Paving the Road to an HIV Vaccine:

Employing Tools of Public Policy to Overcome Scientific, Economic, Social and Ethical Obstacles

Michael Langan and Chris Collins

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Center for AIDS Prevention Studies
AIDS Research Institute
University of California, San Francisco

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PREFACE

In June 1996, the Center for AIDS Prevention Studies published the second occasional paper in this monograph series, entitled ***Sustaining Support for Domestic HIV Vaccine Research: Social Issues Over the Long Haul of Human Trials.*** Authored by Chris Collins, the research was supported by grants from the National Institute of Mental Health, National Institutes of Health and the University of California, San Francisco.

This new report is intended to function as an update to the 1996 monograph. Most of the social and ethical issues discussed in the original paper have not changed during the past two years. Therefore, you will find many of the previously identified challenges and stages of vaccine research and development, concerns about the design of HIV vaccine efficacy trials, goals of community education, potential benefits and harms for impacted communities, and levels of industry involvement, among others, retained.

As a progress report on the state of HIV vaccine research, this paper attempts to highlight, generally, both the progress and lack of progress toward the primary recommendations laid out in the earlier paper. By focusing, up front, on the latest activities of government, affected communities, and industry, a clearer landscape of the state of HIV vaccine efforts comes into view; gaps in certain areas point to the work which remains to be done.

- While the federal government, through the National Institutes of Health, has restructured its vaccine research efforts, it has not developed a long-term, comprehensive public relations and education plan which balances the need for optimism about vaccine development with realistic estimates of the risks, resources and time required to identify an efficacious vaccine for HIV.

- The National Institute of Allergy and Infectious Diseases (NIAID) has begun to provide HIV vaccine trial participants with behavioral interventions; however, the rights of participants have neither been codified nor expanded to guarantee compensation for trial related injuries, ongoing protection from social harm, and free access to whatever HIV vaccine is licensed.

- NIAID has started working with community advisory board members and representatives of HIV-involved community-based organizations to facilitate open community-level debate regarding participation in HIV vaccine trials. However, the Institute has not yet contracted with community-based organizations to produce materials which help prospective trial volunteers consider the personal and communal risks and benefits of HIV vaccine trial participation.

- Congress has significantly increased the federal AIDS research budget; however, new incentives for pharmaceutical industry investment in HIV vaccine development, such as the establishment of a liability claims system, tax incentives or credits, or marketing exclusivity have not been provided.

- The Department of Health and Human Services and the White House Office on National AIDS Policy have failed to make significant progress in securing broad public access to any licensed HIV vaccine.

- Vaccine development has been added to AIDS activists' agendas, but the measure of their advocacy efforts to expand public and pharmaceutical industry vaccine research appears quite varied.

- Elected officials, the media, organizations and individuals based in HIV-affected communities have not engaged in a dialogue about the ethical, educational, decision-making, and equity issues raised by the prospect of HIV vaccine testing and dissemination.

- Pharmaceutical and biotech companies, including those which benefit financially from production of AIDS therapeutics, have not committed significant additional resources towards vaccine research and development efforts.

THE GLOBAL TRAGEDY OF HIV DEMANDS A PREVENTATIVE VACCINE

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) Report on the Global HIV/AIDS Epidemic (December 1998 Update), an estimated 33.4 million people are infected with the deadly HIV virus, including nearly 1 million Americans. During 1998, half of all new infections have occurred in people ages 15 to 24.[1] A total of at least 11.7 million people have already died since the beginning of the epidemic. These alarming figures represent a monumental increase in the annual rate of new infections throughout the world, with an additional 5.8 million new cases of HIV in the past year alone. Now, more than 16,000 people are becoming infected every day.[2]

The scope of the epidemic is worldwide and developing countries are being hit the hardest. "Of the 30 million people living with HIV, 21 million are in Africa and 90 percent do not know they are infected because testing is not widely available. Nearly all are doomed to die from AIDS because few can afford basic care, including costly combinations of drugs," according to Lawrence K. Altman, M.D. of the ***New York Times***.[3]

Well into the second decade of the epidemic, 40,000 people are infected annually in the United States. Injection drug users and women continue to account for a growing percentage of the domestic epidemic. And HIV is making deep inroads in a new generation: one in four new infections in the U.S. occurs in people under 22.[4] With respect to communities of color in the U.S., African Americans "now account for more than half of new HIV infections…blacks are eight times more likely than whites to contract the virus, Hispanics four times more likely."[5]

While a variety of behavioral and other models of prevention efforts have proven to slow the rate of new infections among certain populations in many industrialized nations, only an effective preventive HIV vaccine will ever stop this global tragedy.[6] Furthermore, as Altman alluded, the promising new anti-retroviral drug treatments now proven to help slow the progression of disease in infected individuals remain unavailable to the vast majority of people and around the world.

> ***"Today, let us commit ourselves to developing an AIDS vaccine within the next decade…If the 21st century is to be the century of biology, let us make an AIDS vaccine its first great triumph."[7]***
> ***President Bill Clinton, May 18, 1997***

President Clinton's speech on May 18, 1997, unequivocally launched the United States on the quest for an AIDS vaccine. This proclamation started the countdown toward the goal of development of an AIDS vaccine within the decade and further served as a reminder of the importance of vaccines in disease prevention and control.

A vaccine for HIV/AIDS remains a tremendous scientific and technical challenge. According to ***the 1998 Jordan Report*** of the National Institutes of Health,

> "The process of developing this vaccine from basic research to full-scale development and evaluation will follow the path of the many vaccines that have been developed and put into widespread use in the United States and around the world. The only prediction one can make about development of an AIDS vaccine is the same one that can be made for the development of any vaccine – the path will not be straight and much will be learned in the various disciplines of vaccinology in the process. Despite the rapid incorporation of new technologies in the development of modern vaccines, this remains largely an empiric science."[8]

While an HIV vaccine has been established as a critical priority for the United States, numerous scientific, economic, social and ethical obstacles clearly persist. Relative inattention to vaccines in past years has had its costs: pharmaceutical industry investment has lagged, government research efforts have lacked coordination, and affected communities have only begun to address the many difficult issues involved in vaccine trials. In fact, the President himself further remarked, "There are no guarantees. It will take energy and focus and demand great effort from our greatest minds. But with the strides of recent years it is not longer a question of whether we can develop an AIDS vaccine, it is simply a question of when. And it cannot come a day too soon."[9]

The stakes could not be much higher. The great promise and potential perils of HIV vaccines add up to a clear reason for affected communities to adopt a more aggressive attitude regarding vaccine development: pushing for increased public and private investment in research, tackling the equity, safety and social issues involved, demanding protections from government, and debating what level of risk is justified given the potential benefits of particular clinical vaccine trials. The principal question is not ***whether*** a vaccine would be beneficial, but ***under what conditions*** are vaccine research and dissemination ethical and effective?

This paper begins with a focus on three broad constituencies in the development of an AIDS vaccine: the government, affected communities and industry. Many of the scientific questions that endure as unanswered obstacles to a future HIV vaccine are extraordinarily complex. While this report does not attempt to explain the science, the activities discussed here are directly tied to the advancement of scientific and medical knowledge. It briefly identifies who the players are, what they have accomplished to date, and highlights their vision for the future. There are, of course, many others working toward this common goal. With so many parties involved, the need for renewed leadership and collaboration is absolutely critical.

New Government Programs and Funds

> ***"NIH has consistently been and still is the most active world funder of activities to design and develop an HIV vaccine...NIH is currently trying to develop new mechanisms for bridging the gap between basic research and product development."[10]***
> ***William Snow, AIDS Vaccine Advocacy Coalition, October 30, 1998***

Long before President Clinton's proclamation of an AIDS vaccine as a new national priority, the federal government had already begun to employ public policy mechanisms to refine the course of federally funded AIDS research and bolster the search for an HIV vaccine.

National Institutes of Health

The ***National Institutes of Health (NIH)*** serves as the primary federal agency with responsibility for biomedical research on AIDS. Within NIH, major responsibilities fall to the ***Office of AIDS Research (OAR)*** for setting research priorities and coordinating activities which cross the boundaries of nearly all institutes, centers, and divisions. In particular, it is the mission of the ***National Institute of Allergy and Infectious Diseases (NIAID)*** to maintain the leading portfolio of AIDS-related research projects.

NIH AIDS Research Program Evaluation Task Force

Exactly four years ago, the ***NIH Office of AIDS Research Advisory Committee*** commissioned ***the NIH AIDS Research Program Evaluation Task Force*** to conduct an unprecedented review of all AIDS research programs. Chaired by Arnold Levine of Princeton University and comprised of over 100 prestigious scientists and experts from throughout the world, the task force chose to examine "vaccine research and development" as one of six major areas of research emphasis.[11]

When the ***Report of the NIH AIDS Research Program Evaluation Task Force*** (commonly referred to as the "Levine Report") was released in the Spring of 1996, perhaps the most significant of the recommendations were those pertaining to HIV vaccines research.[12]

AIDS Vaccine Research Committee

To implement a primary recommendation made by the Task Force to "establish a restructured trans-NIH vaccine research effort," a non-governmental advisory committee was established in 1997. The newly created ***AIDS Vaccine Research Committee (AVRC)***, charged with improving the coordination of NIH-supported vaccine activities, is now chaired by Nobel Laureate David Baltimore, President of the California Institute of Technology.[13] The AVRC has developed a comprehensive AIDS vaccine research program and advised the NIH on scientific opportunities, gaps in current knowledge, and future directions of AIDS vaccine research."[14]

According to the Office of AIDS Research, the AVRC was established to increase the focus on new strategies for discovery and development of a safe and effective HIV vaccine. The AVRC has already identified three specific areas of basic research that are needed to support more effective vaccine research:

- understanding the structure and function of HIV envelope protein
- improving animal models to understand correlates of immune protection
- understanding the mechanisms of directing antigen processing ***in vivo***.[15]

NIH Office of AIDS Research

The ***NIH Office of AIDS Research (OAR)***, located within the Office of the Director of NIH, remains responsible for coordinating the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program, as well as promotion of collaborative research activities in domestic and international settings.[16] OAR's first steps toward making HIV vaccine development a higher priority involved giving NIAID an additional $6 million in Fiscal Year 1997 funds for new AIDS vaccine programs and $1 million to the AVRC to support special AIDS vaccine initiatives.[17]

Finding just the right person for a job can make all the difference in the world. On May 15, 1998, NIH Director Harold Varmus appointed Neal Nathanson, an active member of the NIH AIDS Vaccine Research Committee, to serve as the new Director of the NIH Office of AIDS Reseach. Dr. Nathanson is a world leader in viral pathogenesis and has a broad background in virology, epidemiology, and public health. According to Dr. Varmus, "The recruitment of Dr. Nathanson to serve as OAR Director will further enhance our deep commitment to vaccine research."[18]

Vaccine Research Center

To further expedite the discovery and development of a safe and effective AIDS vaccine, a new and unparalleled ***Vaccine Research Center*** is being established on the National Institutes of Health campus "to focus a comprehensive research program and stimulate multidisciplinary research from basic and clinical immunology and virology through to vaccine design and production." The Center will initially focus on AIDS vaccines and complement the comprehensive extramural research with a center drawn from intramural scientists from NIAID and the National Cancer Institute and others across the NIH.[19] According the NIH, physical construction has just begun on the new five-story, $29 million vaccine research facility in Bethesda, Maryland.[20]

The National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases (NIAID), under the leadership of Director Anthony Fauci, has begun the process of significantly restructuring its overall approach to HIV/AIDS vaccine research and steadily increasing targeted funding on vaccine research programs over the past two years.

The new ***Innovation Grant Program for Approaches in HIV Vaccine Research*** was recently unveiled by NIAID and is designed to speed the pace of AIDS vaccine discovery and development. "It will do so by supporting research projects that may involve a high degree of innovation and risk, that show clear promise in improving vaccine design or evaluation, and that bring new investigators into the field of HIV vaccine research."[21] Launched in 1997, the program is aimed at attracting new researchers into the AIDS vaccine development field. To date, 58 two-year grants have been awarded, including 28 grants to investigators new to AIDS research. Total funding for the program in FY 1998 was $13.1 million.[22]

To support mid-stage, pre-clinical vaccine research studies focused on areas such as immune correlates and animal models, NIAID has created the new ***HIV Vaccine Research and Design Program (HIVRAD).*** This is a basic research program supporting traditional, hypothesis-driven basic vaccine research and design. According to the Office of the Director for Vaccine and Prevention Research, Division of AIDS, NIAID, "applications may target an area of AIDS research including but not limited to HIV antigen processing, correlates of immunity, animal model development, DNA vaccination, studies of the structure of HIV immunogens, development of virus and bacterial vectors, studies of existing vaccine cohorts, studies targeting initial infection, and modeling of vaccine concepts in macaques and chimps. Human clinical studies are not conducted through this program."[23]

NIAID has also established ***HIV Vaccine Working Groups***, which include representatives drawn from intramural scientists at NIH, NIH-sponsored extramural scientists, and community constituency groups, to assist in the scientific coordination and planning of NIAID efforts in targeted areas of vaccine design and correlates of immunity. In addition, The ***National Cooperative Vaccine Development Groups (NCVDGs)*** have functioned effectively for several years and have led to the discovery and development of vaccine candidates. Through this program, research teams made up of scientists from industry, academia, and government have collaborated to develop and test novel experimental HIV vaccine concepts in laboratory and animal models. NIAID has expressed its intention to extend the scope of NCVDGs work to include early human clinical trials. The NCVDGs "will be competitively renewed as ***Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD)*** grants in FY 1999."[24]

NIAID Division of AIDS and Clinical Research

The NIAID ***Division of AIDS (DAIDS)*** maintains the primary responsibility for clinical research toward an HIV vaccine. The DAIDS' program of "clinical development" of vaccines to prevent HIV infection or disease is currently centered in two large, multi-center organizations – the ***AIDS Vaccine Evaluation Group (AVEG)*** and the ***HIV Network for Prevention Trials (HIVNET).*** The AVEG has historically focused on early safety and immunogenicity trials, and correlative laboratory studies of candidate preventive vaccines. It has carried out these Phase I and Phase II vaccine studies in a multi-center network of U.S. domestic sites. The HIVNET has had a broader agenda that includes trials of vaccines, topical microbicides, STD treatment, behavioral interventions, and approaches to prevent mother-to-infant transmission. It has focused primarily on efficacy trials in an international multi-center network. Scientific collaborations with scientists in industry and academia, as well as with NIAID staff constitute other key components of the program.[25]

Given the important missions of both AVEG and HIVNET, and the substantial commitment of resources required to sustain them, NIAID initiated an examination of this program to ensure that it is optimally focused and designed to address the scientific as well as public health needs and opportunities which currently face the field of HIV prevention science. Throughout the first half of 1998, NIAID staff engaged a large number of investigators in and outside of the AVEG/HIVET system, industry representatives, community members, advisory groups, and other stakeholders in discussions and focus groups. The goals of this process were to: 1) identify future scientific needs and opportunities; 2) assess the strengths and weaknesses of the current program; and 3) create a foundation for the solicitations which will establish the structure and identity of the clinical trial program for the next five years.[26]

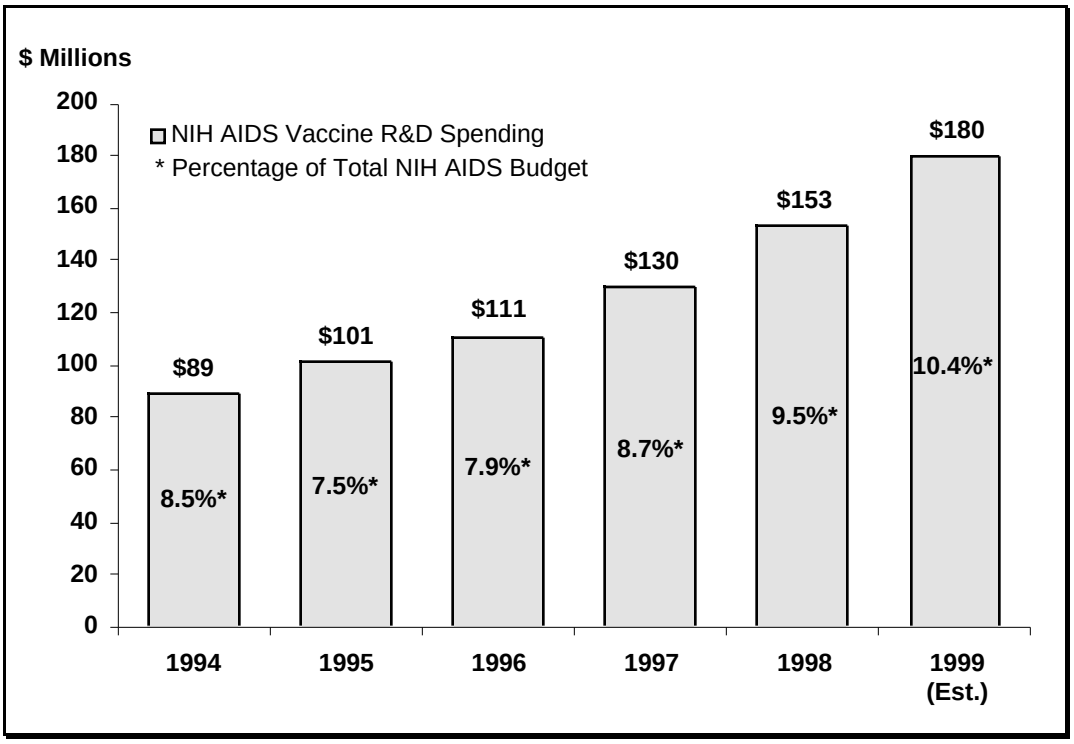
While scientific compartmentalization of vaccine development does exist, one of the main problems of the current system is "the scientifically artificial division of responsibility" (Phase I and II vaccine trials in AVEG, and Phase III in HIVNET). This situation instigates a complex coordination problem between the two different organizations with very different scientific foci, priorities, laboratories, data collection and analysis systems. A seamless program of vaccine development between AVEG and HIVNET is difficult if not impossible.[27]

NIAID is currently planning to consolidate scientific responsibility for HIV vaccine research and development in the ***HIV Vaccine Trials Network (HVTN)*** with an expanded, integrated clinical research and development agenda utilizing domestic and international components. A consolidation in scientific responsibility will also take place for other areas of clinical prevention research previously under the purview of HIVNET in the ***HIV Prevention Trials Network (HPTN).*** While the practical improvements from the new restructuring remain to be seen, there will certainly be a need for cooperation, collaboration, and overlap between the HVTN and the HPTN.[28]

New Funding

Funding for AIDS Vaccine Research at the NIH has increased significantly during the past two years. Total funding in Fiscal Year 1998 was $153 million, a 17.5 percent increase over FY 1997 and a 53 percent increase since FY 1995. The FY 1999 budget includes $180 million for AIDS vaccine research, an increase of 17.5 percent over FY 1998 and an 80 percent increase since FY 1995.[29]

NIH Spending on HIV Vaccine R&D, 1994-1999



Source: ***Scientific Blueprint for AIDS Vaccine Development, International AIDS Vaccine Initiative, June 1998***

To date, this new priority for HIV vaccine research has largely occurred apart from lawmakers in Congress. Interestingly, due to the current popularity of biomedical research generally and a desire among members of Congress to provide NIH with substantial funding increases overall, agency officials are, themselves, more capable of targeting additional resources toward HIV vaccines activities.

White House Office of National AIDS Policy

> ***"I think it is clear that an effective vaccine is way down the road for us and certainly a vaccine that is easy to administer and cost effective is going to be down the road farther yet, but that is what we are going to need to stop the epidemic globally."***[30]
> ***Sandra Thurman, Director, White House Office of National AIDS Policy, September 30, 1998***

Completely independent from the NIH research enterprise is the ***White House Office of National AIDS Policy***. This office maintains responsibility for coordinating federal policy and programs on HIV/AIDS, and works to build partnerships among Federal agencies, the AIDS community, AIDS service providers, state and local officials, and major business leaders. The objective of the Office of National AIDS Policy is to "increase the rate of progress in treatment and education, and to maintain the focus on science and scientific research."[31]

In March 1998, the ***Research Committee of the Presidential Advisory Council on HIV/AIDS (PACHA)*** released its own set of recommendations for federally funded HIV vaccine research efforts. The topics addressed by this committee focused on administrative issues. The most important recommendation called for the Director of the Office of National AIDS Policy to assume the leadership role in the development and implementation of mechanisms to assure the active participation and coordination of all relevant agencies of the U.S. government, as well as the pharmaceutical industry and the international community.[32] The panel also urged that incentives must be developed to increase pharmaceutical company involvement in HIV vaccine research. PACHA suggested that "financial disincentives be overcome through support of phase III trials, subsidies for pilot manufacturing of non-commercially attractive vaccine options, tax rebates, and patent extensions."[33]

The Varied Roles of Advocates and Affected Communities

Throughout the 17-year history of the AIDS epidemic in the United States, affected and concerned individuals have naturally joined together to find new and better ways to fight this deadly disease. At both national and local levels, people have organized into numerous groups to promote effective public policies in areas such as biomedical research, drug development, affordable quality health care and treatment access, civil rights, and education and prevention, just to name a few. In most cases, individual and community activism has developed in response to the ***immediate*** health care needs of people living with HIV/AIDS or through efforts to implement proven and timely prevention strategies. New advocacy efforts have emerged around the goal of developing preventive HIV vaccine and several vaccine-focused organizations have been established.

While effecting change on the road to a preventive HIV vaccine is in many ways no different from other approaches toward ending this scourge, the origin of this latest community activism represents a key distinction. In general, outspoken advocates for vaccine research are not, presently, members of the very high risk populations most needed to serve as the subjects of clinical trials individuals, and most likely to reap the benefit of a preventive vaccine. While many are relatively new to AIDS-related advocacy, others have emerged from previously existing and, often, quite skilled AIDS organizations working at national and local levels. After years on the front lines of national AIDS policy, a number of individuals, many of whom are living with HIV themselves, have arrived at the same conclusion: only an effective vaccine will stem the worldwide spread of the epidemic. Their efforts to forge public policies on vaccine issues and to represent affected communities have provided important leadership and resulted in the creation of broad coalitions and formalized organizations.

AIDS Vaccine Advocacy Coalition

In 1995, the ***AIDS Vaccine Advocacy Coalition (AVAC)*** was founded "to advocate for the development of a safe, effective, and accessible HIV vaccine." The organization came together as a network of volunteers throughout the country to serve as a national voice on vaccines, "providing a well-informed, independent, and honest critique of current HIV vaccine research and development." [34] Since its inception, AVAC has maintained a policy, subsequently adopted by other groups, that public funding for HIV vaccine research must not come from resources for therapeutics or other prevention approaches.

During a relatively short period of time, the ***AIDS Vaccine Advocacy Coalition*** has produced a substantial portfolio of achievements and succeeded in establishing itself as a leading force among AIDS organizations. AVAC issued the first public report demanding that the President set a ten-year goal for an HIV vaccine. In 1996, AVAC published the first in-depth analysis on the pharmaceutical industry's investment in HIV vaccine research. And more recently, its report entitled ***9 Years and Counting: Will We Have an HIV Vaccine by 2007?*** continued to propel HIV vaccine research and AVAC into the national spotlight. [35] AVAC's leadership and active collaborations have built trust and a remarkable amount of consensus and communication about advocacy for HIV vaccines as part of the AIDS advocacy agenda.

In addition to AVAC, many of the nation's leading AIDS advocacy organizations have independently added vaccine development to their agendas. The ***American Foundation for AIDS Research (AmFAR), AIDS Action Council, Gay Men's Health Crisis (GMHC), Treatment Action Group (TAG), and Project Inform*** have all sponsored community forums to educate people and have published articles on vaccine issues. AmFAR also directly funds HIV vaccine research and provides a directory of clinical trials. Recently, TAG began devoting an advocate for vaccines part-time. To date, vaccine advocacy among national AIDS organizations has followed a very unique course characterized by cooperation and general agreement. AVAC Executive Director Sam Avrett suggests this is primarily due to "individual groups deferring to the decisions and positions that are worked out during policy discussions" at meetings of the National Organizations Responding to AIDS (NORA) and various sessions of NIH research advisory committees.[36]

Community-Based Organizations

Community-based organizations such as the ***San Francisco AIDS Foundation***, the ***Whitman-Walker Clinic*** in Washington, D.C., as well as ***Project Inform*** and ***GMHC*** have started taking a message about the need for HIV vaccine research to the streets. As accessible, longtime members of local communities, such organizations maintain the unique ability to educate high-risk populations about the many complex issues related to vaccine clinical trial participation. And as essential providers of health care and social services for people living with HIV/AIDS, community-based organizations are regarded as perhaps the most trusted sources of information among various high-risk populations and the general public.[37]

In cities associated with NIAID-designated clinical trial sites, representatives of community-based organizations are now working collaboratively with community health educators, HIVNET counselors, and AVEG recruiters. These individuals, most often connected with city health departments and academic health centers, contribute an essential level of knowledge and resources to the community dialogue. According to Joe Wright of the San Francisco Department of Public Health's HIV Research Section, the extent and quality of community outreach varies widely among clinical trial sites; for example, "some sites have a single community health educator, some don't have any, some sites have one for women and another for men."[38] In any case, an abundance of opportunities clearly remains for the NIH, and perhaps more appropriately the ***Centers for Disease Control and Prevention (CDC)*** and private philanthropic foundations to initiate community dialogue on HIV vaccine research by funding additional information and education programs.

International AIDS Vaccine Initiative

In addition to the local, grassroots work of community-based organizations and the national-level efforts of leading AIDS advocacy groups, the ***International AIDS Vaccine Initiative (IAVI)*** was established to focus international research and development activities and to "ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world."[39] Founded by the Rockefeller Foundation in 1996 and based in New York, IAVI's advocacy efforts have been specifically designed to help the international research community overcome the ***scientific*** obstacles to a preventive HIV vaccine. In an effort to put HIV vaccine development on the "fast track," IAVI recently published its "***Scientific Blueprint for AIDS Vaccine Development"***[40] and announced plans to fund up to $4 million in research. Notably, NIAID's new Assistant Director and Division of AIDS Associate Director for Vaccines and Prevention Research Margaret Johnston, previously served as IAVI's scientific director.

Need for Increased Private Sector Contributions

> ***"There aren't that many companies involved in vaccine development to begin with. Somewhere over ninety-five of the world's current vaccines are produced by only five companies."***[41]
> ***Dr. Margaret Johnston, NIAID Division of AIDS, August 17, 1998***

Even though "the world's first wide-scale efficacy testing of a vaccine to prevent AIDS received the go-ahead from the Food and Drug Administration (FDA) in June 1998,"[42] only a small handful of private pharmaceutical and biotechnology companies are presently investing in HIV vaccine research and development. Furthermore, those companies which have benefited from the production and sale of AIDS therapeutics, generally, have not committed significant additional resources toward the quest for a preventive HIV vaccine.

Unfortunately, adequate information on the activities and motivations of the pharmaceutical and biotechnology industries is sorely lacking. Company business plans and research strategies are usually classified as proprietary information, making a true picture difficult to obtain. However, several companies in particular should be commended for their investments in products readied for clinical trials, namely: ***VaxGen, Chiron, Pasteur-Merieux-Connaught, Merck, Wyeth-Lederle, Genentech, Therion, and CelSci***.

To date, the most comprehensive study of private sector interest in HIV vaccine research and development was conducted in 1996 by the AIDS Vaccine Advocacy Coalition, entitled ***"Industry Investment in HIV Vaccine Research."*** Through a series of interviews with corporate scientists and managers, AVAC found that the leading obstacle for companies has been "the imperfect state of science for this endeavor at present and for the foreseeable future."[43]

Nevertheless, during the past few months, one company, ***VaxGen,*** has managed to become the first to test an HIV vaccine in a large, phase III human clinical trial. The product, gp120, also known as ***AIDSVAX***, will be studied in 5,000 HIV-negative individuals in the U.S., with another trial beginning shortly in Thailand. The history of AIDSVAX is best characterized by ongoing collaboration between VaxGen and the NIH. NIAID conducted six phase I and one phase II studies of an earlier version of this product. Now, government scientists will collaborate further in the evaluation of immunological responses.[44]

Candidate Preventive HIV Vaccines

Producer	Product	Concept	Clade	Status
ANRS	Lipopeptides	Peptide	B	phase I
Bristol-Myers Squibb	vaccinia-env	viral vector	B	inactive
British Biotech	Ty-VLP-p176/p24	Particle	B	inactive
	Ty-VLP-V3	Particle	B	inactive
CelSci	HGP-30	Peptide	B	phase I
Chiron	gp120	Protein	B	phase II
	gp120	Protein	B+E	phase I
	p24	Protein	B	phase I
Cuban Company	V3	Peptide	B	phase I
Duke/Lederle	C4-V3 peptides	Peptide	multi B	inactive
France	mixed env	Peptide	B	inactive
Genentech	gp120	Protein	B	phase II
ID Vaccines	V3-PPD	Peptide	multi	preclinical
IMMH, Germany	p55	Particle	B,C,A,D	preclinical
	p55 + env	Particle	B,C,A,D	preclinical
ImmunoAG	gp160	protein	B	inactive
KCST, Japan	HBc-V3	viral vector	B	preclinical
Merck	multi	DNA	B	preclinical
NIH	p55	protein	B	preclinical
NIID, Japan	BCG-V3	bacterial vector	B (+ E)	preclinical
Pasteur-Merieux Connaught	canarypox-e	viral vector	B	phase I
	canarypox-e/g/p	viral vector	B	phase II
	canarypox-e/g/p+	viral vector	B	phase I
	canarypox-e/g/p++	viral vector	B	preclinical
	pseudovirions	particle	B	preclinical
Protein Sciences	gp160	protein	B	inactive
(formerly MicroGeneSys)	p24	protein	B	inactive
SSI	V3-PPD	peptide	B	inactive
Therion	vaccinia-e/g/p	viral vector	B	phase I
United Biomedical	gag-lipopeptide	peptide	B	inactive
	V3-MAPS	peptide	B	inactive
	V3-MAPS	peptide	multi B	inactive
Univ. of Maryland	Salmonella-env.	bacterial vector	B	phase I
VaxGen	gp120	protein	B+E	phase II/III
	gp120	protein	B+B	phase II/III
Walter Reed Army Institute for Research	gp160	protein	oligomeric	preclinical
Wyeth-Lederle	env, rev	DNA	B	phase I
(formerly Apollon)	env, rev	DNA	non-B	preclinical
	gag, pol	DNA	B	phase I

Source: ***Scientific Blueprint for AIDS Vaccine Development, International AIDS Vaccine Initiative, June 1998***

NIAID Director Anthony Fauci and Gregory Folkers wrote in a recent ***Nature Medicine Vaccine Supplement*** that "most currently available vaccines, as well as those in the development pipeline, have resulted from collaborations between partners in the public and private sector, including federal and state governments, small and large companies, academic research institutions and non-governmental organizations."[45] There are many ways in which government can harness private industry scientific expertise for HIV vaccine research, including:

- offering tax and licensing incentives
- direct government funding of industry to pursue research in promising areas
- addressing liability concerns
- establishing clearer licensing guidelines
- guaranteeing purchase of a vaccine when licensed, and other options[46]

Equity issues can be addressed by offering these incentives as part of a negotiated package which includes commitments on the part of industry to maximize the availability of a vaccine when licensed (e.g., offering a reduced rate for those unable to purchase the vaccine). To date, however, none of these measures to alleviate

private sector disincentives has even been advocated, much less codified into law or established through federal regulations.

Broadening the Base of Renewed Leadership and Focused Collaboration

Joint United Nations Programme on HIV/AIDS (UNAIDS) & New Ethical Guidelines

The leading force behind a global demand for a preventive HIV vaccine is the ***Joint United Nations Programme on HIV/AIDS***, commonly known as ***UNAIDS.*** This initiative combines and focuses the efforts of six organizations of the United Nations, including the World Health Organization (WHO) and the World Bank. Since 1996, UNAIDS has acknowledged that "better tools are urgently required to slow the expansion of the HIV epidemic and that a safe and effective HIV vaccine would be an invaluable complement to other prevention strategies….the UNAIDS program actively promotes the development, evaluation and availability of appropriate HIV vaccines for worldwide use, especially in developing countries,"[47] according to UNAIDS Executive Director Peter Piot and Vaccine Program Director Jose Esparza.

In preparation for wide-spread international HIV vaccine trials, UNAIDS has paved the way for the establishment of new ethical guidelines designed to protect the rights of those taking part in clinical trials. The guidelines are the outcome of a nine-month consultative process involving representatives of 30 countries – including people living with HIV/AIDS, vaccine researchers, and experts in the fields of law, medical ethics, and public health, as well as representatives of national HIV/AIDS programs, the pharmaceutical industry, and international organizations. One of the most important new guidelines states that "once a vaccine is proved to be safe and effective, the obligation to make the vaccine widely available should be the joint responsibility of all the agencies involved in sponsoring the trials, including the pharmaceutical manufacturers, research agencies, and international organizations."[48]

The issue of access to an eventual preventive HIV vaccine, and other UNAIDS guidelines including the need to obtain informed consent, the need to ensure an appropriate standard of counseling and other HIV preventive measures, and the provision of treatment and care for people who become infected during the course of a trial – are all discussed, in detail, in the second half of this paper regarding the social issues facing prospective vaccine trial volunteers and affected communities.

SOCIAL ISSUES OVER THE LONG HAUL OF HUMAN TRIALS

By the time Kevin Shancady walked into the Denver Department of Public Health to enroll in an HIV vaccine trial, he'd managed to put most of his fears behind him: fears of a government hostile to gay men, fears that researchers might inject volunteers with a dangerous vaccine. "So many people have died," he said, "and I feel an obligation to advance prevention research. I'm willing to take some risk. And if the vaccine works, then I'll have protection."

It's that mix of optimism, altruism and hope for personal benefit that has made it possible for the National Institute of Allergy and Infectious Diseases (NIAID) to recruit over 5000 Americans into a cohort now entering an HIV vaccine efficacy trial. But what Kevin heard when he sat down with a study counselor shows why recruiting volunteers is just the first step on the long and difficult road of HIV vaccine testing. In the best tradition of public health, the study counselor warned him of the possible risks of trial participation. "He told me participants in this trial might not be able to join other vaccine trials," Kevin said, "and if a different vaccine is eventually developed later, it might not work as well in me as in people who had not been in one of these early vaccine studies. I felt blindsided, actually."

Kevin's dilemma is faced by thousands of other potential vaccine trial volunteers, and by whole communities directly affected by the HIV epidemic. The enormous potential benefits of vaccines are accompanied by difficult questions and significant risks. And beyond the physiological unknowns are social complexities. The lengthy, trial-and-error progress of HIV vaccine trials may create unique social dynamics in which media scrutiny, ethics, equity, and the perceived likelihood of success, and factors such as the ability to recruit and retain volunteers and overall public support are all intertwined as they never have been before.

So, given all these conundrums, what made Kevin Shancady decide to become an outspoken advocate for HIV vaccine research? In the history of public health, vaccines have proven to be among the most effective disease

prevention tools. Diseases such as smallpox, polio, measles, and others have been eradicated or brought under control through mass vaccination programs. And in the fight against HIV, its clear that new and powerful prevention technology such as a vaccine is badly needed. Without it, communities will continue to be devastated.

But inherent in the promise of vaccines are very real risks. The potential for behavior change is just one example. When a vaccine is eventually licensed for widespread use, it is very unlikely to be 100% effective. What if recipients of a vaccine which is only partially effective feel newly invulnerable to infection, and greatly increase their risky behavior? Will the number of infections actually increase?

The benefits of HIV vaccine research seem far off and the risks far more tangible. In communities responding to the health care needs of thousands with HIV, the urgent need for a cure is ubiquitous, while the need for expanded prevention technology can be less immediately evident. And it is these same communities which have historical and present-day reasons to be distrustful of government-sponsored biomedical research and the motivations of pharmaceutical companies which will produce a vaccine.

The massive research effort and series of human trials necessary to produce an effective HIV vaccine is only sustainable if it has the support of individual trial participants, affected communities and the general public. This section of the paper outlines concerns and potential remedies at each of those levels. It begins with a review of some of the factors which make HIV vaccine research unique, and concludes that specific action by communities, government, private industry and others will be needed in order to ensure ethical trials capable of sustaining support over the long haul of HIV vaccine research and testing, including:

- the general public
  - education regarding the timeline of HIV vaccine research and introduction of a new definition of "success" in clinical research

- affected communities
  - addressing equity issues which may cause tensions within communities
  - monitoring research efforts, particularly the safety of products and efforts to protect participants
  - providing education and focused efforts at building trust with particular affected communities
  - determining and fostering appropriate models for structured community debate
  - placing value on HIV vaccine research efforts
  - continued emphasis on non-vaccine, HIV prevention efforts

- individuals considering participation in trials
  - expanding the Participant's Bill of Rights
  - contracting with community-based organizations to provide information which will facilitate individual decision making about trial participation
  - providing the highest quality behavioral interventions to members of vaccine trial cohorts
  - reforming and expanding government HIV vaccine research efforts
  - expanding pharmaceutical industry investment in HIV vaccine research and product development

Challenges of HIV Vaccine Research

The search for a vaccine for HIV promises to require, at minimum, a decade of work by researchers and sustained optimism on the part of trial volunteers and the public. The virus presents daunting scientific obstacles: no perfect animal model of HIV disease exists; recovery from HIV infection has not been documented; the "correlates of protection" (immune responses which would protect people from infection) are not known; the virus is highly variable so a vaccine for one "clade" (or type of HIV) may not protect against a different HIV-1 clade; and the virus mutates rapidly and may be able to elude a vaccine.

Traditional approaches to vaccine development, such as "whole killed" or attenuated virus methods raise special safety concerns with HIV, since a faulty vaccine which actually infects a recipient could have lethal consequences. Finally, it may be impossible to find a vaccine which prevents actual infection (also called "sterilizing immunity"). Instead, research goals may focus on a product which can inhibit progression to disease, or lower viral load in infected persons. Assessing a vaccine's ability to meet these post-infection goals may add years to human trials.

These obstacles may translate into a product development and human trial timeline measured in decades. When many people think of a vaccine trial, they picture one large trial that proves efficacy in a few years. Progress will

probably be more incremental in the case of HIV vaccines.[49] It is likely that a series of human trials will continue for many years and require tens of thousands of volunteers in several countries.

Vaccines for HIV are not the first to require multiple human trials over many years. The vaccine for haemophilus influenzae type B (HIB) was developed over a 17-year period and involved hundreds of thousands of individuals in human trials.[50] The HIB vaccine may have limited application as a model of the social dynamics of HIV vaccine research, however. Like HIB, HIV has a relatively low annual infection rate in the United States, meaning that efficacy trials will likely be lengthy, expensive, and generate results which are sometimes difficult to interpret. Unlike HIB, human trials for HIV will take place under intense media scrutiny and political activity, and involve adults in stigmatized risk groups, rather than children in the general population.

During the extended testing timeline for HIV vaccines, results from efficacy trials may create controversy even as they advance research. NIAID has developed the new concept of "Intermediate Sized Trials" to test early vaccine candidates. Unlike standard large-scale ("Phase III") human trials, intermediate trials will involve fewer volunteers and be less expensive, allowing researchers to test several different products and pursue only the most promising with full-scale efficacy trials. The drawback of intermediate trials is that their results have lower "statistical power" and may provide ambiguous results. For each intermediate sized trial, public health officials and researchers will need to decide whether the results justify expanding to a full-scale Phase III trial.

Three Phases of Human Clinical Trials

Phase I	***Involves small numbers of low risk volunteers and is designed to test the safety, acceptability and appropriate dosage of a product.***
Phase II	***Involves larger numbers of volunteers (usually several hundred) and is designed to test safety and immunogenicity (the ability of the product to induce responses from the immune system).***
Phase III	***Large scale trials, usually involving several thousand volunteers designed to test the safety and efficacy (effectiveness) of a product.***

Intermediate Sized Trials are intended to give an indication of whether or not a product may be efficacious. These trials involve smaller numbers of volunteers than Phase III trials and can be expanded to full-scale efficacy trials if the product being tested shows promise.

If, in the early 21st century, trials have not succeeded in identifying a broadly licensable vaccine, thousands of new volunteers will be needed to sustain HIV vaccine research. Scientists will still be making difficult decisions about the threshold for advancing to full scale trials, and each of these decisions may be an occasion for renewed public debate. Recent history suggests that the public perception of this process — its ethical conduct, its use of resources, its hope for success — will have a powerful impact on the successful development and distribution of vaccines for HIV.

The Need for Support from the General Public

Vaccine development has historically been influenced by many social forces, including media attention, the interests of pharmaceutical companies, and the hopes and fears of the general public. In the past, the interplay of these forces has had a critical impact on the ultimate public health outcomes of vaccine research.

Public enthusiasm was an essential ingredient in the race to find a vaccine for polio. Most of the funding for research came from the National Foundation for Infantile Paralysis (better known as the March of Dimes) which depended on individual contributions. Public support was needed to maintain financial contributions, but also played an important role in pushing the scientific establishment towards endorsement for a massive human trial. The press gave extensive coverage to polio vaccine research. In his analysis of the politics and public relations of polio vaccine development, Harvard medical school historian Allan M. Brandt observed that,"...where public demands and expectations are great, sound scientific judgment may be jeopardized. The Salk vaccine was sold to the public before its safety and efficacy were proven."[51]

Three decades later, it was fear of public reaction which prompted medical professionals to take the opposite approach and minimize the general public's knowledge of an epidemic in their midst. High rates of hepatitis B infection had been identified in some sectors of the population, including health care workers, gay men, Asian immigrants, and others. What followed was a series of decisions designed to quiet public concern about the problem: the medical community played down the potential threat of patient infection by health care workers, and physician organizations resisted large-scale testing of their members. Hepatitis B was portrayed as primarily a problem of particular groups and not a major concern for the general population.

In 1982, a hepatitis B vaccine was developed with the assistance of the pharmaceutical company Merck, but because of previous efforts to keep the epidemic quiet, the public remained largely ignorant of the danger of the disease or the new potential to prevent it. William Muraskin, a professor at City University of New York, has observed that, "since there was no public concern, there was not public outrage at the high cost of the vaccine or the quasi-monopoly that Merck had obtained for itself."[52] The result was a costly vaccine which failed to stem the epidemic for years after it was licensed.

In both these examples, leaders in the medical establishment and the media made choices about what should become general knowledge because it was assumed the public's expectations would play a pivotal role. A similar dynamic with HIV is likely.

Redefining "Success"

Researchers, the public, and trial volunteers will need to be willing to take reasonable risks and expect incremental successes on the road to an HIV vaccine. Neither the polio nor hepatitis B examples of public relations will sufficiently prepare people for this incrementalism. Media coverage or statements by researchers which fails to convey the complexity of the issues or which enthusiastically promotes early trials without acknowledging the incremental nature of progress, could damage public confidence if trials do not quickly produce a "magic bullet."

In May 1994, the Chicago Tribune ran a front page story reporting that an experimental HIV vaccine had failed to protect several people from becoming infected with HIV. The story itself was not startling news. No vaccine in history is 100% effective, and some number of "breakthrough" infections (infections of vaccinated trial participants) are expected in any vaccine trial.

As June Osborn, chair of the former National Commission on AIDS, has written, "the brief excitement generated by any failure to protect served as a reminder that public expectations were exorbitant."[53] Osborn pointed out that those expectations "will be of central importance to the capacity to conduct any HIV vaccine trials." But if collective hopes are dashed every time a vaccine candidate fails to prove highly efficacious, the search for an HIV vaccine may not be able to sustain long-term support from the public and affected communities. Community activist Mark Harrington has warned, "the potential consequences of an early failure, broadcast widely through a hysterical, fearmongering media, are grave. The vaccine trials will be subjected to unprecedented worldwide scrutiny."[54] In order to avoid the sensationalizing of research findings it is incumbent upon researchers to provide the media and the public with enough information and education to put research findings in context.

There is also the danger that, like hepatitis B, HIV will increasingly come to be seen as a disease of isolated groups and of limited concern to the general American public. In the United States, HIV has always affected primarily stigmatized groups and is increasingly a disease of the poor, people of color, and drug users. Ninety-five percent of all new infections are now occurring in the developing world. As these trends accelerate, the general public may not continue to see HIV as a public health priority and support and funding for research and broad access may wane.

Sustaining public support for vaccine research while communicating the complexity of the research task will require a delicate balance of honesty and optimism. As Barney Graham and Peter Wright of the NIAID Phase I/II AIDS Vaccine Evaluation Group have written, "there is a need for a measured approach to communicating information, so that the public can be adequately informed. The sense of urgency the epidemic demands must be maintained, without overstating results and creating expectation of unrealistically rapid progress."[55]

Researchers must redefine for the public the meaning of "success" in HIV vaccine research so that a human trial is not considered a failure if it contributes to knowledge which can eventually lead to an effective vaccine. Such a redefinition will require the public and potential trial volunteers to re-orient their

expectations to gradual progress and to participation in trials which may not immediately produce a licensable product. The new understanding may make trial recruitment more challenging, but it will also likely make it more sustainable.

This re-orientation will be complicated by the fact that for each proposed trial there will need to be a reasonable expectation of ultimate success — of identifying a licensable vaccine. A trial which has little or no chance of demonstrating the efficacy of the candidate vaccine would be unethical and be unlikely to receive public, trial volunteer, and scientific community support. Faith in each separate trial will be required, as will ongoing support for vaccine research if a trial fails to prove the efficacy of a product.

However realistic it is, this "delayed gratification" definition of success can only become widely accepted by the public and affected communities if they have faith in the integrity of researchers and research efforts. While researchers tackle the difficult science, they must also continue to build a product development and testing infrastructure which can withstand scrutiny and maintain the faith of volunteers over time. Mistrust of government and cynicism about the medical establishment and pharmaceutical industry contrast with the relative faith of the Salk polio vaccine era. Today, building trust in researchers is more important than generating blind enthusiasm.

Urgency and Distrust in Affected Communities

The concept of "community," will play a central role in HIV vaccine research. Individuals' perception of community membership is a prime motivator for individual trial participation, and community-based institutions (including media, service, and civil rights organizations) will help determine the level of support for vaccine research among trial participants and the public. At least two areas will require closer attention: the implications of community identity and community involvement in decision making.

Community Identity

Trial participants are of interest to researchers primarily because of a specific HIV-risk behavior they practice, and not because of the community, or communities, with which they identify.[56] Yet ties to one or more communities may help determine a person's desire to volunteer for vaccine trials, how they receive information, whom they trust, how they interpret the motivations of government and industry, and how they gauge their level of risk for HIV.[57] Some volunteers in trials will have a sense of belonging to more than one "at-risk" community; some will not identify with any of these communities. Though the importance of community will vary with each individual, we can anticipate that tensions within communities and trust-building efforts in particular communities will be import factors in vaccine testing.

Populations Being Recruited for Domestic HIV Vaccine Trials

- ***Men Who Have Sex with Men (Gay and Bisexual Men)***
- ***Injection Drug Users***
- ***Women at High Risk***

Populations Within Populations

It is important to note that investigators seek to recruit "higher risk" individuals within each of these populations. For example, younger gay men and gay men from communities of color are generally at higher risk for HIV, and this is one reason investigators at trial sites recruiting gay men seek to include members of these populations in trials.

Tensions Within Communities

Concerns about the equitable sharing of risks and benefits of trials within communities have the potential to undermine volunteer enthusiasm. For example, researchers need to recruit higher risk members of the gay community for trials. Currently, these volunteers are younger, have lower incomes and educational levels, and have lower rates of health insurance coverage, than much of the gay community. Without a method to assure access to licensed vaccines by all people at high risk, only gay men with health insurance or financial resources to purchase a vaccine will benefit from this research. Many HIV vaccine trial volunteers might find that other gay men "like them" have limited access to a vaccine.

Injection drug users, people of color, young men who have sex with men and others enrolled in vaccine trials may face stigma within their own networks or communities, because they are seen as having been "co-opted" by researchers. The potential for being labeled a "guinea pig" may be particularly strong in communities which have experienced unethical biomedical research or which perceive themselves to be less likely to receive the benefits of research. The prospect of this stigma argues for offering participants as many protections and benefits as is appropriate without being coercive.

Vaccine trials may also spark tensions between infected and uninfected people within communities if it is perceived that vaccine funding is draining resources for therapeutics or other prevention approaches, or that significant effort is being expended to fight discrimination based on false positive (vaccine induced) HIV seropositivity, while discrimination against HIV-infected persons is allowed to continue in insurance and other areas. Equity issues such as these have the potential to undermine support for trials in the communities in which HIV vaccines must be tested.

The result of increased community dialogue on these issues might be:

- setting guidelines for advocacy that vaccine funding will not come from resources for therapeutics or other prevention research
- demanding a plan to secure subsidized access to vaccines to low-income, at-risk individuals
- requesting personal statements and action on the part of vaccine researchers to support an end to discrimination against people with HIV infection

Why do individuals at increased risk for HIV need to be recruited for trials?

In order to determine the effectiveness of a candidate vaccine, investigators randomly divide volunteers into two groups: those who receive the vaccine, and those who receive a placebo. Investigators then keep track of how many infections occur in each group after the vaccine and placebo has been administered. If there are a significantly smaller number of infections in the "vaccine group" this probably means the vaccine is effective.

Volunteers at higher risk are needed because they are more likely to be exposed to HIV, allowing researchers to see if the vaccine was effective. If vaccine efficacy studies were done in low-risk populations, there would such a small number of HIV exposures, and such a small difference in the number of infections between the vaccine and placebo groups that investigators would not be able to tell for sure if the vaccine was having any effect.

Communication and Building Trust

The goal of building trust between researchers and communities involves more than simply educating affected community members about the mechanics of vaccine research and testing. Also necessary is an open dialogue about community concerns regarding biomedical research and specific, concrete ways in which researchers can address or alleviate those concerns. For example, African-Americans may have less trust and willingness to participate in trials given historical incidents of abuse in biomedical research. Infamous examples, such as the Tuskegee Syphilis experiment during which penicillin treatment was withheld from the African-American study participants up through the early 1970's, remain powerful indictments of biomedical research which resonate with prospective research participants.[58] In this case and others, community-specific dialogue and trust building which addresses unique historical concerns and establishes appropriate assurances and safeguards is necessary.[59]

Involvement in Decision Making

When a single trial quickly identifies an effective vaccine (as in the case of polio or hepatitis B) the structure of the decision making process is unlikely to become an immediate, burning issue. When progress is incremental and extended over years, confidence in the quality of decision making may prove to be an important factor in sustaining volunteer willingness. Vaccine trials will require a series of complex and difficult decisions, including which candidate vaccines to test, when to begin large-scale human trials, whether or not to expand intermediate sized trials, and how to use the cohorts and Phase III infrastructure when vaccine products are not available for

testing. As it becomes clear to the media, the public and volunteers that these decisions require judgment calls and engender controversy within the scientific establishment, there may be increased attention to how those decisions are made.

Representatives of communities enrolled in trials and community-based organizations must be involved in every stage of trial design and decision making. And their perception of whether the potential benefits of a trial justify the risks should inform research decisions and help fuel community debate on trials. NIAID and individual researchers have already shown commitment to involving representatives of trial volunteers in trial planning and implementation. Yet the complexity of scientific and social issues involved in HIV vaccine testing requires additional attention to the details of community discussion, debate, and decision making.

Affected communities are unlikely to reach consensus on the merits of an HIV vaccine trial — what they can achieve is a thorough discussion, and a clear articulation of different viewpoints which individuals can then choose to accept or reject. A "community town hall"[60] design, as discussed by Christine Grady in ***The Search for an AIDS Vaccine***, would be more useful if its stated goal was to provide an open and structured debate covering the relevant issues. Individual trial volunteers at each trial site could draw upon this discussion (perhaps after viewing it on video tape if they were not present) in making their own personal decisions about whether or not to participate in the trial. The only vote taken would be trial volunteers "voting with their feet" — using this debate and other information to decide for themselves whether or not to participate in the trial.

Altruism and Ambivalence Among Trial Participants

Controversy may be a way of life in HIV vaccine research. Given the history of HIV vaccine product development, we can assume that the merits of future candidate vaccines being considered for trial will be the topic of intense debate within the scientific community, and that this debate will receive ample media attention. As a result, prospective volunteers may be making decisions about trial participation in an atmosphere of intense scientific debate.

Volunteers will need to be prepared to negotiate this controversy; embrace altruism as one of the few defensible motivations for trial participation; accept the physiological risks of being injected with an experimental product; face possible discrimination based on trial participation; get accurate information if the media misinterprets breaking vaccine news; and, finally, accept these difficulties knowing their participation may make them less likely to benefit from a vaccine which is eventually licensed.

Researchers will be asking HIV vaccine trial volunteers to take part in a long-term and risky collaboration, and volunteers will assume numerous risks and inconveniences. The experimental vaccine may make them test positive on standard HIV antibody tests, leaving them vulnerable to discrimination in international travel, health and life insurance, and several forms of government employment. They may experience difficulties simply by being labeled members of a "high risk" group under study.

Social Harm

Vaccine-induced seropositivity (testing positive on a standard HIV test due to the vaccine) may cause discrimination in:

- ***health and life insurance***
- ***international travel***
- ***some forms of government employment (such as Job Corps or Peace Corps)***

Being identified as someone participating in an HIV vaccine trial (or someone considered sufficiently "high risk" to be accepted into a trial) may lead to discrimination in employment, housing, other venues, or among the volunteer's peers, family or co-workers. Participants may also be perceived as "suckers" at the service of researchers with little chance for personal benefit.

To date, candidate HIV vaccines have proven to be safe. But there is at least a theoretical risk that vaccines will cause physiological harm by accelerating progression of disease in those who become infected or cause autoimmunity disease. Second and later generation vaccines may pose additional risks.[61] It is also possible that participants in early vaccine trials may be excluded from future vaccine research and benefit less from more effective vaccine products developed in subsequent studies. These risks, compounded by potential social and personal pressures resulting from participation in a high profile (and perhaps controversial) experimental trial will demand commitment on the part of those who volunteer and resilience from those who are retained in vaccine studies over years.

Participant satisfaction with trials will be essential to sustain a base of trial volunteers. Staff involved in Phase I/II studies for HIV vaccines have observed that, "...the best recruiting tool in minority populations, as well as all groups, is the satisfied customer. Our current and former volunteers are still the best recruiters for new volunteers."[62]

It is already clear that more needs to be done to allay the fears and maintain the confidence of trial participants if the government wants to recruit and retain multiple cohorts over many years or decades. A survey of 1660 participants in a preparatory study for HIV vaccine trials (the "Jumpstart" study) found "high levels of altruism and optimism regarding HIV vaccine trials," but also "major areas of concern in the areas of trust, confidentiality, and insurability" among recruits.[63]

More than half the participants (58%) said they were not sure the federal government could be trusted. Two of the questions related to the participants' sense of optimism are particularly interesting: 58% agreed that an HIV vaccine is likely within 10 years, and 52% agreed that being in an HIV vaccine trial would be "exciting." The results suggest that many participants expect a licensed vaccine much sooner than most in the scientific community. And these responses prompt the question: if your vaccine trial is just one of many trials in an extended research and testing effort, for how long will it seem sufficiently "exciting"? To remain interested, these trial recruits need their specific concerns addressed, and they need to understand and be prepared for the realities of the trial timeline.

Another study on the Jumpstart cohort looked at participants' willingness to participate in a vaccine trial.[64] Of the 1386 surveyed, 36% were "definitely" willing, 57% were "equivocal" and 7% were "not at all" willing. Responders were asked questions about their motivations for participation in the trial. Of the "equivocal" group — the largest group in the cohort — a third (33.3%) said they were participating to reduce their risk.[65]

This report is troublesome, since even if a volunteer receives a vaccine rather than a placebo, any vaccine tested in the near future may have a very low efficacy rate, if it is effective at all. The danger is that volunteers will increase their risky behavior because of a false sense of protection, and there exists the frightening possibility that a vaccine trial will lead to more, rather than fewer, infections. (The converse is also possible, that behavioral interventions associated with the trial or the process of discussing risk behavior on a regular basis with a study counselor may lower risk taking among the cohort.[66]) When they fully understand that they cannot assume any personal protection from trial participation, will "equivocal" volunteers move over to the "not at all" column? When affected communities hear of seroconversions in trial populations, will their support for HIV vaccine research waver?

Articles like these have been quoted to make the argument that it is feasible to recruit and retain a large enough cohort for vaccine trials. That is very likely true — for the first trial. But it is expected that the process will require multiple efficacy trials of various sizes, and it is possible that recruitment of thousands of new trial participants will become increasingly difficult. The implication is not that vaccine trials are unworkable, but that to reach and maintain "readiness," outstanding concerns must be addressed and motivations for participation enhanced.

Action in at least four areas may contribute to the ability of researchers to recruit and retain thousands of individuals in a series of vaccine trials:

- expanded rights and protections
- development of adequate materials to assist individuals in making informed decisions
- high quality behavioral interventions
- establishing the integrity of the product development process

A New Generation of Rights

If an HIV vaccine is to be found, thousands of individuals will need to take some amount of personal risk. What is needed is a compliment of rights and protections to make these risks acceptable to, and equitable for, many thousands of people over years of multiple vaccine research studies. People considering an altruistic contribution to society may expect concrete efforts to protect them from harm. In addition, trial volunteers will be asked to assume a series of responsibilities (***i.e.***, periodic reporting of risk behavior, consent to regular HIV testing, agreement to refrain from attempting to learn whether they have received a vaccine or placebo, and other obligations of trial participation).

It is widely accepted that a Participants Bill of Rights should be developed for HIV vaccine trial volunteers.[6768] In accordance with standard clinical research practice, NIAID has already agreed to many basic rights for HIV vaccine trial participants, including access to one's medical file, free counseling and HIV testing, permission to leave the trial without penalty, and others.[69]

Given that participants will instructed not to assume physical protection and the potential for social harm which participants will experience, the prospect of prolonged trials for HIV vaccines is an occasion to consider a "new generation" of participant rights and protections. The rights currently agreed to by NIAID fail to fully address several areas which may be critical in HIV vaccine trials: compensation for injury, lifetime efforts to alleviate social harm, and guaranteed free access to any HIV vaccine which may be found efficacious by later studies.

At the present stage in HIV vaccine research, these concerns are no longer theoretical. With the commencement of the first Phase III efficacy trial this year, guarantees in these areas are more tangible and will most likely prove to be important to long-term recruitment and retention of volunteers. The fact that prospective volunteers have voiced concerns about their ability to trust the government and come from largely disenfranchised communities also argues for comprehensive protections and a guarantee they will have access to the eventual benefits of research.

Compensation for Trial-Related Injuries

A wealth of medical ethics literature argues that participants in clinical trials should be compensated for injuries related to their participation. Guideline 13 of the International Ethical Guidelines for Biomedical Research Involving Human Subjects states that, "Research subjects who suffer physical injury as a result of their [trial] participation are entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability."[70] Other documents, including those prepared by an AIDS Action Foundation working group[71] and a report from the Office of Technology Assessment,[72] have provided arguments for such protection.[73] And medical ethicist Robert Levine has pointed out the practical side of this issue: "one of the purposes of establishing a compensation system is to encourage individuals to volunteer to take certain sorts of risks of injury to serve the interests of society."[74]

Absent a liability system, vaccine researchers and manufacturers might face a series of lawsuits which would damage public and volunteer confidence in trials. Lack of an established liability system may to some degree also impede pharmaceutical industry investment in vaccine research and development.[75] [76] A system which provides compensation for physical harm need not absolve pharmaceutical companies from liability for damages caused by their own negligence, a move which would very likely undermine public confidence. But as of today, trial volunteers are promised no extended medical care or compensation to balance the risks they will be taking in HIV vaccine trials.

Ongoing Efforts to Alleviate Social Harm

Early phase testing of HIV vaccines has demonstrated that trial volunteers are putting themselves at social, as well as physiological, risk. Because current vaccine candidates make some vaccines test positive on the Elisa HIV antibody test, some uninfected trial volunteers have experienced difficulty with international travel, government employment, and life and health insurance[77] — all areas in which discrimination against people with true HIV infection is legal.

So far, NIAID has been effective in working with insurers, government agencies and others to restrain much of this discrimination against vaccine trial participants, though, as the AIDS Action Foundation document attests, this has been "quite a labor intensive effort." But in preparation for the Phase III trial,

the Institute has not been able to guarantee these services will be provided as needed for the life of the participant, even though the false positive test and hence the risk of discrimination could continue indefinitely.

As thousands of individuals become involved in trials, a dedicated staff may be needed to address social harm against trial volunteers — to distinguish between government-sanctioned discrimination and discrimination from vaccine-induced seropositivity. The issue may be compounded as HIV vaccine candidates become more sophisticated and complex, and therefore more difficult to differentiate from actual infection.[78]

One solution to this large and looming problem requires legislative action: outlawing discrimination against people with HIV in all government employment, travel into the United States, and health and life insurance. In the absence of that, NIAID could make a commitment in writing to provide intensive efforts to address social discrimination for HIV vaccine trial participants as long as such protection is needed.[79] These efforts might include designating NIAID staff to handle specific discrimination issues, and agreements in advance with insurance companies, government employers, and countries which require foreign travelers to take HIV antibody tests.

Free Access to Eventually Licensed HIV Vaccine for Trial Participants

NIAID has indicated its intention to guarantee that all trial participants will receive any HIV vaccine licensed within five years of the conclusion of the trial in which they are enrolled, but this promise may be of limited worth given the expected timeline for HIV vaccine development. A guarantee without a time limit would provide a more meaningful benefit for many volunteers, since trials will draw from younger, lower-income populations which are less likely to have health insurance coverage for vaccines.[80]

Free access is consistent with the principle of equal sharing of benefits and risks of research — in this case adjusted to reflect the potential time line of vaccine trials. It is also consonant with the likely development path of vaccine research: knowledge gleaned from early trials (which may fail to prove a product efficacious) will aid future vaccine design and trials. It follows that all those who have assumed risk to aid the HIV vaccine enterprise receive the eventual product of those efforts.

Helping Volunteers Make Informed Decisions About Trial Participation

To facilitate truly informed decisions on the part of individual trial volunteers, it may be useful for the government to fund community-based organizations (CBOs) to provide information which helps prospective trial participants think through complex issues involved in the decision about whether to participate in trials. Many volunteers will be more comfortable receiving information when it originates from community-based organizations, rather than government agencies.[81]

As noted above, altruism is one of the few defensible motives for entering an HIV vaccine trial, since volunteers should not expect personal protection from the vaccine candidate (or placebo) they receive. This fact is implied in discussions about trial participation, but it must become explicit. To safeguard trial participants, it must be clear that personal protection from HIV is not a well-founded reason to participate — receiving behavioral interventions and regular interaction with a study counselor and the desire to make a contribution to humanity are the primary benefits one can hope to receive.

Yet there is limited literature available to help people put a value on this contribution — to understand the potential benefits of an HIV vaccine at various efficacy levels — so that they can weigh this value against personal and communal risks. It is relatively easy to list the social and physiological risks of doing a trial. It is more difficult to list the long-term implications of never accepting the risks inherent in doing a clinical trial. Derek Hodel writes that, "ambivalence toward vaccines runs high in general, let alone for AIDS vaccines."[82] Individuals and communities may need to wrestle with this ambivalence directly if they are to maintain support for trials over time.

This is also the potential for a skewed public debate concerning the merits of particular vaccine trials. Some may argue for a trial of a proposed vaccine product simply because new prevention technology such as a vaccine is desperately needed. But an informed decision about participation in a trial should be based on an assessment of ***the likelihood that that specific trial will meaningfully contribute to HIV vaccine research*** —not solely on the obvious urgency of the epidemic.

Materials produced by CBOs could help address these complex areas of trial participation, including weighing risks and benefits and assistance unraveling the issues in scientific controversy. These materials would help

people put risks and benefits in the context of their communities and their own lives. They would help individuals understand both the personal risks of trial participation, and the reasons why some level of risk may be justified by the potential benefits. They would recognize the potential dangers of participation, be absolutely clear that participants could expect no personal benefit, and explain the potential communal benefits of a vaccine.[83]

It is an ethical essential that educational materials not be coercive in any way. What is needed is an objective discussion of risks and benefits, not materials which encourage individuals to take risks they would not otherwise take. Materials should be developed by credible community-based organizations and provide a variety of perspectives on the sensitive and complex issues involved in trial participation. By offering a variety of perspectives — rather than attempting to provide the one "right" answer — organizations can facilitate informed decisions and avoid appearing as the "hired gun," of trial sponsors.

Counselors at trial sites are often themselves members of affected groups and develop trusting relationships with trial participants over time. They should be acknowledged as important conveyers of information who will likely be influential in helping volunteers think through the pros and cons of trial participation. Counselors need adequate training both on the scientific issues involved in a trial and on how to engage in an open and objective discussion about trial issues with volunteers.

Behavioral Interventions Beyond Reproach

Reports of high seroconversion rates in vaccine trial cohorts — not an unlikely occurrence among "high risk" trial participants — also have the potential to weaken community support for trials. Other analyses of the ethical issues of HIV vaccine trials have warned of the inherent conflict of interest of trial researchers: needing to counsel participants that they should not assume any protection from a candidate vaccine, while knowing that participants will need to practice high risk behavior in order for the efficacy of the vaccine to be tested.[84]

Built-in contradictions like this may raise legitimate issues of trust, particularly among individuals from communities mistreated in previous biomedical research. The only way to run an ethical trial and maintain community support in the face of this is to provide trial participants with prevention interventions which have been shown to work: sustained behavioral interventions of the highest quality. The perception that behavioral interventions are receiving only limited attention from trial researchers could severely undermine sustained community support for trials.

The Integrity of Product Development Efforts

The perception trial volunteers have of the integrity of vaccine research and development efforts may affect their willingness to participate in trials. For a series of large-scale human trials to be successful among potentially skeptical populations, it may be important for trial volunteers to have confidence that the candidate vaccine going into their arms is the most promising product science can currently produce for efficacy testing, rather than an experimental agent chosen for testing because lack of public or private investment left few other good options.

One of the differences between a trial for an HIV vaccine and a trial for an AIDS therapeutic is that HIV negative participants in a vaccine trial will have a lower risk threshold and less of a sense of urgency about receiving the experimental product. Vaccine participants can be expected to have greater concerns about the safety and potential usefulness of the candidate vaccine than they would for a therapeutic because most will feel a less immediate need for the product.

As a series of trials begins in largely stigmatized populations which have a high level of distrust of the government and industry, participants and community leaders will begin to scrutinize more closely government and pharmaceutical industry efforts on vaccine research. Over the long-term of HIV vaccine testing, volunteer willingness could be jeopardized if it is widely perceived that vaccines proposed for testing are of limited promise because, 1) private and public investment and coordination were lacking, or 2) the goal of encouraging private investment in vaccines is coloring the decision to advance to trials.

In order to produce candidate vaccines in which volunteers can have confidence, public and private investment in HIV vaccine research should match the magnitude of the public health emergency and the scientific challenges. NIAID has funded an array of basic science research and Phase I/II trials and taken steps to encourage private investment, including setting "milestones" which provide industry with criteria to be used in deciding when to advance with human trials. But a decade and a half into the AIDS epidemic, private pharmaceutical industry interest in developing HIV vaccines has been disappointing. Companies are more likely to recoup their

investment in therapeutic drugs than in HIV vaccines. And scientific challenges, licensing uncertainties, questions about the size of the market, and liability concerns make investment in HIV vaccines comparatively unattractive.[85]

Extremely damaging to confidence in trial efforts is the argument that efficacy trials should proceed with candidate vaccine products if only to encourage pharmaceutical companies to maintain interest in HIV vaccine development.[86] To date, there is no indication such arguments are affecting decision making at NIAID. But if affected community members — perhaps reacting to controversy-driven media coverage — perceive that they are being injected with experimental vaccines in part to entice private industry to serve public health needs, support for trials is unlikely to be sustainable.

As conflicting media coverage focuses on the first large-scale HIV vaccine trial, volunteers are more likely to understand the many aspects of their participation if they believe they are working in concert with researchers and industry scientists who show a similar level of dedication. Trials are less likely to be supported over an extended timeline if volunteers come to believe that they are taking risks to fill in the gaps left by public and private disinterest.

An effective and widely available vaccine for HIV is our best hope to bring an end to the epidemic which causes over 16,000 new infections every day. But in order for HIV vaccine research to ultimately be successful, sustained support will be needed at several levels, including the general public, affected communities, and many thousands of individual trial participants. Members of affected communities have a crucial role to play in pushing for increased private and public HIV vaccine research, addressing safety and equity concerns, ensuring informed decisions on the part of trial participants, and securing dissemination of a vaccine to all those at-risk.

Communities, government, researchers and the private sector will need to form a partnership on HIV vaccine efforts, a partnership which is most likely to be successful in a atmosphere of mutual trust. The areas outlined above could play an important role in establishing and maintaining that trust. In the shadow of the Tuskegee Syphilis experiments and more recent revelations about government-sponsored radiation research on unwitting individuals, attention to the issues involved in building trust is timely, practical and an ethical prerequisite to success.

ENDNOTES

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[14] ***HIV/AIDS Vaccine Research***, NIH Fact Sheet, Office of the Director, National Institutes of Health, May 15, 1998.

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[18] ***National Institutes of Health Names New Director for AIDS Research***, Press Release, Office of the Director, National Institutes of Health, May 15, 1998.

[19] Gellin, Bruce, MD, ed., ***The Jordan Report '98:Accelerated Development of Vaccines***, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 1998.

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[23] E-mail Correspondence from Blanche O'Neill, Special Assistant to the Director for Vaccines and Prevention Research, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, November 20, 1998.

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[43] ***"Industry Investment in HIV Vaccine Research: An Investigation by the AIDS Vaccine Advocacy Coalition,"*** December, 1996, p.14.

[44] "Phase III Clinical Trial of AIDSVAX," VaxGen Website Document (www.vaxgen.com), November 21, 1998.

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[46] For a partial list of incentives to increase private investment in vaccines, see Office of Technology Assessment, ***Adverse Reactions to HIV Vaccines: Medical, Ethical and Legal Issues***, Congress of the United States, September 1995, pgs. 145-146.

[47] Esparza, J.; Piot, P., ***HIV Vaccine Development: UNAIDS Perspsectives***, Presented at the meeting "HIV Vaccines for South-East and South Asia: The Challenges and Opportunities, Bangkok, Thailand, January 17-19, 1996.

[48] UNAIDS Press Release, "***New Ethical Guidelines on HIV vaccine research pave the way for large-scale international trials of HIV vaccines,"*** Joint United Nations Programme on HIV/AIDS, Geneva, June 29, 1998.

[49] For example, an article in the ***Chicago Tribune*** reported that "Dr. John Killen [Director, Division of AIDS at the National Institutes of Health] believes 'it will be a minimum of five years before we have a vaccine,' and other researchers say an effective AIDS vaccine may be 15 to 25 years away, assuming one can be developed at all." ***Chicago Tribune***, 11/12/95, p.12; A NIAID publication quotes Director Tony Fauci, "'It is very likely that progress toward the ultimate goal of an "ideal" vaccine will occur in incremental steps in which important lessons are learned from less-than-perfect vaccines.'" ***AIDS Agenda***, NIAID, p.19, March, 1996.

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[53] Osborn, June E. "The Rocky Road to an AIDS Vaccine," ***Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*** 9:26-29, 1995.

[54] Harrington, Mark. "Constituency Priorities in AIDS Vaccine Research: One Perspective," in ***AIDS Research and Human Retroviruses***, 8(8):1431, 1992. In addition, Olga A. Grinstead, has written that, "Overly enthusiastic or inaccurate media portrayals of a vaccine efficacy trial could increase risky behavior in a community or generate negative press that could severely hinder recruitment or result in unacceptable levels of drop-out." Quoted from "Social and Behavioral Issues in Phase III HIV Preventive Vaccine Trials." ***AIDS*** 9:S246 (suppl A), 1995.

[55] Graham, Barney S.; Wright, Peter F. "Candidate AIDS Vaccines," ***The New England Journal of Medicine***, 333(20):1337, 1995.

[56] In the current Phase III HIV vaccine prepatory study, community membership is an element of the initial recruitment procedure, but prospective volunteers must confirm that they have practiced specific behaviors within a particular time frame in order to be accepted into the cohort. Individuals need not self-identify as "gay" to be accepted into a "men who have sex with men" cohort.

[57] The Centers for Disease Control and Prevention is currently funding Project LinCS. This project will examine the dynamics of information dispersal between researchers, trial participants, and community members, and also look at the role of community leaders in communities at high risk for HIV.

[58] Stephen B. Thomas and Sandra Crouse Quinn have reported that, "...almost 60 years after the experiment began, the Tuskegee Syphilis Study's legacy is a trail of distrust and suspicion that hampers HIV education efforts in Black communities...Public health professionals must recognize that Blacks' belief in AIDS as a form of genocide is a legitimate attitudinal barrier rooted in the history of the Tuskegee Syphilis Study," in "The Tuskegee Syphilis Study, 1932 to 1972: Implications for HIV Education and AIDS Risk Education Programs in the Black Community," ***American Journal of Public Health***, 81(11):1503, 1991.

[59] Those involved in human subjects research continue to have an important role to play in ensuring the ethical conduct of this research. "Today's oversight of tens of thousands of HHS-funded research and FDA regulated drug studies appears to have reduced the likelihood that serious abuses of human subjects, comparable to past tragic events, will occur...Various time, resources, and other pressures, however, have reduced or threaten to reduce the effectiveness of local review board and federal agency oversight." General Accounting Office, ***Scientific Research: Continued Vigilance Critical to Protecting Human Subjects***, March 8, 1996, p.2.

[60] Grady, Christine, The Search for an AIDS Vaccine, Indiana University Press, 1995, p.145.

[61] Office of Technology Assessment, ***Adverse Reactions to HIV Vaccines: Medical, Ethical and Legal Issues***, Congress of the United States, September 1995, pgs. 10-11.

[62] Westcott, Susan; Savarese, Barbara; Smith, Carol. "Participation of Minority Populations in Phase I/II Clinical Trials of Candidate AIDS Vaccines: Conference Summary; Conference on Advances in AIDS Vaccine Development, 1994," ***AIDS Research and Human Retroviruses***, 11(10):1307, 1995.

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[65] More recent research presented by Amy Sheon at a February 1996 NIAID Vaccine Conference is consistent with these results. In an anonymous survey of 247 participants in Phase II HIV vaccine trials, Sheon found that among those with a motivation other than pure altruism, 20% of volunteers identified "hoping for protection" from a vaccine candidate as their main motivation for being in the trial.

[66] The same research reported in the previous footnote also reported that "overall, more volunteers decreased their risk [behavior] than increased it." But those volunteers who said they thought they had received the candidate vaccine rather than a placebo were 2.3 times more likely to believe they had unsafe sex with an HIV positive person than those who thought they received the placebo or who were uncertain what they received.

[67] AIDS Action Foundation, ***HIV Preventive Vaccines: Social, Ethical, and Political Considerations for Domestic Efficacy Trials***, July 1994, p.24, and, "The New York City Community Vaccine Working Group, Perspectives on Feasibility and Efficacy Trials for Preventive HIV Vaccines," October 1993.

[68] Examples in the literature include: Prentice, Ernest D.; Reitemeier, Paul J.; Antonson, Dean L.; Kelso, Timothy K.; Jameton, Andrew. "Bill of Rights for Research Subjects," ***IRB: A Review of Human Subjects Research***; 15(2):7-9, 1993.

[69] NIAID continues to negotiate with community representatives on an expansion of this list, and all rights will need to be negotiated with individual trial sites. Trials may also be launched by private companies without the direct sponsorship of NIAID. The rights and responsibilities of participants should apply equally to non-governmental trials.

[70] The Council for International Organizations of Medical Sciences in collaboration with the World Health Organization, International Ethical Guidelines for Biomedical Research Involving Human Subjects, Geneva, 1993, p. 36.

[71] AIDS Action Foundation, ***HIV Preventive Vaccines: Social, Ethical, and Political Considerations for Domestic Efficacy Trials***, July 1994, p. 34.

[72] Office of Technology Assessment, ***Adverse Reactions to HIV Vaccines: Medical, Ethical and Legal Issues***, Congress of the United States, September 1995, pgs. 76 and 83.

[73] The obligation to compensate for harm in non-therapeutic research is echoed by many other medical ethicists, and is particularly clear with HIV vaccines: as Christine Grady has pointed out, no good animal model exists to test HIV vaccines, and scientists cannot be absolutely sure of the safety of any vaccine product, so the physiological risks for participants are to some degree unknown. (Grady, Christine, p. 96) Other writers, such as Robert J. Levine and Wendy K. Mariner have questioned the fairness of the "informed consent" contract when the risks are unknown and compensation or necessary medical care not provided. (Levine, Robert J., ***Ethics and Regulation of Clinical Research***, 2nd edition, Yale University Press, 1986, p. 157; Mariner, Wendy; Office of Technology Assessment 1995, p.82). Also see the earlier referenced paper by The New York City Community Vaccine Working Group.

[74] Levine, Robert J., ***Ethics and Regulation of Clinical Research***, 2nd edition, Yale University Press, 1986, p.157.

[75] Office of Technology Assessment, ***Adverse Reactions to HIV Vaccines: Medical, Ethical and Legal Issues***, Congress of the United States, September 1995, p.79.

[76] Office of Technology Assessment, ***Pharmaceutical R&D: Costs, Risks, and Rewards***, Congress of the United States, February 1993, p. 179.

[77] Sheon, Amy. "Preventing Discrimination against Volunteers in Preventive HIV Vaccine Efficacy Trials: Conference Summary. Conference on Advances in AIDS Vaccine Development, 1994," ***AIDS Research and Human Retroviruses***, 11(10):1309, 1995. Research reported by Sheon at a February 1996 NIAID Vaccine Conference found that "social harms/discrimination was common (29%), but mostly from voluntary disclosure."

[78] Office of Technology Assessment, ***Adverse Reactions to HIV Vaccines: Medical, Ethical and Legal Issues***, Congress of the United States, September 1995, p. 11. Research on more sophisticated tests which can differentiate HIV infection from vaccine-induced seropositivity is ongoing. An Elisa test which can distinguish between infection and vaccination with the ALVAC/gp120 vaccine candidate is now under development.

[79] As a cost control measure, this might be limited by guaranteeing protection only as long as the participant continues to test positive for HIV on standard antibody tests.

[80] This guarantee is consistent with recommendations from numerous sources, including: AIDS Action Foundation, ***HIV Preventive Vaccines: Social, Ethical, and Political Considerations for Domestic Efficacy Trials***, July 1994, p.27; Christine Grady, ***The Search for an AIDS Vaccine***, Indiana University Press, 1995, p. 120; and The New York City Community Vaccine Working Group paper, October 1993, though only the third document explicitly calls for participant access to licensed vaccines from subsequent trials.

[81] San Francisco's Project Inform is one example of a community-based organization with an established track record for leadership and independence which may be able to deliver sensitive, complex information more effectively than a government agency. It is essential that contracts issued by government allow a wide degree of autonomy and editorial freedom to community organizations providing information on vaccines. To retain their legitimacy with members of affected communities, these organizations need to be candid about risks and benefits of trials from the perspective of communities which may be disenfranchised and distrustful of government-sponsored research or pharmaceutical industry motives. These organizations may provide reasons why an individual might choose to participate in a trial, but CBOs will lose credibility if they attempt to play the role of recruiter.

[82] Hodel, Derek. "Negotiating an AIDS Vaccine," ***AIDS & Public Policy Journal,*** p. 173, Fall 1995.

[83] A similar recommendation is made by other writers, "...to facilitate vaccine trial recruitment, the community-based campaign should provide clear messages about the need for the trial and about the importance of the individuals in the community in meeting that need. Such an approach could help create a community norm supportive of participation." Chesney, Margaret A.; Lurie, Peter; Coates, Thomas J., "Strategies for Addressing the Social and Behavioral Challenges of Prophylactic HIV Vaccine Trials," ***Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology***, 9(1):31, 1995.

[84] AIDS Action Foundation, ***HIV Preventive Vaccines: Social, Ethical, and Political Considerations for Domestic Efficacy Trials***, July 1994, p.13.

[85] International AIDS Vaccine Inititiative, ***Accelerating the Development of Preventive HIV Vaccines for the World***; Financial and Structural Issues, Rockefeller Foundation, August 17, 1995, p.4-5.

[86] A summary of comments at a 1994 AIDS vaccine conference noted that, "Other investigators expressed the belief that the interest of vaccine manufacturers might be lost if clinical testing of the current candidates does not continue," quoted from "Alternative Trial Designs: Conference Summary. Conference on Advances in AIDS Vaccine Development, 1994," by Ride, Wasima; Fleming, Thomas; Stevens, Cladd. ***AIDS Research and Human Retrovirus***, 11(10):1317, 1995; and a more recent article commented that, "Many attribute the loss of momentum in AIDS vaccine development to NIAID's 1994 decision not to stage large-scale, real world tests of two vaccines...," Cohen, Jon, ***Science***. 271(5253):1227, 1996.