Policy Research Working Paper #16 December 2007

The Journey Toward an AIDS Vaccine: Perspectives on Conducting Trials in Developing Countries

IAVI Public Policy Department

The Journey Toward an AIDS Vaccine: Perspectives on Conducting Trials in Developing Countries

ISBN: 978-0-9792432-7-1

This paper was written by Holly Wong (International AIDS Vaccine Initiative) and Ann Levin (consultant to IAVI).

The authors are grateful to IAVI colleagues who served as an advisory group for this project: Julie Becker, Jean-Louis Excler, Pat Fast, Robert Hecht, Chrispin Kambili, Alex Menezes, and Kate Taylor. In addition, the authors thank Donald Burke (University of Pittsburgh), Alex Coutinho (The AIDS Support Organization), Jerome Kim (U.S. Army Medical Component of the Armed Forces Research Institute of the Medical Sciences), Keren Middelkoop (Desmond Tutu HIV Centre), and Sweta Das, Keren Etzion, Jonathan Grund, Thomas Harmon, Marilyn Piels, Sarah Post, Eva Roca, Sagri Singh, Rachel Steinhardt, and Helen Thomson (IAVI) for their comments and contributions to this paper. Last but not least, the authors are indebted to those interviewed for this study, who gave their time and insights to inform this work.

This study and report were made possible in part by the generous support of the American people through the United States Agency for International Development (USAID) under Cooperative Agreement No. GPOA-00-06-00006-00. The contents are the responsibility of the International AIDS Vaccine Initiative and do not necessarily reflect the views of USAID or the United States Government.

To request additional print copies of this working paper or other information from IAVI please contact:

Publications Unit
International AIDS Vaccine Initiative
110 William Street, 27th Floor
New York, NY 10038 USA
Tel: + 1.212.847.1111
Fax: + 1.212. 847.1112
Email: pubs@iavi.org
Web: www.iavi.org

IAVI's mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world.

Printed on recycled paper. ♻

The Journey Toward an AIDS Vaccine: Perspectives on Conducting Trials in Developing Countries

Policy Research Working Paper #16
December 2007

IAVI's Policy Research Working Paper series disseminates important new research findings in order to promote the exchange of information and ideas that facilitate the effective development and global distribution of vaccines to prevent HIV infection.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACRONYMS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CAB	community advisory board
CBO	community-based organization
CDC	U.S. Centers for Disease Control and Prevention
GCP	good clinical practice
GCLP	good clinical and laboratory practice
CRO	contract research organization
HPV	human papillomavirus
IRB	institutional review board
IAVI	International AIDS Vaccine Initiative
ICASO	International Council of AIDS Service Organizations
IDU	injecting drug user
KANCO	Kenya AIDS NGO Consortium
KAVI	Kenya AIDS Vaccine Initiative
MSM	men who have sex with men
NGO	nongovernmental organization
PI	principal investigator
R&D	research and development
STI	sexually transmitted infection
USMHRP	U.S. Military HIV Research Program
VCT	voluntary counseling and testing
VSN	Vaccine Support Network

EXECUTIVE SUMMARY

The journey toward an AIDS vaccine has been long and at times discouraging. More than 20 years after the discovery of HIV as the cause of AIDS, a vaccine is still proving elusive. During this time, over 75 vaccine candidates have entered clinical trials, but none has yet proven efficacious. The recent decision to halt the STEP and Phambili trials prematurely is a new disappointment. Some feel little progress has been made and suggest that perhaps an AIDS vaccine will never come to fruition.

While it is frustrating that a safe and effective vaccine has not yet been discovered, it would be short-sighted to conclude that efforts to date have failed. Criticisms focus on a successful final product as the only outcome of interest for the AIDS vaccine field. Yet while all would like to see a safe and effective vaccine, ongoing R&D efforts have yielded other tangible, intermediate benefits. Our ultimate goal is an AIDS vaccine; however, we should also recognize the value of what we encounter and accomplish as part of that journey.

IAVI undertook this review of AIDS vaccine studies in developing countries to document their impact at the individual, community, national, and global levels, and to highlight key strategies and lessons for future clinical studies. The focus on developing countries stems from the limited prior experience with vaccine trials in those settings and because this is where most vaccine efficacy trials are now conducted. Some have suggested that conducting trials in settings with limited resources, where infrastructure and skilled personnel are in short supply, is not feasible. The past decade has demonstrated, however, that it is possible to conduct AIDS vaccine research in developing countries to the highest ethical and technical standards.

Nearly 100 individuals involved in AIDS vaccine studies in developing countries were interviewed for this paper. These respondents reflect the diversity of geographic regions in which AIDS vaccine trials have taken place, the range of vaccine studies to date (from preparatory studies to Phase III efficacy trials), and the spectrum of stakeholder categories: research staff (both local and expatriate), clinic staff (doctors and nurses), participants, community members, government officials, donors, and advocates for the field.

This paper highlights a broad range of impacts of AIDS vaccine studies in 10 developing countries, at the individual, community, national, and global levels. Most have been beneficial, although there have also been challenges and some less positive side effects.

The most important elements identified by respondents are the following:

- For study **volunteers,** taking part in AIDS vaccine studies has helped improve their health and well-being. Greater *self-esteem* and a sense of contributing to a valuable effort have been the most personal impact, but increased *access to health information* as well as *health services* were also significant. Challenges have included *potential stigma and discrimination* and the *time demands* for participation.
- Professional development has been a primary benefit of working on AIDS vaccine studies for **research staff.** The *skills and experience* gained, *career enhancement*, and the greater *exposure to social science and non-clinical areas* have been overwhelmingly positive. At the same time, these individuals gained *personal satisfaction* from contributing to a noble cause. Research staff have also faced challenges from the *workload* and the *uncertain sustainability of projects* and employment.

- At the **community** level, the primary benefits of AIDS vaccine studies have been *enhanced health education and better healthcare services*. Vaccine studies have *empowered community organizations and structures*, including community advisory boards and civil society groups. A significant and recurring challenge for vaccine studies has been to address *misinformation and unrealistic expectations* about the trials within communities.
- For **host countries,** AIDS vaccine studies have *built capacity* and *strengthened institutions* within the scientific and research sectors. These studies have led to enhanced physical infrastructure and laid the groundwork for future access to vaccines. It remains a challenge to maintain, if not further develop, the *institutional capacity* established through these research efforts.
- At the **global level,** much of the impact of AIDS vaccine studies has been in the scientific and research realm. In addition, there has been a *significant contribution to knowledge* of how to better conduct future studies, especially in developing country settings. These studies have also created new *champions for AIDS vaccines and prevention efforts* and demonstrated how the *global community can come together* to address common problems.

The issues and lessons identified in this paper underscore two important themes. First is the ***critical need for communication about vaccine studies***. All respondents mentioned the need to ensure more, better, earlier, and continuous communication as part of vaccine studies. This must be done with the broadest range of stakeholders possible, especially the media, and should err on the side of too much rather than too little communication. Second, although significant investments in capacity building have been made as part of these AIDS vaccine studies and have generated major benefits, ***sustaining those benefits requires additional resources***. Many sites and staff risk loss of continuity and employment when grant funding expires before new studies begin. Developing the capacity to undertake clinical studies has led to growing demands on regulatory agencies. While regulatory capacity has generally increased, in many cases it remains insufficient to meet current needs. There is further need for investment, from external sponsors and donors and particularly from national governments, to build and maintain the cutting edge research capability and infrastructure that have emerged in the past two decades.

This review seeks to provide insight into how those involved in AIDS vaccine research perceive the impact of those studies. Overall, the intermediate benefits of conducting such research are substantial at all levels. Going forward, it may be useful to undertake additional quantitative research to further document these results and to more fully understand how to improve vaccine studies. As we strive to develop an AIDS vaccine, no matter how long or short that search may be, we should remember that the journey itself is also significant – and can make important contributions to better public health and to social and economic development.

> *"No matter whether the vaccine works or not – at least we have started to move forward. It's like riding a bicycle; you start to push the pedals – once, twice, then a million times, that's how you make progress." Chief Provincial Medical Officer, Thailand*

1 INTRODUCTION

1.1 Background

More than 20 years after the discovery of HIV as the cause of AIDS, the world still does not have a vaccine against this disease. During this time, over 75 vaccine candidates have entered clinical trials, although none has yet proven efficacious. Only three large-scale efficacy (Phase III) trials have been undertaken to date, with the latest one still ongoing in Thailand. In the first two, the vaccine candidate, though safe, did not prevent HIV infection. Other vaccine candidates failed to generate promising immunogenicity in earlier phases and were not pursued. More recently, two Phase IIb trials, the STEP study and the Phambili study in South Africa, sponsored by Merck, the National Institute of Allergy and Infectious Diseases, and the HIV Vaccine Trials Network, were halted when an interim analysis concluded that the product was not efficacious.

Some view this situation as a lack of progress and suggest that perhaps an AIDS vaccine will never come to fruition. While it is frustrating that a safe and effective vaccine has not yet been discovered, it would be short-sighted to conclude that the efforts to date have failed. Criticisms focus on a successful final product as the only outcome of interest for the AIDS vaccine field. While all would like to see a safe and effective vaccine, there are other tangible, intermediate benefits from ongoing research and development (R&D) efforts. While our ultimate goal is an AIDS vaccine, we should not lose sight of what we encounter and accomplish as part of that journey.

The basic research and clinical trials undertaken to date have led to significant advances in scientific knowledge, especially in the domains of molecular biology, virology, epidemiology, and immunology. Research is an iterative process, and investigations into current vaccine candidates have incorporated the incremental gains from prior efforts. As important as these scientific advances, but sometimes overlooked, are other *social, economic, psychological,* and *educational benefits* from conducting AIDS vaccine research. These impacts may be at the level of the individual, affecting volunteers participating in trials or members of the trial teams. They may be at the community level, influencing those not directly participating in but touched by some of the trial activities. And they may be national or global, strengthening institutions, processes, and systems. Identifying these impacts can help provide a more comprehensive picture of the results of AIDS vaccine research efforts.

1.2 Objectives of This Review

The International AIDS Vaccine Initiative (IAVI) undertook this review of the impact of conducting AIDS vaccine clinical trials in developing countries during 2006 and 2007. The primary objective was to document the intermediate benefits such research efforts have had, both positive and negative, at the individual, community, national, and global levels, and to highlight key strategies and lessons to strengthen future clinical trials.

1.3 Focus on AIDS Vaccine Clinical Trials in Developing Countries

We chose to focus this analysis on AIDS vaccine research efforts in developing countries for several reasons. It is important to conduct AIDS vaccine research, particularly large-scale trials, in those countries hit hardest by the epidemic, and these are predominantly in the South. Given the genetic diversity of HIV, vaccine candidates must be tested where targeted subtypes (clades) are present, and this requires testing in the developing regions of Africa, Asia, and Latin America. Some have claimed that it is not feasible to conduct trials in resource-poor settings, because few of these countries have

had significant prior experience in this area and have poor infrastructure and few skilled personnel. This paper seeks to document the actual experience with such trials in the South, which has turned out to be very successful – although we do not yet know whether these trials will meet U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMEA) requirements for licensure.

In addition, the history of vaccines has shown that developing countries have been the last to benefit from new health technologies, often waiting decades before the products are available to them (Lieu et al. 2005; McCluskey et al. 2005). In the case of HIV/AIDS, given the scope of the pandemic and its disproportionate burden on developing country populations, it is critical that all possible steps be taken to avoid such delays. One way to accelerate the availability of an AIDS vaccine is to conduct clinical trials in developing countries. This would provide not only scientific evidence but also increase awareness of AIDS and prevention methods and lay the groundwork for political, social, and cultural commitment and acceptance of a vaccine when it becomes available.

1.4 The Context of AIDS Vaccine Clinical Trials and Related Research Studies

The impact of AIDS vaccine studies on individuals and institutions is likely to differ depending on the study and its phase. Phase I clinical trials assess the safety of vaccine candidates among small numbers of volunteers (20 to 100 persons) and provide preliminary information on their immunogenicity. Phase II trials evaluate the immunogenicity and safety of the vaccine trial study among a larger number of volunteers (often a few hundred persons). Phase IIb and III trials assess the efficacy of vaccine candidates with relatively large groups (2,500 to 20,000 volunteers). Other studies, such as feasibility studies, evaluate the morbidity, prevalence, and incidence of HIV and AIDS among a population or assess scientific parameters that may help to guide the design of new vaccine candidates.

Researchers have conducted AIDS vaccine trials and related studies in developing countries since the 1990s. Low- and middle-income countries involved to date include Botswana, Brazil, China, Cuba, the Dominican Republic, Haiti, India, Jamaica, Kenya, Malawi, Peru, Rwanda, Russia, South Africa, Tanzania, Thailand, Trinidad and Tobago, Uganda, and Zambia.

Table 1 provides information about AIDS vaccine trials conducted by respondents in different countries.

Table 1. AIDS Vaccine Trials in Countries of Interviewees

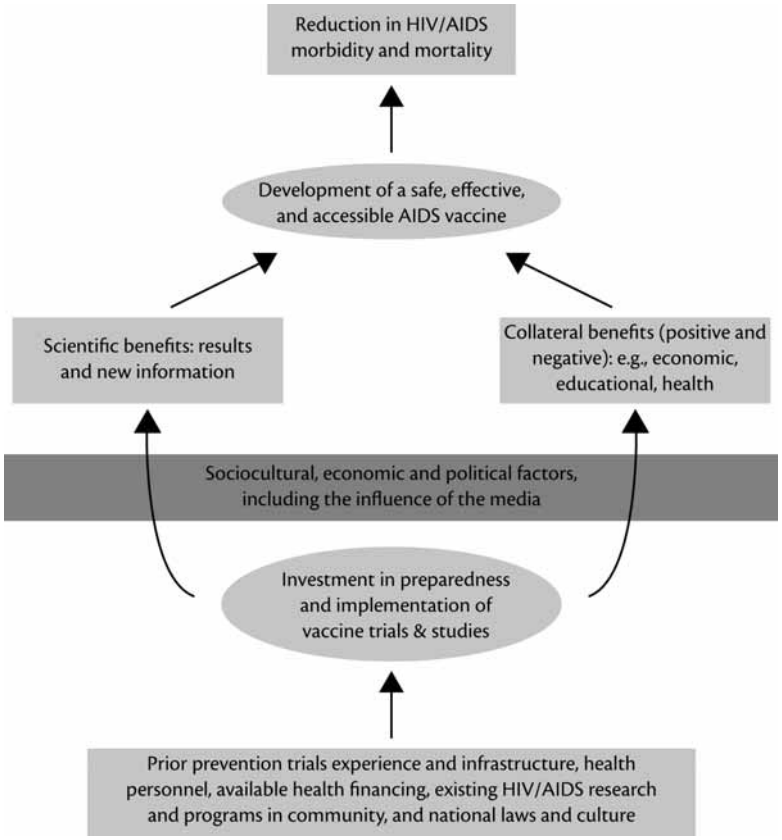
COUNTRY	OVERALL HIV PREVALENCE (%)	YEAR FIRST TRIAL INITIATED	# OF PHASE I TRIALS	# OF PHASE II TRIALS	# OF PHASE III TRIALS
Brazil	0.5	1995	9	5	0
Haiti	3.8	2002	2	4	0
India	0.9	2005	2	0	0
Kenya	6.1	2001	4	1	0
Peru	0.6	2000	3	4	0
Rwanda	3.1	2006	1	0	0
South Africa	18.8	2003	4	3	0
Thailand	1.4	1994	5	8	2
Uganda	6.7	1999	3	2	0
Zambia	17.0	2006	1	0	0

Source: UNAIDS 2006.

2 METHODS AND APPROACH

This paper builds upon earlier work by IAVI (Hecht et al. 2006) that focused on the recent exponential growth of vaccine and drug trials and the way in which clinical trials in developing countries have changed. We began with a literature review on the potential impact of AIDS vaccine studies and AIDS research in developing countries. This literature review, combined with discussions with key informants on AIDS vaccine studies, led to the design of an overall framework for identifying the impact of these research efforts (Figure 1).

Figure 1. Potential Impact of HIV/AIDS Vaccine Trials



2.1 General Framework

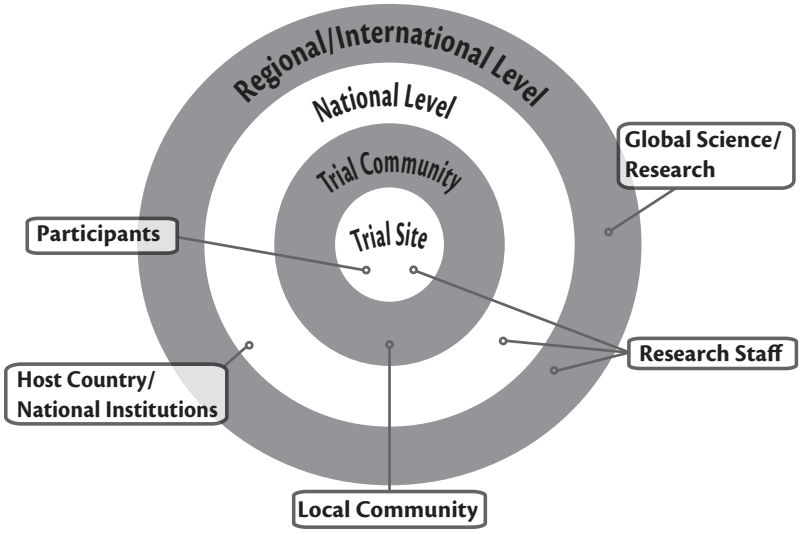
This framework suggests several points. First, all trials take place within the context of existing interventions, infrastructure, personnel, and knowledge. For many AIDS vaccine trials, substantial groundwork was laid by prior research efforts, making it difficult to distinguish the impacts of the vaccine trials from earlier studies. Second, while this analysis focuses primarily on the trials, substantial preparatory efforts are needed in the form of feasibility studies (epidemiology, virus subtyping, natural history of HIV infection, biological references, and social science studies). This

analysis includes these preparatory studies, since they have a potential impact on the individuals and communities involved in later vaccine trials.

Third, the framework recognizes that these studies yielded both scientific and collateral benefits, although details of the scientific advances are beyond the scope of this paper. Finally, while the framework captures the concept that the ultimate goal of AIDS vaccine studies is to reduce morbidity and mortality through the development of safe, effective, and accessible AIDS vaccines, intermediate impacts can nonetheless be achieved along the way to that milestone.

The team analyzed the impact of AIDS vaccine studies by focusing on different levels of stakeholders (Figure 2).[1] At the trial site itself, the study affects individual participants and research personnel. Beyond that is the community in which the trial takes place, defined as a geographic area or a social group, if a particular group – such as injecting drug users (IDUs) – is the focus of the study. At this level, stakeholders include participants' families, friends, colleagues, employers, neighbors, and social networks. At the national and regional/international levels, AIDS vaccine studies can affect government institutions as well as broader research efforts. Some impacts reach across levels of stakeholders; for example, employment opportunities benefit not only individuals hired at the trial site, but also the community at large.

Figure 2. Impact of AIDS Vaccine Studies, Key Stakeholders



2.2 Survey Respondents

The research team interviewed individuals chosen to reflect the diversity of geographic regions in developing countries where AIDS vaccine trials have taken place, and the type of vaccine studies to date. The team sought respondents from specific stakeholder categories: research staff (both local and expatriate: investigators, medical doctors, data managers, nurses, counselors, laboratory personnel), trial participants, community members, government officials, donors, and advocates. Interviewees represented a variety of entities, including academic organizations, government agencies, research institutions and networks, pharmaceutical companies, nongovernmental and community-based organizations (NGOs and CBOs), community advisory boards (CABs), and international organizations.

[1] This figure is adapted from a graphic developed by IAVI's Country and Regional Programs Department.

The team conducted 97 interviews with stakeholders (see Appendix 1), the majority of them members of local research teams, with greatest representation from Kenya, South Africa, Thailand, and Uganda (Table 2). There is some overlap across categories, because many research personnel are also government employees; however, for this review, those directly involved in conducting vaccine studies were counted as research team members, while government employees included only those with indirect involvement (e.g., regulatory authorities and vaccine subcommittee members).

Table 2. Interviewees by Category and Region

Group	SUB-SAHARAN AFRICA					ASIA		LATIN AMERICA/ CARIBBEAN			OTHER	TOTAL
	Kenya	Uganda	S. Africa	Rwanda	Zambia	India	Thailand	Brazil	Haiti	Peru	U.S. & EU	
Research teams (local teams and expatriates; all levels and categories of study personnel)	12	8	10	1	1	2	20	3	1	3	6	67
Community and civil society participants	4	6	2	-	-	-	4	-	-	-	-	16
Government employees	3	2	-	-	-	-	5	-	-	-	-	10
Donors/advocates from international organizations			-			-			-		4	4
Total			49			31			7		10	97

2.3 Survey Questionnaire and Responses

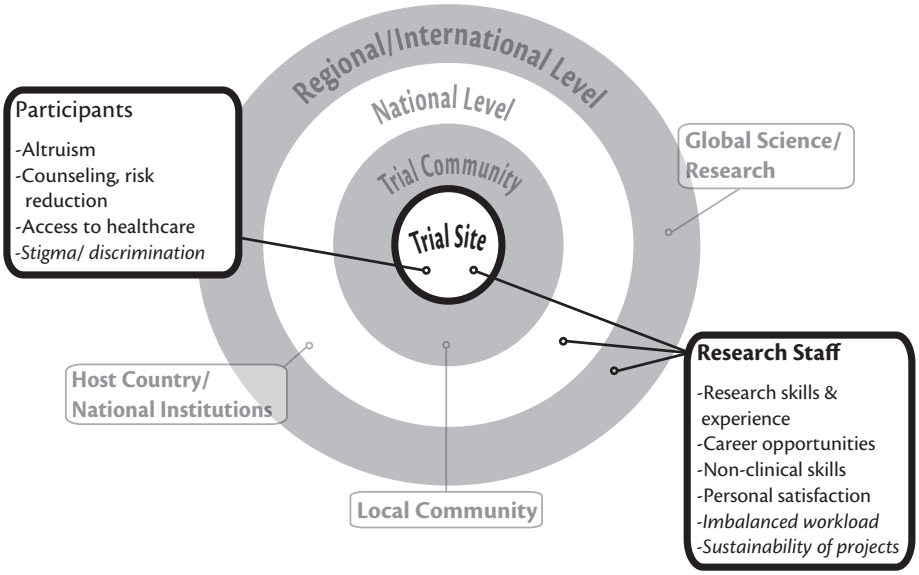
The team developed an open-ended questionnaire for interviews with the different stakeholder groups. Researchers interviewed most of the respondents in Kenya, Thailand, and Uganda in person, with the remainder conducted primarily by telephone. All respondents received the questionnaire in advance.

The interview responses reflect individual perspectives and anecdotal evidence about the impact of AIDS vaccine studies, rather than quantifiable and verifiable data. Many respondents also discussed their views on *likely* impacts in the future, such as faster rollout of an AIDS vaccine due to the groundwork laid by the vaccine trials. However, it is impossible to know if that will actually happen when a vaccine becomes available.

3 IMPACT AT THE INDIVIDUAL LEVEL

3.1 Study Participants/Volunteers

Figure 3. Impact of AIDS Vaccine Studies, Individual Level



Note: *Italicized items* refer to challenges or concerns cited by respondents

Summary: For volunteers, enhanced health and well-being have been important benefits of participating in AIDS vaccine studies. Greater self-esteem was the most significant personal impact, along with increased access to health information and services. Yet volunteers have also faced challenges from potential stigma and discrimination, as well as from the time demands of participation.

Altruism and personal satisfaction: Altruism is one of the primary reasons volunteers gave for participating in AIDS vaccine studies, especially for those who have lost friends and family to AIDS. For many, this motivation led to a positive personal benefit: a sense of fulfillment and satisfaction for having contributed to a social goal, as well as greater self-esteem. In Thailand, some IDUs saw their involvement in the first efficacy trial as an "honorable" contribution, particularly important given the value placed on altruism in Thai Buddhist culture. In South Africa, some respondents said volunteering has given unemployed young people something to do and enabled them to feel better about themselves.

Counseling, information, risk reduction: Study participants received substantial information about HIV prevention, AIDS vaccines, and clinical research, which helped them not only to understand the basics of the research study but also to reduce the risk of contracting HIV. Research personnel consistently cited greater knowledge about HIV prevention among participants as a critical outcome of the studies. Although little quantitative data were available, nurse counselors, often the first line of contact with study participants and the community at large, were convinced that trials and preparatory work had made a difference in awareness and health education levels.

Two Ugandan volunteers mentioned that what they learned about HIV and prevention from the trial helped them lower their level of risk behavior. In fact, they found their trial experience so fulfilling that they volunteered as peer leaders once the trial ended and began providing support and information to people living with HIV and AIDS. In Thailand, there were decreases in IDU risk behaviors and increases in condom use. Injecting drug use dropped from 98.3% to 66.5%; needle sharing went from 33% to 16% (Van Griensven et al. 2004). During the trial, HIV incidence declined from 5.8% to 3.4%.

Access to healthcare services: Vaccine trials provided access to healthcare services, including both HIV treatment and prevention services, such as voluntary counseling and testing (VCT). Participants received monitoring and treatment (or referrals to another provider) for health issues that arose during the trials. In resource-poor settings where health systems are limited in capacity and quality, this access to care can represent a significant benefit. Many research staff helped study participants access care outside of the trials, using their networks with colleagues to get needed treatment. In some cases, study participants found their entry into the health system facilitated simply because they had someone to ask where to go and what to do.

> *"Many of our participants needed outside healthcare – to see specialists or to have surgery. We were able to see them here and refer them – this wasn't a formal program, but rather something we were able to do because of our informal network of colleagues who were health workers." Research Site Coordinator, Brazil*

An important aspect of healthcare services for trial participants has been access to antiretroviral therapy (ART) for those who become HIV-infected during trials. Provided by some study sponsors, this was particularly critical in environments where access to treatment may be limited. At a research center in Kwa-Zulu Natal, prospective volunteers who tested HIV-positive received counseling and referrals to another study for HIV-infected persons, and received ART if they became symptomatic. In Thailand, the Phase III trial currently underway has established a trust fund for treating breakthrough infections for those in the trial; these funds supplement government-provided antiretrovirals. When AIDS vaccine studies began in India, there was no government ART program. Trial sponsors held a national consultation to define appropriate guidelines for AIDS vaccine trials, ensuring that participants who contracted HIV during the trial would receive free care, support, and treatment, including at least five years of ART (Jesani and Coutinho 2007).

During routine screening tests for trials, research staff have discovered such undiagnosed health problems as high blood pressure and provided treatment or made referrals to appropriate facilities. Participants found to be HIV-positive have received counseling and referrals for treatment and encouragement to participate in other research studies.

Stigma and discrimination: Some volunteers encountered discrimination when their participation in a trial became public. In a few cases, volunteers withdrew from trials due to pressure from family members who disapproved of their participation. Some friends and family of participants expressed concern about the perceived dangers of vaccine trials, believing that volunteers would be injected with HIV or otherwise harmed. In extreme cases, a Kenyan medical student lost her job and encountered difficulties with the medical board, and several Thai volunteers lost their jobs when their participation became public. In these cases, the principal investigators (PIs) advocated on behalf of the volunteers, and provided education and greater awareness about the trials to dispel myths and misinformation. Research teams now proactively work with volunteers to discuss how best to explain their participation in both private and public situations.

Locating studies within health facilities or multi-functional sites has helped minimize stigma for participants. In Kenya, South Africa, and Thailand, researchers noted that having volunteers go to health facilities, especially hospitals, where trial participation was not obvious was an important way to protect individuals' confidentiality. In one of the Thai trials, incarcerated volunteers received follow-up visits, yet they faced no stigma because research personnel maintained confidentiality; researchers characterized this as an important aspect of "taking the trial to the volunteers."

Some volunteers have faced the consequences of a vaccine-induced HIV seropositivity. These false-positive test results can affect their ability to find employment or obtain a visa for overseas travel. As such, many trial sites now provide an explanatory letter for volunteers about their participation and HIV status.

Time commitment: Although study participants generally viewed their experience positively, some noted that the amount of time required for participation was problematic. Volunteers must return to the study site for monitoring, blood draws, and related activities, which can affect their work schedules or other obligations. In the Phase III trial underway in Thailand, some employers have not been supportive of factory workers who take time off for trial visits. In Chonburi Province, for example, some volunteers lost year-end bonuses because they missed work for study follow-up visits. Trial personnel have tried to respond to these issues by explaining to employers that volunteers are making contributions to society and presenting plaques to factories in recognition of employees' participation to instill a sense of pride among employees and employers alike. In addition, many study sites have expanded their hours, enabling volunteers to come in on weekends and after work.

3.2 Research Staff

Summary: Professional development has been the primary benefit of working on AIDS vaccine studies for research staff. The skills and experience gained, career enhancement, and exposure to social science and non-clinical fields were overwhelmingly positive. At the same time, these individuals gained personal satisfaction from contributing to a noble cause. However, research staff have faced the challenges of a heavy workload, a high emotional toll, and the unreliability of funding.

Trial management skills and experience: All research personnel gained new skills in conducting clinical research to international standards and implementing complex research protocols. Trial staff received training in many areas, including research methodology, good clinical practices (GCP), good clinical laboratory practices (GCLP), standard operating procedures, gender sensitization, research ethics, quality assurance, and data management. This training took place both on the job and in formal courses; many respondents cited the number of training programs and courses available to them that had upgraded their skills. A senior researcher in Uganda noted that although implementing GCP and GCLP are not the major objectives of vaccine trials, they are a significant collateral benefit – and without them the field would never reach its primary goal. Research staff have enhanced their academic credentials through publications in peer-reviewed journals, presentations at international conferences, and participation in numerous scientific workshops and symposia. They have shared their experiences, disseminated their knowledge and training, and taken advantage of professional networks, regionally and internationally.

Because of the experience gained through vaccine studies, many research personnel have been able to transfer skills to other areas. In Thailand, data management staff responsible for the AIDS vaccine efficacy trials are now applying their expertise to malaria vaccine trials, and their institution competes with contract research organizations (CROs) for work in a variety of domains. Other AIDS vaccine research staff have expanded their efforts to microbicide trials, human papillomavirus (HPV) vaccine trials, and drug trials.

"We developed a whole new category of medical personnel turned clinical researchers, since we took on people with limited experience and trained them." Expatriate Researcher, Uganda

"Following graduate school, people don't have much experience with clinical research. We've made training a big part of our effort, and we've become like a training center for private research sites and for industry. We open doors for those people." Research Site Coordinator, Brazil

Some scientists appreciated the chance to work on early product development rather than simply being investigators of vaccines already tested in developed countries. Indian researchers highlighted their first opportunity to participate in vaccine trials. But there were other cases where more experienced researchers felt undervalued by participating in global activities. Some South Africans noted that on global projects, expatriates led the research, and local PIs felt like implementers or data handlers, with limited input into protocol development and little ability to drive research agendas, despite their significant levels of experience.

"It's hard to participate in global initiatives – it feels like losing your identity. It's very challenging personally – there are conference calls at odd hours, and you have to fit into a pattern that detracts from creative thinking." Principal Investigator, South Africa

Career opportunities: Many involved in vaccine studies found their career opportunities enhanced, given the technical skills and experience they gained. While beneficial to individuals, the downside for the research field has been that junior staff often leave after a few years, recruited by companies or competing projects. The study teams know that personnel become more marketable with trials experience, and while there has been some frustration in watching trained people leave to pursue other opportunities, there has also been recognition that they did a good job of training new personnel. At the same time, a few researchers have noted that the work on clinical trials can be somewhat limiting. For example, in East Africa, two PIs said that tasks for their staff became rather monotonous, requiring them to seek collateral activities to keep them interested and motivated. Similarly, in Thailand, one senior researcher noted that his commitment to leading a Phase III trial (five to seven years) has had a negative impact on career mobility and promotion in the short and medium term, despite the potential for long-term career growth.

"Many people on our trial team, because of their experience, training, and exposure, got good opportunities and moved on. But we consider this a benefit because we have been able to spread them to other places where they can do important work." Principal Investigator, India

Non-clinical skills and training: Many trial personnel gained experience in negotiating with regulatory committees and international sponsors. Equally important has been the chance to improve their communication skills through dealing with volunteers, communities, and the media. The latter has posed particular challenges, as research teams everywhere have had to respond to criticism about the trials and charges that volunteers were "guinea pigs." Many research staff, previously unaccustomed to the glare of the limelight, have learned to work effectively with journalists to dispel myths and proactively provide accurate educational messages.

Several research personnel cited the vaccine studies as their first opportunity to work with public health and social science experts. This interaction opened their eyes to a broader perspective for their work and helped them appreciate the impact of their research beyond clinical details. A Brazilian researcher suggested that by working with colleagues from social science backgrounds, clinical staff became more sensitive to participants and open to new ideas. In Kenya, nurses said that the trial and the necessity of interacting with the community had affected the internal structures of their research institute: the PIs had become much more receptive to ideas from their own staff, and actively sought out the nurses for their input, signifying a fundamental shift in the hierarchy within the organization.

Personal satisfaction and well-being: Many researchers have gained a sense of personal accomplishment by working on AIDS vaccine studies. Like the volunteers, many have been personally affected by AIDS, losing friends and family to the disease, and have dedicated their careers to finding solutions. Many health professionals were also proud to participate in a noble effort. As a result, they acknowledged that, despite their workloads and frustrations, they gained tremendous satisfaction from their work on AIDS vaccine studies.

Yet some highlighted the personal toll this work has taken. Many trial staff become engaged in the lives of the volunteers and cannot avoid feeling overwhelmed. In South Africa, a researcher cited the need to provide support to trial staff; one nurse, 13 of whose 200 volunteers seroconverted, felt devastated and needed counseling herself.

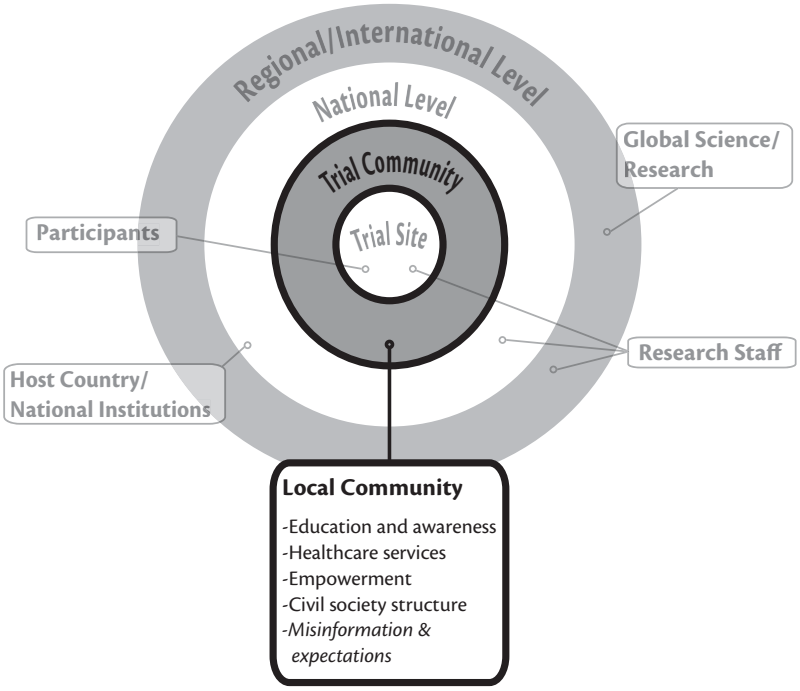
> *"When you feel like your work really matters, you do your own part and others' as well."*
> *Nurse, Kenya*

Workload: In studies conducted in public health facilities and staffed with public sector workers, government employees have sometimes faced the dual burden of doing their routine work in addition to implementing the research studies. This sometimes had a negative impact on the health professionals themselves and also affected the quality of healthcare services provided. A provincial chief medical officer in Thailand noted that the trial created additional duties for his staff, including training, meetings, data tracking, and volunteer visits; however, trial-related work was not mandatory and workers did receive salary supplements. More generally, study staff mentioned the long hours required for their work, including the need to be available evenings and weekends, for volunteer appointments, training sessions, meetings with sponsors and community members, and dissemination activities.

Sustainability of employment: Some research staff expressed concern about their job security because their contracts with study sponsors were of relatively short duration (one or two years). In Latin America and the Caribbean, researchers felt overly dependent on donors for funding and were concerned about being able to sustain important work. Researchers in East and Southern Africa noted the difficulty of maintaining trained staff when grants expired before new ones were obtained, and having to watch capacity built up over several years dissipate.

4 IMPACT AT THE COMMUNITY LEVEL

Figure 4. Impact of AIDS Vaccine Studies, Community Level



Note: *Italicized items* refer to challenges or concerns cited by respondents

Summary: At the community level, the primary benefits of AIDS vaccine studies were enhanced health education and healthcare services. Conducting vaccine studies has empowered community organizations and structures, including CABs and civil society groups. At the same time, a recurring challenge for vaccine studies has been addressing misinformation and unrealistic expectations within communities about the trials.

HIV education and awareness: Through efforts to recruit volunteers, vaccine researchers often conducted educational events and activities to provide HIV prevention information. Although study participants received the most educational benefit, others learned more about risk reduction and health education as well. Research teams in Kenya, South Africa, and Uganda mentioned numerous examples of groups formed to present HIV prevention messages at community events, through storytelling and drama. One of those, "The Future Fighters," a group of South African adolescents participating in an ongoing vaccine study, conducted training and vaccine advocacy throughout their township. Their ability to relate to and connect with other young people was particularly important in disseminating prevention messages.

Because Phase II and III trials often involve participants from vulnerable groups, recruitment efforts have provided educational messages and opportunities at specific venues, such as clinics for sexually transmitted infections (STIs), community centers with programs for men who have sex with men (MSM),

or VCT centers. In Uganda, volunteers were recruited from VCT centers, and in Peru, researchers recruited MSM for studies in the course of counseling them on risk reduction and providing STI services.

> *"It's no longer just us recruiting – it's the whole community. Everyone comes to believe in the need for a vaccine." Community Liaison, South Africa*

Strengthened healthcare services: While access to healthcare services primarily benefited study volunteers, the impact also extended to the broader community. Those found ineligible to participate in the studies received diagnoses and referrals for appropriate treatment. For example, as part of general outreach, the Kenya AIDS Vaccine Initiative (KAVI) staff took part in medical camps where they provided treatment and information on HIV prevention and vaccines. At the Kangemi feasibility study site, the research team trained health clinic staff to deliver ART. In Thailand, researchers felt they had improved service delivery by introducing practice standards into health facilities where they worked. In Uganda, the research team cited improved service standards and documentation in the facilities where vaccine studies were taking place.

Researchers in Thailand felt that conducting trials and gathering background data have contributed to national health information and policy development. The medical checkups given to volunteers as part of the screening process of each trial discovered hypertension among young people, something that health officials were not aware of previously. As a result, programs were implemented for early diagnosis and treatment. A Kenyan research scientist similarly noted that ongoing studies on sub-populations, incidence data from feasibility studies, and HIV progression studies would all contribute to better information and policy decisions.

Community advisory boards (CABs): In most vaccine studies, CABs were established to provide a forum for voicing concerns, communicating between the study teams and the community, and protecting the interests of participants and the broader community. CAB members usually included a diverse group of stakeholders, drawn from NGOs, CBOs, the legal community, medical doctors, women's groups, soccer clubs, and other social and political organizations, as well as HIV-infected individuals and former vaccine trial volunteers.

While CABs were established specifically for research studies, they have also strengthened community institutions and information-sharing. The CAB at the Kangemi site in Kenya sought opportunities to speak at such gatherings as *barazzas* (chiefs' meetings) and even funerals. Another CAB challenged itself to be KAVI's "mouthpiece" and advised researchers on how to reach out to the community by targeting different age groups, organizing programs through drama and songs, and conducting interviews to determine how best to disseminate information.

> *"Information is power, and has been the major benefit of the trials. As people volunteer, information has come out from the counseling; the CAB has been able to use this information in the community regarding preventive measures. This has led to increased interest in developing a vaccine, and gives everyone hope that things can change/improve." CAB Member, Kenya*

The CAB's role in facilitating relationships with communities has been particularly important in supporting research teams, including help with recruitment, retention, and acceptability of the trial.

In South Africa, one CAB helped researchers identify a suitable site for a vaccine center and worked with the community to convert the former soup kitchen into a research facility and pharmacy.

> *"The old adage that it's easier to apologize than get permission? It doesn't work in communities. There is always a specific process to follow in each community, but researchers might not know it; you need people like [community liaisons and CAB members] to help you navigate the process." Senior Investigator, South Africa*

In the first efficacy trial in Thailand, some researchers felt that external sponsors imposed the CAB concept on them, rather than accepting the traditional Thai approach of forming advisory councils. However, a Community Relations Committee was established during the trial, serving as an intermediary between the IDU community and researchers. This approach was so successful that it continued after the trial, providing a voice to the community on a number of political and scientific issues.

In India, a gender advisory board was established to address gender issues in the vaccine trials, something that had never existed before. The board oversaw development of a first-of-its-kind gender training manual, revisions to the informed consent form, and a gender training workshop. As the head of a local NGO noted, this process "sets a new standard for conducting ethical and gender-sensitive trials in India. That in itself is a tremendous achievement" (Kochhar and Excler 2007; ICASO 2006).

Empowerment of vulnerable communities: Some vulnerable populations have also benefited from group activities as part of the vaccine studies. Members of these communities are often alienated and unable to advocate for their own rights. Vaccine studies have developed targeted activities for these communities so that volunteers and peer leaders can ask questions, talk about their grievances, and discuss how to reduce their risk of contracting HIV. For example, a Brazilian researcher noted their study site had become identified as a safe meeting spot for MSM, where individuals could seek care, talk about their concerns, get advice, and share social interests.

Role of civil society groups: Vaccine studies have helped strengthen civil society structures, particularly groups focused on AIDS issues. In Kenya, more than 600 groups have come together under the umbrella of the Kenya AIDS NGO Consortium (KANCO). KANCO established the Vaccine Support Network (VSN) to advocate for and support AIDS vaccine development and testing within communities, directly supporting trials where they are taking place and laying a foundation for future efforts in other communities. The VSN ensures that members have access to information from researchers about trials at quarterly meetings and provides training on vaccines and HIV.

Other vaccine studies have directly involved NGOs in their work. In Uganda, AIDS vaccine studies worked with an NGO that provides VCT at clinics and mobile sites. In Peru, scientists conducting trials formed the NGO IMPACTA, which receives financial support, training in clinical research methods, and the opportunity to be part of regional and international networks.

Misinformation and unrealistic expectations: Vaccine studies often faced misinformation in the media, requiring responses from trial staff. In virtually every country where vaccine studies have taken place, the media have charged that participants were "guinea pigs." In Kenya, local media circulated the myth that "HIV was created in a laboratory as a means to annihilate the African race" (ICASO 2006). Just prior to launch of a vaccine trial in Haiti, a *New York Times* article questioned the ethics of ongoing HIV research work and of the principal investigator. Rumors circulating within communities also disseminate misinformation. In Rayong and Chonburi provinces in Thailand,

misunderstanding of trial terminology led to rumors that the Phase III trial would actually induce "Clinical Stage III of HIV infection" in volunteers. In Zambia, the blood draws required for vaccine trials led to rumors that volunteers' blood would be used for satanic purposes.

In such instances, research teams have worked with the press, community groups, and government officials to respond to the misinformation and to better explain the nature of vaccine trials. In Uganda, one respondent noted that during the first trial they made the mistake of avoiding the media, and as a result, publicity was negative. Then, researchers involved journalists so much that the latter became blasé; now a happy medium has been reached, and positive working relationships have been established. In India, researchers regularly updated the media about the process of preparing for AIDS vaccine trials, with efforts made to involve members of parliament, the prime minister, and the president. Consultations were also carried out with technical experts and CABs, resulting in the creation of an informed consent process (Jesani and Coutinho 2007).

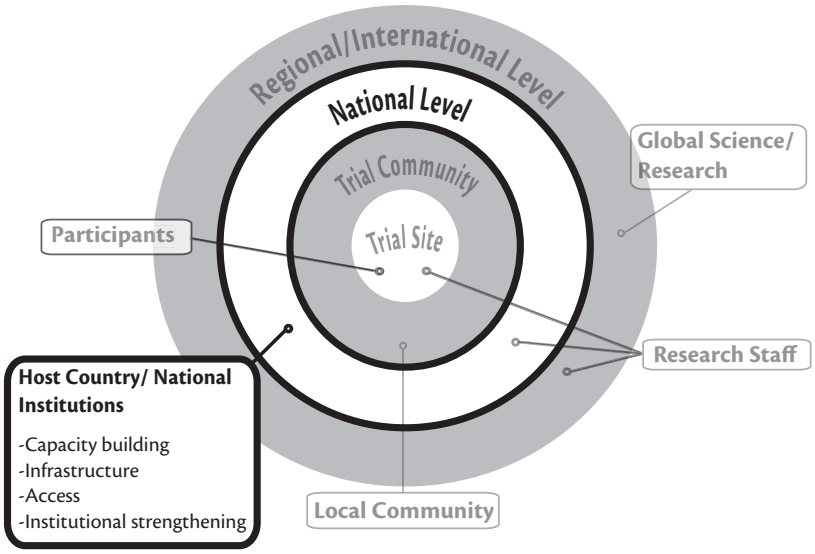
> *"Journalists rotate frequently, and they don't always attend the one-off meetings. It's a mistake to assume you are finished after one of these [meetings], and move on. It needs to be a constant ongoing process." Researcher, South Africa*

Sometimes vaccine studies have led to the mistaken impression that the vaccine will necessarily work successfully. The disappointment with results from early trials underscores the need to manage expectations, at all levels. Respondents in Kenya, Peru, and Thailand felt that the failure of vaccine candidates was a blow to volunteers, government officials, and the general public, and required specific communications strategies and follow-up. Volunteers in Peru felt that their participation was irrelevant, given the negative results of the trial. Kenyan respondents noted that much effort had gone into building enthusiasm and hope for the vaccine trials, which was severely deflated when the results came out. Respondents felt that better efforts to educate constituencies are needed before initiating trials, throughout trial implementation, and again when results become available.

> *"There were many rumors, especially having to do with how much blood was being taken, which made the community apprehensive. You need to continuously be aware of these rumors and continuously be able to explain what you are doing." Principal Investigator, Zambia*
>
> *"There is a growing sense of impatience in some communities – they feel like they have been talking about AIDS vaccines for 10 years, and now they're being told that it will take another 10 years." Principal Investigator, South Africa*

5 IMPACT AT THE NATIONAL LEVEL

Figure 5. Impact of AIDS Vaccine Studies, National Level



Summary: At the national level, AIDS vaccine studies have built capacity within scientific and research sectors, strengthened institutions, enhanced physical infrastructure, and laid the groundwork for future access to vaccines. It remains a challenge to maintain, if not further develop, the institutional capacity developed through these research efforts.

Capacity building: Carrying out AIDS vaccine studies has helped build national research capacity. In many cases, the impact extends beyond AIDS vaccines by strengthening research and science skills applicable to other diseases and technologies.

In Uganda, the medical school curriculum now includes a component on clinical research, due in part to the country's experience with vaccine trials. During the first Thai efficacy trial initiated in 1999, the sponsor, VaxGen, sent all data to its U.S. headquarters for analysis. But at the insistence of Thai government officials, the company invested in a facility at Mahidol University, paying for office space, equipment, and training. As a result, the Data Management Unit of Mahidol's Vaccine Trial Centre manages the primary database for the Phase III trial currently underway. The study statistician performs safety and efficacy analyses under contract with the sponsor, and sends data to the U.S. sponsor on a monthly basis. The Thai team's skills are transferable to other clinical trials, and the team now manages data for a malaria vaccine trial.

> *"The training is left with them forever, and they can adapt it to new situations." Principal Investigator, Zambia*

Vaccine studies have also provided employment for national researchers, helping to reverse at least temporarily and in modest ways the "brain drain" that often afflicts low- and middle-income countries. Many researchers trained abroad never return, or leave to find work in clinical research elsewhere (Zarocostas 2007). However, researchers in many countries with vaccine studies have had

the opportunity to remain at home, or in some cases, to return and help address the epidemic in their own countries. Having local researchers leading studies has also provided role models for the next generation of scientists. As a government official noted, "Kenyan researchers were perhaps not taken seriously before; now there is greater appreciation for what they are doing."

Although the capacity building resulting from vaccine studies has been significant, sometimes tensions have arisen between health workers and vaccine study staff working in the same facility or on the same project. Respondents from many countries mentioned the recurring issue of the disparity in salaries between government health workers and project staff, the latter usually being externally funded. Other issues included recruiting staff away from public sector programs, leaving already understaffed public facilities worse off. These potential issues require careful evaluation of human resource needs and efforts to balance project wages with local salary structures.

Improved infrastructure: In many studies, sponsors upgraded laboratory and healthcare infrastructure, enabling researchers to conduct state-of-the-art research. The equipment and facilities remain long after the research project is completed to support other research and healthcare activities. A building at Kenyatta National Hospital in Nairobi received an upper floor constructed expressly for vaccine study work as well as modern laboratory equipment. The latter, combined with training of staff, resulted in an upgrade of laboratory performance to the same level as European facilities. In Bangkok, a U.S. Centers for Disease Control and Prevention (CDC) project has supported the construction of a VCT clinic for MSM where clients currently are being recruited for a cohort study. At the Tuberculosis Research Centre in Chennai, India, an entire floor was converted into a vaccine trial site and was modified and equipped exclusively for AIDS vaccine trials. At the Kangemi site in Kenya, the vaccine study has brought in renovated shipping containers for use as counseling, testing, and treatment rooms. In Uganda, the U.S. Military HIV Research Program (USMHRP) project upgraded services at the health center and placed equipment in the labs. In Rwanda, facilities benefited from improved water supplies.

Access to future vaccines: Several government officials cited increased confidence that access to a successful vaccine would be more timely, thanks to the vaccine studies taking place in their countries. Although speedier access is only speculative at this time, countries that host vaccine efficacy trials might not have to undertake additional studies when licensure is sought. Thai government representatives negotiated with trial sponsors and manufacturers to ensure that the vaccine would be made available in Thailand and would be affordable. In the current Phase III trial, manufacturers made a commitment: should the vaccine be successful, they would vaccinate those who had received placebos, vaccinate all others in the provinces studied, and provide a price discount to the Thai government. The government has initiated discussions about establishing manufacturing capability in Thailand and explored the possibility of licensure for both local production and export.

> *"With hepatitis B, the clinical trials took place in developed countries, and the distribution of the vaccine has not yet trickled down. We have recognized that it is critical to test HIV/AIDS interventions in developing countries as well." Researcher, South Africa*

Institutional strengthening: Some governments did not initially have the capacity to approve vaccine trials, but have strengthened their regulatory approval processes as a result of undertaking vaccine studies. In Uganda, securing regulatory approval for the first vaccine trial took almost two years, involving six different committees and reaching the Cabinet level. The government has since streamlined the process, with only one regulatory committee required for approval. As a result, guidelines for research with human subjects appeared in 1997, followed more recently by the current *Guidelines for AIDS Vaccine Trials in Uganda*. A government official felt that the greatest contribution of the AIDS vaccine trials has been building the regulatory capacity for all kinds of trials, with the country's regulatory system now coherent and able to evaluate scientific, ethical, and safety issues.

> *"Our country had to develop regulatory mechanisms as a result of AIDS research: the first institutional review board (IRB) was at our institution. For vaccine trials, a national IRB was created. This movement helped a lot because it made the government aware of the need for such an institution, so there is now a law establishing a permanent national IRB."*
> *Principal Investigator, Haiti*
>
> *"HIV vaccines, which have been such a high-profile new technology, have really forced developing country regulators to prepare in a way we hadn't done for anything else."*
> *Researcher, South Africa*
>
> *"HIV vaccine research has had much more impact on regulatory bodies than other research."*
> *Research Director, U.S.*

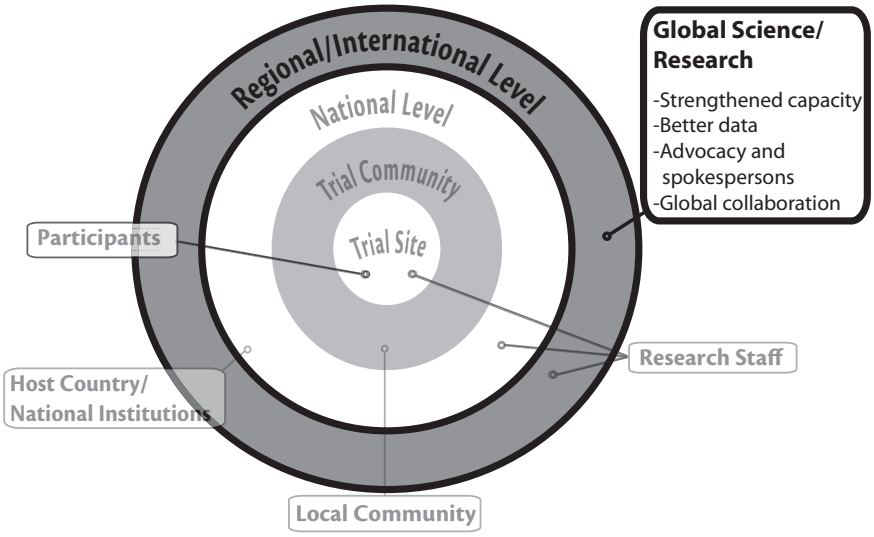
In Zambia, the government established a Vaccine Working Group, although it had few resources to initiate trials. Having recently approved the country's first AIDS vaccine trial, the group is now able to develop rational policy and guidelines for the country. The regulatory bodies (the Institutional Biosafety Committee and the Pharmacy Regulatory Agency) have been exposed to the latest knowledge on vaccine research and can meet both local and international standards for regulating drugs and vaccines and for conducting other clinical trials.

In addition to establishing guidelines and strengthening regulatory processes, several countries have developed national AIDS vaccine plans, providing an overall framework and rationale for vaccine studies. Brazil, Kenya, and Thailand have created such plans, helping to establish a clear road map for future research and investment needs.

Several respondents noted that having AIDS vaccine trials within their borders gave their countries greater credibility and international stature. This was sometimes expressed as national pride in making concrete contributions to the battle against AIDS and, in other cases, meant immediate credibility in international discussions about AIDS. For example, the Kenyan Minister of Health was able to propose initiatives for vaccine trials at international fora (e.g., the UNGASS meeting and the Abuja meeting of health ministers), since she was one of the few ministers with experience in this area and was thus regarded as a leader among peers.

6 IMPACT AT THE GLOBAL LEVEL

Figure 6. Impact of AIDS Vaccine Studies, Global Level



> *"We shouldn't see the experience thus far as a failure, even if the vaccine candidate failed; much of the path forward has now been developed, so we haven't failed at all. Being able to say yes or no, the vaccine worked or not, that is a success in research terms."*
> *Principal Investigator, Thailand*

Summary: At the global level, much of the impact of AIDS vaccine studies has been in the scientific and research realm. However, the experience of conducting such studies has contributed significantly to knowing how to better conduct future studies, especially – but not only – in developing country settings. These studies have also established new champions for AIDS vaccines and prevention efforts and serve as an example of how the global community can come together to address common problems.

Capacity to conduct trials in limited-resource settings: The global body of knowledge on AIDS vaccines has benefited from studies based in developing countries. The trials have demonstrated that it is feasible to implement AIDS vaccine trial studies in resource-poor settings. Research teams have been able to obtain informed consent from trial participants, even within populations with limited education. They have been able to set up and build world-class infrastructure and operate at international standards. With each new trial undertaken in a low- or middle-income country, it becomes clearer that there are no reasons to restrict research efforts to developed countries. In 1997, AIDS vaccine trials had been conducted in a total of six countries, but only two of them – Cuba and Thailand – were developing countries. At the end of 2007, a total of 19 low- and middle-income countries had hosted AIDS vaccine research efforts, reflecting dramatic growth in just a decade (IAVI 2007a).

Laboratory reference ranges: While vaccine studies have led to the collection of locally relevant scientific and medical data on health issues in specific countries, they also contribute to global research. Recent studies that examined medical criteria for including African volunteers in AIDS

vaccine trials concluded that many healthy Southern and East Africans were excluded from trial participation based on laboratory reference ranges developed for Western populations, which may not be appropriate locally. These findings will help set appropriate criteria for volunteer participation by improving vaccine safety assessment and streamlining the recruitment process. Other vaccine studies have generated data on the prevalence of antibodies to other bacteria and viruses (e.g., adenoviruses) which could be used as vectors for an AIDS vaccine. Researchers note that these results are "important for a range of research on neglected diseases, from HIV vaccines to malaria and TB drug therapy" (IAVI 2007b).

Advocacy for AIDS vaccine research from the South: Conducting AIDS vaccine studies in the developing world has led to a greater role for those countries in political advocacy for global health research. Ugandan President Museveni, whose country undertook the first AIDS vaccine trial in Africa, has advocated for increased funding for vaccine research with G8 leaders. The heads of state of India, Brazil, and South Africa have formed a tripartite coalition to advocate jointly on behalf of AIDS vaccine research and development, largely because of the role each country has played in R&D efforts.

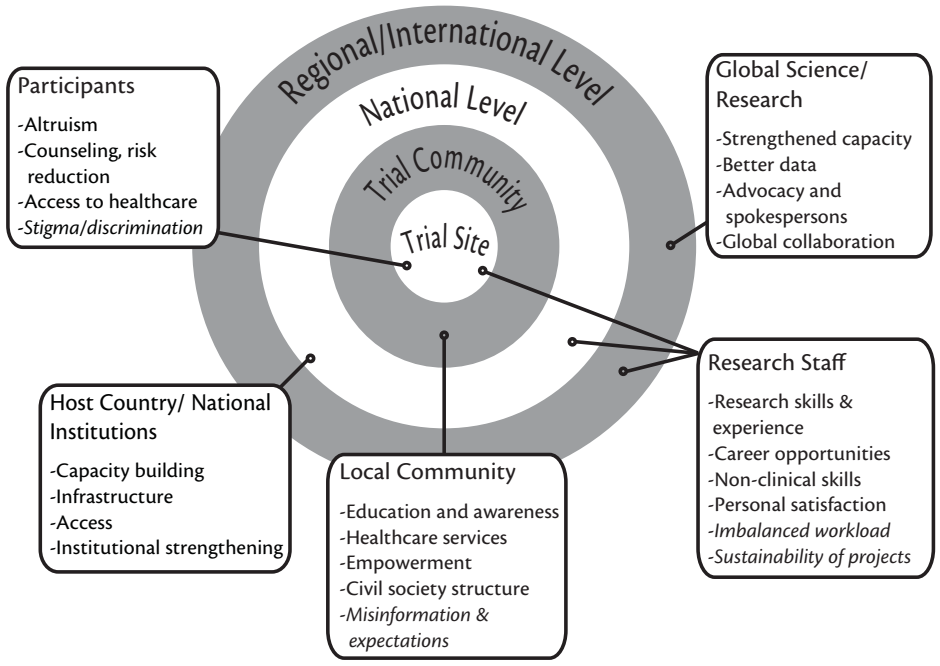
Global cooperation: More broadly, one of the biggest impacts of these research efforts may be the value of cooperative problem-solving. Working across borders to tackle the AIDS pandemic, all of those involved in AIDS vaccine studies, both directly and indirectly, have had the opportunity to contribute to a common goal. Whether they consciously realize it or not, they are working together to solve joint problems. These studies have created and validated a model of multi-country and North-South collaboration that could serve many other global goals.

> *"The fact that you are doing it globally helps increase the momentum, and the sense that this might really work...The momentum must be kept going, because in some ways it is our last hope in controlling the epidemic." Principal Investigator, Zambia*

7 CONCLUSIONS AND KEY LESSONS

7.1 Conclusions

Figure 7. Summary of Impact of AIDS Vaccine Studies



Note: *Italicized items* refer to challenges or concerns cited by respondents

This paper has highlighted a broad range of impacts from conducting AIDS vaccine studies in 10 developing countries. As summarized in Figure 7 above, most have been positive, although there have also been challenges and some less positive side effects.

The most important elements identified by respondents are the following:

- For study **volunteers**, taking part in AIDS vaccine studies has provided benefits for their own health and well-being. Greater *self-esteem* and a sense of contributing to a valuable effort were the most personal impact, but increased *access to health information* as well as *health services* were also significant. At the same time, volunteers faced challenges from *potential stigma and discrimination* and significant *demands upon their time*.
- The benefits of working on AIDS vaccine studies for **research staff** were primarily in professional development. The *skills and experience* gained, *career enhancement*, and greater exposure to social science and non-clinical areas were overwhelmingly positive, as was the *personal satisfaction* gained by contributing to a noble cause. Yet research staff also faced challenges from the *workload* and *uncertain sustainability* of projects and employment.

- At the **community** level, the primary benefits of AIDS vaccine studies were *enhanced health education and better healthcare services*. Conducting vaccine studies has *empowered community organizations and structures*, including community advisory boards and civil society groups. A significant and recurring challenge for vaccine studies has been addressing *misinformation and unrealistic expectations* about the trials within communities.
- For **host countries**, AIDS vaccine studies have *built capacity* and *strengthened institutions* within scientific and research sectors. These studies led to enhanced physical infrastructure, and laid the groundwork for future access to vaccines. It remains a challenge to maintain and further develop the institutional capacity developed through these research efforts.
- At the **global** level, much of the impact of AIDS vaccine studies has been in the scientific and research realm. In addition, there has been a significant *contribution to knowledge* about how to better conduct future studies, especially in developing countries. These studies have also established new *champions for AIDS vaccines and prevention efforts* and show how the *global community can come together* to address common problems.

Appendix 2 contains a summary of these key issues and possible solutions, including both suggestions for the future and steps already taken by study teams.

7.2 Key Issues and Lessons for Implementing Future Vaccine Studies

The issues and lessons identified in this study underscore two important themes. First is ***the critical need for better communication about vaccine studies***. Virtually all respondents mentioned the need to ensure more, better, earlier, and continued communication as part of vaccine studies. This should be done with the broadest range of stakeholders possible and err on the side of too much rather than too little communication. Most felt that research personnel did not anticipate how much time this aspect of the studies would take, and that they should work closely with social scientists and community liaisons to ensure common understandings of issues and potential problems. In addition, there was universal agreement that the media cannot be ignored but must rather become an integral part of any communication strategy for vaccine studies.

Second, although AIDS vaccine studies have led to major investments in capacity building and have generated significant benefits, ***additional resources are required to maintain those benefits***. Many of the study sites and individual research personnel risk loss of continuity and employment when grant funding expires before new studies begin. In addition, developing the capacity to undertake clinical studies has led to growing demands on regulatory agencies. While regulatory capacity has generally improved, in many instances it remains insufficient to meet current needs. There is further need for investment, from external sponsors and donors and especially from national governments. In particular, host country recognition and funding of cutting-edge research are critical to make these benefits sustainable over the long run.

This paper seeks to provide insights into how those involved in AIDS vaccine research perceive the impact of those studies. The intermediate benefits of conducting such research are reported to be substantial at all levels. Going forward, it may be useful to undertake additional quantitative research to further document these results and to more fully understand how vaccine studies can be improved. As we continue to strive to develop an AIDS vaccine, no matter how long or short that search may be, we should remember that the journey itself is also significant, and can make important contributions to better public health and to social and economic development.

BIBLIOGRAPHY

Choopanya, K. et al. (2003). "HIV risk reduction in a cohort of injecting drug users in Bangkok, Thailand." *Journal of Acquired Immune Deficiency Syndrome*. Vol. 33, no. 1: 88-95.

Excler, J. (2006). "AIDS vaccine efficacy trials: expand capacity and prioritize." *Expert Review of Vaccines*. Vol. 5, no. 2: 167-170.

Hecht, R., Becker, J., and Roca, E. (2006, April-May). "AIDS Vaccine Research Today: A Deeper Partnership between Countries." *Global HealthLink*. Issue 138: 4-5, 16.

International AIDS Vaccine Initiative. (2007a). IAVI Database of AIDS Vaccines in Human Trials, accessed on October 25, 2007: http://www.iavireport.org/trialsdb.

International AIDS Vaccine Initiative. (2007b). "IAVI and Partners, CDC and the USMHRP Release New Data Redefining Laboratory References Ranges in Africa." Press release, 21 August 2007.

International Council of AIDS Service Organizations. (2006). *Community Involvement in HIV Vaccine Research: Making it Work*.

Jesani, A. and Coutinho, L. (2007). "AIDS vaccine trials in India: ethical benchmarks and unanswered questions." *Indian Journal of Medical Ethics*. Vol. 4, no. 1: 2-3.

Kahn, P. (ed.) (2005). *AIDS Vaccine Handbook 2nd Edition: Global Perspectives*. New York: AVAC.

Kochhar, S., and Excler, J. (2007). "The first AIDS vaccine trial in India breaks myths." *Sankalp – IAVI India Newsletter*. Vol. 6, no. 1: 1-2.

Lieu, T., McGuire, T. and Hinman, A. (2005). "Overcoming Economic Barriers to the Optimal Use of Vaccines." *Health Affairs*. Vol. 24, no. 3: 666-679.

McCluskey, M. et al. (2005). "An HIV Vaccine: As We Build It, Will They Come?" *Health Affairs*, Vol. 24, no. 3: 643-651.

Pitisuttithum, P. et al. (2006). "HIV Vaccine Research and Development in Thailand." Bangkok: Mahidol University.

Rerks-Ngarm, S. et al. (2006). "HIV/AIDS Preventive Vaccine 'Prime-Boost' Phase III Trial: Foundation Lessons Learned from Thailand." *AIDS*. Vol. 20, no. 11: 1471-1479.

Safreed-Harmon, K. et al. (2004). "The HIV Netherlands Australia Thailand research collaboration: lessons from 7 years of clinical research." *AIDS*. Vol. 18, no. 15: 1971-1978.

Slack, C. et al. (2000). "Ethical issues in HIV vaccine trials in South Africa." *South Africa Journal of Science*. Vol. 96: 291-295.

UNAIDS. (2006). *Report on the Global AIDS Epidemic*, accessed on June 29, 2007: http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp.

Van Griensven, F. et al. (2004). "Lack of increased HIV risk behavior among injection drug users participating in the AIDSVAX(R)B/E HIV vaccine trial in Bangkok, Thailand," for the Bangkok Vaccine Evaluation Group 2004. *AIDS*. Vol. 18, no. 2: 295-301.

Zarocostas, J. (2007). "Poor countries lose 15% of their skilled staff to rich countries, UN Report says." *British Medical Journal*. Vol. 335, no. 7611: 119.

APPENDIX 1. Interviewees

NAME	AFFILIATION (AT TIME OF INTERVIEW)
Nicholas Agaba	AIDS Information Center, Uganda
Omu Anzala	Kenya AIDS Vaccine Initiative, Kenya
David Apuuli	Uganda AIDS Commission, Uganda
John Barizi	CAB member, Entebbe site, Uganda
Michael Benenson	USAMC-AFRIMS, Thailand
Chris Beyrer	Johns Hopkins University, U.S.
Job Bwayo	Kenya AIDS Vaccine Initiative, Kenya
Judith Bwonya	Ministry of Health, Kenya
Gabriela Calazans	Centro de Referência e Treinamento DST/AIDS, Brazil
Sitthisat Chaimwongpaet	Bangkok AIDS Vaccine Evaluation Group, Thailand
Elwyn Chomba	Zambia-Emory HIV Research Project, Zambia
Kachit Choopanya	Bangkok AIDS Vaccine Evaluation Group, Thailand
Julius Ecruru	National Council of Science and Technology, Uganda
Regina Ferro do Lago	Projeto Praça Onze-Rio de Janeiro, Brazil
Donald Francis	Global Solutions for Infectious Diseases, U.S.
Pedro Goicochea	Asociación Civil Impacta Salud y Educación, Peru
Glenda Gray	Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, South Africa
Dirceu Greco	Federal University of Minas Gerais, Brazil
Ashraf Grimwood	SAAVI, South Africa
Walter Jaoko	Kenya AIDS Vaccine Initiative, Kenya
Jaranit Keawkungwal	Mahidol University, Thailand
Pontiano Kaleebu	Uganda Virus Research Institute, Uganda
Fiona Kalinda	Uganda Virus Research Institute, Uganda
Quarraisha Abdool Karim	South Africa Fogarty AIDS Training Program, South Africa
Etienne Karita	Projet San Francisco, Rwanda
Marriana Karras	European and Developing Countries Clinical Trials Partnership, the Netherlands
Drake Katongole	AIDS Information Center, Uganda
Anthony Kebba	Medical Research Council, Uganda
Hannah Kibuuka	Walter Reed Project, Makerere University, Uganda
Jerome Kim	USAMC-AFRIMS, Thailand
Tom Klambi	Former volunteer, Entebbe site, Uganda
Prayura Kunasol	Ministry of Public Health, Thailand

NAME	AFFILIATION (AT TIME OF INTERVIEW)
Javier Lama	Asociación Civil Impacta Salud y Educación, Peru
Odile Leroy	European and Developing Countries Clinical Trials Partnership, the Netherlands
Rose Mahira	Kenya AIDS Vaccine Initiative, Kenya
Roselyn Malogo	Kenya AIDS Vaccine Initiative, Kenya
Sophie Manyonjo	Former volunteer, Entebbe site, Uganda
Michael Martin	Ministry of Public Health-CDC Collaboration, Thailand
Timothy Mastro	Centers for Disease Control and Prevention, U.S.
Edward Mbidde	Uganda Virus Research Institute, Uganda
Margaret McCluskey	United States Agency for International Development, U.S.
James McIntyre	Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, South Africa
Sanjay Mehendale	National AIDS Research Institute, India
Keren Middelkoop	Desmond Tutu HIV Centre, South Africa
Monica Millard	Walter Reed Project, Makerere University, Uganda
Koleka Mlisana	Center for the AIDS Program of Research in South Africa, South Africa
Francis Mmiro	Makerere University, Uganda
Khun Moo	Thai Network of Positive People, Thailand
Prudence Mthimunye	Desmond Tutu HIV Centre, South Africa
Emmanuel Mugisha	Uganda Virus Research Institute, Uganda
Solomon Thuki Murugi	CAB member, Kangemi site, Kenya
Gaudensia Mutua	Kenya AIDS Vaccine Initiative, Kenya
Supatra Nacapew	Centre for AIDS Rights, Thailand
Jeckoniah Ndinya-Achola	Kenya AIDS Vaccine Initiative, Kenya
Josephine I. Nguuh	CAB member, KAVI site, Kenya
Sorachai Nitayaphan	USAMC-AFRIMS, Thailand
Nkuli Ntlabati	Desmond Tutu HIV Centre, South Africa
Jane Odada	Kenya AIDS Vaccine Initiative, Kenya
Rispah Oduwo	National Council for Science and Technology, Kenya
Hilda Ogutu	Kenya AIDS Vaccine Initiative, Kenya
Kepha Ombacho	Ministry of Health, Kenya
D. Malaki Owili	Aga Khan Hospital, Kenya
Jean-William Pape	HIV Vaccine Trials Network, Haiti
Punnee Pittisuttitham	Mahidol University, Thailand
Nakorn Premsri	Ministry of Public Health, Thailand
D. Raghunath	Tata Center for Research in Tropical Diseases, India

NAME	AFFILIATION (AT TIME OF INTERVIEW)
Allan Ragi	Kenya AIDS NGO Consortium, Kenya
Helen Rees	Reproductive Health Research Unit, University of Witwatersrand, South Africa
Supachai Rerks-Ngarm	Ministry of Public Health, Thailand
Manuel Romaris	European Commission, Belgium
Jorge Sanchez	Asociación Civil Impacta Salud y Educación, Peru
Eduard Sanders	Centre for Geographic Medical Research – Kenya
Suebpong Sangkharomya	USAMC-AFRIMS, Thailand
Udomsak Sangkum	Bangkok Metropolitan Administration, Thailand
Nono Simelela	International Planned Parenthood Federation, South Africa
Pakorn Siriyong	Ministry of Public Health, Thailand
Wonchat Subhachaturas	Bangkok Metropolitan Administration and Global AIDS Program, Thailand
Pravan Suntharasamai	Mahidol University, Thailand
Weerawan Tangkeo	Food and Drug Administration, Thailand
Nusara Thaitawat	USAMC-AFRIMS, Thailand
Tim Thomas	CDC-Kemri, Kenya
Vipa Tiamchai	Ministry of Public Health, Thailand
Nimit Tien-Udom	AIDS Access Foundation, Thailand
Rose Tumusiime	CAB member, Entebbe site, Uganda
Vinit Usavakidviree	Food and Drug Administration, Thailand
Frits Van Griensven	Ministry of Public Health-CDC Collaboration, Thailand
Suphak Vanichseni	Bangkok AIDS Vaccine Evaluation Group, Thailand
Efythia Vardas	Perinatal HIV Research Unit, University of Witwatersrand, South Africa
Sabina Wakasiaka	Kenya AIDS Vaccine Initiative, Kenya
Steven Wakefield	HIV Vaccine Trials Network, U.S.
Mitchell Warren	AIDS Vaccine Advocacy Coalition, U.S.
Judith Wasserheit	HIV Vaccine Trials Network, U.S.
Sonchai Wattana	Ministry of Public Health, Thailand
Somsak Wiangyangkung	CAB member, Chonburi site, Thailand
Carolyn Williamson	University of Cape Town, South Africa
Wipas Wimonsate	Silom Community Clinic, Thailand
Wiwat Wiriyakijja	Ministry of Public Health, Thailand

IAVI STAFF

NAME	TITLE
Paul Amornkul	Regional Director, Efficacy Trials and Feasibility, Kenya
Prince Bahati	Program Officer, Country and Regional Programs, Kenya
Julie Becker	Senior Director, Country and Regional Programs, U.S.
Bonnie Bender	Program Manager, Country and Regional Programs, Kenya
Seth Berkley	President and Chief Executive Officer, U.S.
Jean Louis Excler	Senior Director, Medical Affairs, India
Patricia Fast	Executive Director, Medical Affairs, U.S.
Jill Gilmour	Senior Director, Clinical Research, U.K.
Robert Hecht	Senior Vice President, Policy, U.S.
Sam Kalibala	Regional Representative, Country and Regional Programs, Kenya
Nzeera Ketter	Consultant on Efficacy Trials, U.S.
Sonali Kochhar	Medical Director, Research and Development, India
Jennifer Lehrman	Senior Clinical Program Manager, Research and Development, U.S.
Andrea von Lieven	Clinical Program Manager, Research and Development, Uganda
Megan McBride	Senior Director, Clinical Operations, U.S.
Alex Menezes	Director, Country and Regional Programs, U.S.
Leslie Nielsen	Country Director, Uganda
Kate Taylor	Senior Director, Policy Advocacy, U.S.
Helen Thomson	Regional Clinical Operations Director for Africa, Kenya
Carl Verlinde	Director, Medical Affairs, U.S.

APPENDIX II. Potential Issues in AIDS Vaccine Studies and Lessons Learned

POTENTIAL ISSUES	KEY LESSONS
PARTICIPANTS	
Stigma and discrimination are sometimes encountered by participants	• Locate studies in multi-function sites and facilities • Study staff should work proactively with volunteers on how to disclose their participation • Study staff should have plans/documentation in place for participants who test false positive due to the vaccine, and be prepared to intervene on behalf of volunteers
Trial success depends on the willingness and ability of volunteers to continue participating	• To improve retention, establish convenient hours and comfortable surroundings for volunteers to make follow-up visits • In addition to many other stakeholder groups in the community at large, research teams may need to work with volunteers' employers to ensure that there is buy-in and understanding of the vaccine study from that group as well
RESEARCH STAFF	
Skills development and career experience may require strengthening and longer-term planning	• While global R&D efforts and protocols must adhere to strict standards and maintain consistency, local research teams must also be able to provide substantive input at early stages, and be truly involved in decision making throughout the study • Career opportunities for research personnel are generally positive, but making long-term commitments to trials may restrict growth and mobility; staff retention efforts should consider reasonable salary levels, long-term career development, and possible rotation of staff (including PIs) • Clinical staff have underscored the benefits of collaborating with social science and public health colleagues, particularly in developing communications strategies to work with participants and communities; such efforts have had positive impacts on the studies themselves (recruitment, retention) and should be consistently undertaken
Workload problems encountered by study personnel	• To avoid overworking personnel in public health facilities, vaccine studies need to carefully evaluate human resource needs, and probably rely on project staff to a large extent • It is important that such efforts do not skew local salary structures and that studies minimize departures from public health positions
Vaccine studies are tied to grant funding, and staff positions may not be sustainable when funding ends	• Study sponsors and research institutes should seek ways to even out funding over time to avoid gaps when studies end; this may include diversifying into other types of trials • National governments should consider investments to maintain research sites and capabilities, as a supplement to external funds, and to ensure that established capacity can be maintained consistently

POTENTIAL ISSUES	KEY LESSONS
COMMUNITY	
Need to ensure that broader community understands and supports the vaccine study	• It is essential to have an overall strategy for communicating with the study community, beginning well in advance of study implementation and continuing throughout the duration • It is critical to work with a broad range of stakeholder groups, whether through CABs or other mechanisms • Clinical staff should collaborate with public health personnel, social scientists, and community liaisons to ensure appropriate and adequate communication
Myths and rumors often arise, and expectations about study outcomes and availability of a vaccine are frequently not realistic	• To address such problems research personnel must have a communications strategy in place before the study begins, and should proactively deal with them through the CABs and community engagement • Research teams also need to work with the media, early and often, to ensure that appropriate and accurate messages are disseminated • Messages about the study should provide a realistic picture of what the outcomes would be and the timeline for a vaccine to become available
Vaccine studies can have an important impact on health care services within the community	• The health education and AIDS awareness that result from vaccine studies are felt to be significant; it might be useful to undertake social research studies to measure this impact • Integrating vaccine study activities with ongoing healthcare programs/activities may enable important synergies, not only in terms of raised levels of awareness, but also in terms of greater utilization of STI clinics, reproductive health services, and other programs
HOST COUNTRIES / NATIONAL INSTITUTIONS	
Capacity building for regulatory and related authorities is needed	• Undertaking vaccine studies requires and has often led to the strengthening of capacity to review protocols, study designs, and research activities; this is predicated upon a commitment from host countries to invest in these capabilities, but also translates into greater ability to oversee other research efforts
Countries should build access provisions into their agreements in undertaking vaccine studies	• Governments can and should work with sponsors and manufacturers at very early stages to ensure that adequate provisions are made for access to a vaccine that proves safe and effective • Such negotiations with sponsors should also include specific provisions for treatment and care for those participating in the vaccine studies

IAVI PUBLIC POLICY PUBLICATIONS SERIES

Policy Research Working Papers

POLICY RESEARCH WORKING PAPERS		
#1	Global Investment and Expenditures on Preventive HIV Vaccines: Methods and Results for 2002	September 2004
#2	Promoting R&D in Preventive Health Technologies: Opportunities for the Indian Pharmaceutical and Biotechnology Sector	March 2005
#3	Demand for a Preventive HIV Vaccine: A Review of the Literature	April 2005
#4	Estimating the Global Impact of an AIDS Vaccine	October 2005
#5	Modeling the Impact of AIDS Vaccines: A Review of the Literature	October 2005
#6	Methodologies for Modeling the Impact of a Preventive AIDS Vaccine in Developing Countries: Recent Studies	October 2005
#7	An Advance Market Commitment for AIDS Vaccines: Accelerating the Response from Industry	May 2006
#8	The Impact of an AIDS Vaccine in Developing Countries: A New Model and Preliminary Results	October 2006
#9	A Review of European Commission Funding for HIV/AIDS, Tuberculosis and Malaria Health Technology R&D	December 2006
#10	HIV Vaccine Research & Development: Modeling the Path to Speedier Success	December 2006
#11	Accelerating AIDS Vaccine R&D in India: An Assessment of Obstacles and Possible Solutions	April 2007
#12	The Introduction of New Health Technologies in India	May 2007
#13	Forecasting Demand for Preventive HIV Vaccines in India	June 2007
#14	R&D Models: Lessons from Vaccine History	June 2007
#15	Forecasting the Global Demand for Preventive HIV Vaccines	October 2007
#16	The Journey Toward an AIDS Vaccine: Perspectives on Conducting Trials in Developing Countries	December 2007

IAVI also publishes series of Policy Briefs, Discussion Papers, and other publications on these and other topics. For a complete list of IAVI published materials, please see www.iavi.org.

IAVI gratefully acknowledges the generous support provided by the following major donors.*

Provided with the support of the European Union

Alfred P. Sloan Foundation
Basque Autonomous Government
Becton, Dickinson and Company (BD)
Bill & Melinda Gates Foundation
Broadway Cares/Equity Fights AIDS
Canadian International Development Agency
Continental Airlines
Crusaid
Deutsche AIDS-Stiftung
European Union
Google Inc.
The Haas Trusts
Irish Aid
The John D. Evans Foundation
Kathy Bole & Paul Klingenstein
Merck & Co., Inc.
The Netherlands Ministry of Foreign Affairs
The New York Community Trust
Norwegian Royal Ministry of Foreign Affairs
Pfizer, Inc.
The Rockefeller Foundation
Royal Danish Ministry of Foreign Affairs
The Starr Foundation
Swedish International Development Agency
Swedish Ministry of Foreign Affairs
U.K. Department for International Development
Until There's a Cure Foundation
The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development
The World Bank/Global Forum for Health Research

And many other generous individuals from around the world.

* As of 11/06

IAVI–East Africa
PO Box 340 KNH
Nairobi, 00202
Kenya

IAVI–Europe
Herengracht 208
1016 BS Amsterdam
The Netherlands

IAVI–Headquarters
110 William Street, Floor 27
New York, NY 10038-3901
USA

IAVI–India
193 Floor 1, Jorbagh
New Delhi, 110003
India

IAVI–Southern Africa
Postnet Suite 099
Private Bag X11
Craighall 2024
South Africa