Greater International Effort

In 1997, the Summit of the G-8 acknowledged the need for the member countries to do more on HIV vaccine research and development. Since 1991, the World Health Organization Global Programme on Vaccines (GPV) and the UNAIDS have, to their credit, assisted several countries in developing plans for HIV vaccine research and development, and in overcoming challenges in preparing for clinical trials.

But without serious commitment at the highest political levels, it will be impossible for any country to play a major role in HIV vaccine development. This high level of commitment has begun to exist in the United States, France, Thailand, and possibly Uganda and China. In other countries, work is needed to build political and public support for HIV prevention, and for clinical trials of HIV vaccines as part of the strategy for combating the HIV epidemic.

Adequate global support and integration of HIV surveillance, prevention, research, and care have long been needed in this epidemic. In the case of protease inhibitors, vaginal microbicides, and HIV vaccines, there seems to be an inability of the UNAIDS, World Bank, G-8 governments and U.S. agencies such as the CDC and USAID to adequately support broad research on treatments and prevention technologies, and to provide access to those treatments and prevention technologies once they are proven effective. Globally, 16,000 people become infected with HIV each day. Much, much more is needed.

Appendix A. Steps in HIV vaccine research and development.

Research HIV and the immune system, and develop vaccine concepts

- Research immune system components and functions.
- Research virus structures and mechanisms of action.
- Research HIV epidemics in populations around the world.
- Identify and define substances that may elicit protective immune responses.
- Explore correlates of protection against HIV in people.
- Develop improved animal models.
- Test candidate vaccines in animal models.
- Develop useful adjuvants.

Make vaccine products

- Develop reliable, reproducible processes for vaccine production.
- Produce well-characterized, stable candidate vaccines.
- Develop valid, reproducible measures of activity and immune responses.
- Examine safety and immunogenicity of candidate vaccines in animals.
- Set up pilot lot production facilities compliant with GMP guidelines.
- Validate consistent production processes.
- Manufacture consistency lots and product for clinical testing.

Test for safety and immune response in Phase I / II Trials

- Design clinical trials; develop protocols and assays.
- Determine safety, administrative schedule, optimal dose, and immunologic effects in a small number of people at low risk for HIV infection.
- Gather expanded data on safety, administration schedule, optimal dose, and immunologic effects in larger number of volunteers, including those at higher risk for HIV infection.

Test for efficacy in Phase III Trials

- Prepare communities and trial sites for large-scale recruitment.
- Develop high quality risk-reduction interventions.
- Set up production facilities compliant with GMP guidelines.
- Validate consistent production processes.
- Manufacture consistency lots and clinical product for testing.
- Assess efficacy in target populations.
- Examine correlates of protective immunity and immunogenicity of product for possible re-design of candidate vaccines.

Appendix B. Funding mechanisms: The way money gets spent at NIAID.

The $98 million spent by NIAID in 1997 consists of 355 awards, the average being $277,000, but in some cases only a small part of a larger award is coded to vaccines.

These awards can be broken down as follows:

	# Awards	$$ Vaccine Portion	Average $$ Vaccine
Investigator Initiated/Outside Investigators (R01, P01, U01, other "R" grants):	224	$37,480,000	$167,000
Government Initiated Outside Investigators (N01/contracts):	39	$37,401,000	$959,000
Other Mechanisms/Outside Investigators:	66	$10,034,000	$161,000
Research Management Support	10	$4,240,000	$424,000
Intramural/Government Investigators (Z01)	10	$7,277,000	$727,000
Inter-agency (3) and Intra-agency (3) Agreements	6	$1,568,000	$261,000
TOTAL NIAID VACCINE	355	$98,000,000	$277,000

Virtually equal amounts were spent on investigator initiated grants and government initiated contracts, though individual contracts are much larger. The contracts also include clinical trials groups whose investigators in large measure set their own scientific agendas.

Appendix C. HIV Preventive Vaccines in Clinical Trials Under IND (Investigational New Drug) Status by the U.S. Food & Drug Administration.

	Cumulative Total	Added
Before 1994	12	gp160 (3) gp120 (4) peptide (3) vaccinia canarypox
Spring 1995	15	vaccinia (+1) peptide (+1) virus like particle
Spring 1996	18	canarypox (+2) DNA
Spring 1997	18	no change
Current	24	carypox (+2) gp120 (+3) DNA (+1)

In the last 4 years, only two entirely new approaches have entered human trials, virus-like particles and DNA; the other approaches in human trials since before 1994 have undergone redesign and refinement.

Appendix D. Can we get there in 9 more years?

I. Preclinical

Approach	History	Time
gp160	1984-1987 MicroGeneSys	3 years
Vaccinia prime+boost	1985-1988 Oncogen/Bristo-Myers	3 years
	1988-1994 Therion	6 years
gp120	1987-1991 Chiron	4 years
	1987-1992 Genentech	5 years
	1994-1997 VaxGen	3 years
ALVAC	1989-1993 Viral Genetics/Pasteur Merieux	8 years
DNA	1988-1996 Robinson/Apollon	9 years
Other vectors attenuated, whole killed	Mid 1980s-present	More than10 years
Best Case	Approach already in development	1-2 years
	New approach	3 years

II. Clinical

gp160	1987 Phase 1 MicroGeneSys 1992 Phase 1 Immuno 1995 ended development	7 years, dropped as single product
Vaccinia prime+boost	1988 Phase 1 Bristol/Oncogen 1993 ended development 1994 Phase 1 Therion	5 years, dropped begun again
gp120	1991 Chiron env 2-3 1991 Genentech IIIB Phase I 1992 Chiron SF2 Phase I 1992 Genentech MN Phase I 1993 Chiron/Genentech Phase II 1994 Decision not to proceed Redesign by VaxGen 1998 VaxGen B/B' Phase I/II (1998-2003 VaxGen Phase III projected)	12 years projected
ALVAC	1993 vCP 125 Phase I 1995 vCP 205 Phase I 1996 vCP 300 Phase I/dropped 1997 vCP 205 Phase II 1998 vCP 1433/1452 Phase I (2000-2003 ALVAC Phase III projected)	10 years projected
Best Case	Phase I (1 year) Phase II (1.5 years) Decision Making (??) Phase III (2.5 years) Licensing (??)	5+ years

Internet Resources and Links for Vaccine Advocacy

ACTIS	http://www.actis.org
AmFAR	http://www.amfar.org
The Body	http://thebody.com
Food and Drug Administration	http://www.fda.gov
UCSF HIV InSite	http://hivinsite.ucsf.edu
IAVI	http://www.iavi.org
National Library of Medicine	http://www.nlm.nih.gov
National Institutes of Health	http://www.nih.gov
NIH HIV Vaccine Web Site	http://www.niaid.nih.gov/daids/vaccines
UNAIDS	http://www.unaids.org
Vaccine Advocates	http://www.avac.org
WRAIR	http://wrair-www.army.mil
WHO Global Program on Vaccines	http://www.who.org/gpv

The AIDS Vaccine Advocacy Coalition

Founded in December 1995, AVAC's mission is to speed the development of preventive HIV vaccines by analyzing obstacles to HIV vaccine development and advocating to remove these obstacles. AVAC is committed to achieving this mission without taking resources away from basic HIV research, drug development or prevention efforts.

In this report, as in our December 1996 report Industry Investment in HIV Vaccine Research, AVAC seeks to provide an independent, honest, well informed critique of current efforts toward developing an HIV vaccine. We hope this report furthers both dialogue and progress in the many organizations whose missions relate to public health and eradication of disease throughout the world.

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