CHAPTER 7
Conducting Phase III Trials of Candidate HIV Vaccines
Challenges in Performing Phase III Trials of HIV Candidate Vaccine

Donald P. Francis

Designing and conducting any Phase III vaccine trial for a new drug or vaccine is a complex and expensive endeavor. Conducting one for a candidate HIV vaccine in a less developed country is an even greater challenge. As two highly successful trials of VaxGen’s candidate HIV vaccines have been completed, one in North America and Europe and one in Thailand, perhaps reviewing the challenges of these trials, highlighting the one in Thailand, could serve well those considering additional Phase III trials in the future.

Before launching into specifics, concentrating on our experiences with the Thailand-based trial, it is best to start this discussion with an overview of the demand for an HIV vaccine. This demand discussion is important as it will surely affect those organizations, primarily pharmaceutical companies, considering entering into late-stage HIV vaccine development.

From the public health perspective, the demand for a vaccine is based on the burden of disease caused by the intended infectious disease target of the vaccine (which for HIV is huge). But from the business side, demand determination involves two very different and important questions. First, for the long term, businesses will ask what potential profits they can expect from the vaccine’s sales once licensed. Second, for the immediate need to test the efficacy of their vaccine,
company executives will ask what interest a population or country may have in participating in a Phase III trial and whether the large amount of money invested in the study will actually result in solid answer to the questions of safety and efficacy. In other words: Is the trial feasible?

**Potential future profits.** For business to invest the hundreds of millions of dollars required to develop an HIV vaccine, the business must answer two additional questions: 1) is there a business opportunity with this vaccine that justifies the expense (i.e. will the financial return from selling the product be significant)?; and 2) is there another business opportunity that is likely to offer a better return on the investment?

Both of these questions pose serious challenges when a pharmaceutical company decides whether or not to invest in HIV vaccine development for less developed countries. Indeed, when compared to any of the “blockbuster”, big selling drugs, even the worldwide market for vaccines as a whole is small - the market for all vaccines is equivalent to but one of the blockbuster drugs. For developing countries, the market (i.e. profits) from any vaccine is tiny (Figure 1).

**Figure 1. Why vaccines fail to compete**

![Why Vaccines Fail to Compete](image-url)
Since the development costs for a vaccine would be equivalent to those for other drugs, one must ask, if I were on the board of directors of a pharmaceutical company, would I support investment in any vaccine? This is a hard question for a vaccine targeted for industrialized countries. It is not a hard question for a vaccine targeted for less developed countries: “No way!”

But there were other issues that drove VaxGen’s decision in Thailand to go ahead. There was a scientific justification that made sense and that scientific justification ultimately drove the business decision to move ahead. It centered around the desire to demonstrate that the candidate vaccine could protect from the two major routes by which HIV is transmitted among adults. For VaxGen, the American-European study explored the potential for protection against sexually transmitted HIV infection [1]. The Thai study was designed to explore the potential for protection against blood-borne infection. It was felt that, for regulatory and public health officials to recommend wide use of a successful HIV vaccine, proof of protection from both routes would be advisable.

Once the decision to go ahead has been made, one must find the money to pay for it. A high-quality Phase III study of this size is expensive. Getting the money to pay for it was a challenge in itself. VaxGen raised private investor money to finance the study. The logic for a private company to pay the tens of millions of dollars to conduct such a study needs to be explored. The hope for the company was to gain data from the study that would lead to the licensure of the product. With a license the company hoped to get profit from selling the vaccine. But significant profit would not be expected for Thailand itself. The market there is too small. Here the company had a dilemma. Thailand was a good place to test a vaccine but a poor place to market one. The decision was made to test regardless of the market because the company felt that, regardless of the market size, the data that would be generated from the study would be valuable for the overall task of developing a worldwide HIV vaccine.

But another scientific challenge complicated the decision whether or not to undertake the Phase III study in Thailand—matching the vaccine to HIV strains circulating among Bangkok Injecting Drug Users (IDUs). When the initial epidemiologic studies were conducted in Bangkok, the virus infecting drug users was quite similar to the subtype B used to make the first generation vaccine. This was important to VaxGen because it meant that the company could use the same vaccine in
Thailand that had been developed to prevent the subtype B infections in North America and Europe. Since developing each new strain into a vaccine is expensive (millions of dollars) and time consuming, it was hoped that VaxGen had to develop but one candidate vaccine to test in both places.

But that was not to be. Towards the end of the 1990s, the Thai subtype E virus (actually an A/E recombinant) entered the IDU population and began to replace the subtype B virus. It could not be ignored. As a result, VaxGen turned to Genentech to revive its HIV vaccine manufacturing effort and make a candidate vaccine containing envelope proteins from both subtype B and subtype E viruses. This vaccine was called “AIDSVAX B/E”.

Trial feasibility. Few things are worse for a company than investing millions of dollars in a Phase III trial only to have the trial fail to provide solid answers to the question of efficacy. Companies are willing to take risk of scientific failure of a candidate vaccine. Scientific failure, although not pleasant, is acceptable. It’s truth - a reality of the acquisition of knowledge. However, study conduct failure, where a large investment produces ambiguous results or no results at all, is not acceptable.

Thus, as a company, government or academic institution interested in conducting a Phase III trial searches for a site, they will look for a constellation of factors that will maximize the chance for success of the study. First in this constellation will be commitment of the people and their government to have a vaccine, in this case for HIV. Without commitment of the society, concern for the disease and a desire to help develop a vaccine for at least a segment of the society, it is not possible to successfully conduct a Phase III trial. Fortunately, for our trial in Thailand, the government of Thailand and its people were very concerned about HIV/AIDS and understood the immense need for a vaccine to prevent it.

To this point, both the National Thai Government and the Bangkok Metropolitan Government, through early partnering with the World Health Organization (WHO), the US Centers for Disease Control (CDC) and others, had done much to demonstrate both their interest in undertaking HIV vaccine trials and the feasibility of conducting Phase III trials in at risk people in Thailand. These collaborating groups had conducted pilot studies to determine the rates of infection among potential volunteers and, through follow-up of at risk volunteers, determined
what proportion would likely continue in studies over several years. As a result of these efforts, in 1993 the WHO identified Thailand as a potential WHO-sponsored vaccine site for HIV vaccine trials [2].

Important for those of us interested in conducting HIV vaccine trials in high risk volunteers in Thailand, an official government process was established through vaccine testing proposals could be approved. Moreover, with Thailand’s long tradition of strong medical education, there was university centers with which one could join in collaboration. Foremost in this arena was Mahidol University’s Vaccine Trial Centre having medical and nursing staffs with extensive experience in the conduct of vaccine trials.

Both of these, the official government approval process and the availability of competent local collaborators, markedly facilitated the conduct of VaxGen’s Phase III trial. From all sides of this complex effort, the involvement of both WHO and CDC allowed for the early establishment of trusting relationships between all parties. Especially since one party was a profit-motivated pharmaceutical company, having trusted third parties (trusted by all sides) with which all involved could discuss issues and smooth out bumps was invaluable.

Other challenges. Anytime one decides to undertake a complex phase III trial in a distant land, there are many other challenges that had to be addressed. Some key ones are: sponsor oversight, data management, laboratory testing, regulatory oversight, ethical, financial and structural issues. Let’s look at these individually.

Oversight, to ensure proper conduct of a study, is essential when one invests millions of dollars into a study. The Thai trial, with approval of the U.S. Food and Drug Administration, was part of critical path that was intended to lead, ultimately, to the vaccine’s approval. Thailand was well organized in this regard. Before VaxGen arrived on the scene, a history of international collaboration had been established in Bangkok. The local government agency, the Bangkok Metropolitan Administration (BMA), had been accustomed to working with international public health collaborators. Indeed, Dr. Kachit Choopanya, who headed up the health side of the BMA, had spent his early years establishing, with considerable international collaboration, the methadone treatment program in Bangkok. Moreover, in the years preceding the start of the study, he, together with the World Health Organization and the Thai branch of the U.S. Centers for Disease Control, had extensively investigated the epidemiology of HIV in Bangkok’s IDU population [3].
His personal familiarity with IDUs and the clinics that cared for them made him an ideal candidate for being the leader of the Phase III study.

With oversight of the clinics assured, the next issue was data management. With a study of 2,500 volunteers followed for 3 years having multiple interviews, medical examinations and laboratory assays, the data management task was large. This was especially challenging given the new regulatory quality requirements for such studies. Fortunately, Dr. Dwip Kitayaporn at the Faculty of Tropical Medicine at Mahidol University was interested in establishing a world-class data management center for Thailand. VaxGen committed to equipping and training the staff for this center that continues to operate today.

Given the thousands of blood specimens that needed to be processed, tested and shipped to our labs in the U.S., a strong, organized and experienced laboratory was required to manage the thousands of blood specimens from the study. Fortunately, the BMA’s own laboratory was interested in taking on this task. Under the guidance of Ms. La-Ong Srisuwanvilai, who headed the lab, VaxGen equipped and trained the staff in all of the Good Laboratory Practices necessary to conduct a world-class study.

The Good Clinical and Good Laboratory Practice requirements were new to Thailand and required in-depth training and follow-up assessment of everything from the clinic to the laboratory to the data management systems. Once trained, all of the Thai staffs performed outstandingly. Dr. Punnee Pitisuttithum led the clinical team that was responsible for all of the highly regulated clinical tasks including clinical examinations, clinical records and storing and administering vaccine/placebo.

To assess the study conduct, multiple visits by VaxGen staff and outside consultants were arranged throughout the study period. In addition, international assessment of the ethical conduct of the study was conducted by WHO/UNAIDS.

Study conduct using high ethical standards was required by all of parties involved in the review and approval of this study (Table 1). Many of the procedures for conducting a study with such ethical standards were well known and had been practiced by the collaborators. However, specific issues surrounding studies of IDUs, given their illegal activities and their frequent incarcerations, brought up new challenges. Moreover the ethical review of HIV vaccine trials required the establishment of a new Thai national ethical review system. For this the WHO/UNAIDS assisted the government in their planning, review
and execution of this new system. Despite the challenges, the initial review process and ongoing ethical reviews went well over the study period.

Table 1. List of institutional review boards for the phase III AIDSvax® study in Thailand

<table>
<thead>
<tr>
<th>Institutional review boards</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Technical Subcommittee on AIDS Vaccine, National AIDS Committee, Thailand</td>
</tr>
<tr>
<td>* Ethical Review of Research Committee, Ministry of Public Health, Thailand</td>
</tr>
<tr>
<td>* Institutional review boards:</td>
</tr>
<tr>
<td>- Committee on Human Rights Related to Human Experimentation, Mahidol University, Bangkok</td>
</tr>
<tr>
<td>- Ethical Committee of the Bangkok Metropolitan Administration, Thailand</td>
</tr>
<tr>
<td>* UNAIDS Vaccine Advisory Committee, UNAIDS Ethic Review Committee and selected external reviewers</td>
</tr>
<tr>
<td>* Centers for Disease Control and Prevention Institutional Review Board, Atlanta</td>
</tr>
<tr>
<td>* Office for Protection of Research Rights, NIH</td>
</tr>
</tbody>
</table>

One of the key ethical issues involved the potential harm that participating in the trial could place upon volunteers. One, the harm from the vaccine itself, appeared minimal at the time of the start of the trial, but the possibility of other harms was less certain. The major one of these was the possibility that volunteers, despite advice to the contrary, would assume protection from the vaccine and increase their risk-taking behaviors. Such potential risk was publicly stated by some as a reason not to proceed with the Phase III trial in Thailand. By design, data from the trial provided assurance that such a trial could be conducted without harm and indeed decrease the risk of volunteers [4].

Finally, it is worthwhile to discuss the structural issues of the study. By structural issues I mean the organizational pieces that had to be put in place to actually conduct the study. People are the key to successfully doing these complex studies. But without a structure through which they can operate, the undertaking could fail despite the assembly of a talented team.
To ensure success of the Thai trial all collaborating parties were incorporated into a single group called the Bangkok Vaccine Evaluation Group (BVEG). Dr. Kachit Choopanya chaired the group and was the Principal Investigator (PI) for the phase III study. BVEG had a very elaborate structure (Figure 2) that, besides the collaborating research institutions, incorporated a variety of government and community leaders. Overall oversight required the construction of a new office complex to house the PI. In addition, VaxGen supported its own physician on site (Dr. Sricharoen Migasena) and its own clinical research associate (Ms. Carolyn Geel). Meetings of all key parties were held regularly to air all issues and plan for solutions. Such meetings were crucial to ensure that the expertise and needs of all parties (clinical recruitment and follow-up, data management, laboratory testing, regulatory affairs, etc.) were addressed.

In the end, this complex trial was completed with the highest of international standards (See Punnee, et al in this book). The trial did just what it was supposed to do—demonstrated, in a highly ethical way, whether or not the candidate vaccine induced protection against HIV-1 infection. All involved should be proud of what they did.

---

**Figure 2. BVEG structure**

- **VaxGen Inc.**
  - Donald F.
- **Principal Investigator**
  - Dr. Kachit Choopanya
- **ADVISOR**
  - Dr. Praphan K.

---

- **BMA**
  - Director: Dr. Krit H.
  - BMA Clinic Coordinator Team: Dr. Suphak V.
  - BMA Medical Services Team: Dr. Wanachat S.

- **Mahidol U.**
  - VTC-GCP Monitoring Team: Dr. Punnee P.
  - VTC-Data Management Team: Dr. Dwip K.

- **TUC**
  - TUC = Thai MOPH-US CDC Collaboration
  - HAC = HIV AIDS Collaboration

---
References


CHAPTER 7

CHALLENGES IN PERFORMING PHASE III TRIAL OF HIV CANDIDA
Phase III Efficacy Trial of Bivalent B/E rgp120 HIV Vaccine (AIDSVAX® B/E) in Bangkok

Punnee Pitisuttithum
Suphak Vanichseni
Dwip Kitayaporn
Kachit Choopanya

Preamble: “The reputation of the country now lies on your shoulders”

“The late Professor Natth Bhamarapravati, former President of Mahidol University, founder of the Vaccine Trial Centre (VTC) and, at that time, chair of the technical subcommittee on AIDS vaccines informed me in early 1999 that the technical subcommittee had granted the final approval for the Phase III trial. At that moment, I suddenly understood the full extent of the responsibility that I and the other members of the team were undertaking. Yet, at that time, I was not thinking of my own professional career, or the amount of work this trial would require for the following three or four years. 1998-2003 was the toughest period in my career”.

“My only thinking was that if I were going to be the principal investigator, the trial has to be successful!”

This is what one of us (Kachit Choopanya), then Deputy Governor of the Bangkok Metropolitan Administration (BMA) said at that time, when he was proposed as the Principal Investigator for the trial. It was a very strong commitment and strong determination. This was one of the most important factors leading to the success of the trial.

Punnee Pitisuttithum
CHAPTER 7

PHASE III EFFICACY TRIAL OF BIVALENT B/E RGP 120 HIV VACCINE (AIDSVAX® B/E) IN BANGKOK

Historical background

Soon after launching the Thai National AIDS Vaccine Plan in 1993, preparations were initiated to conduct a phase III efficacy trial of an HIV-1 vaccine. Requirements for conducting candidate HIV vaccine efficacy trials included: the availability of a suitable candidate vaccine matching the virus circulating in the target population, a suitable cohort of volunteers having well characterized incident viruses, a high follow-up rate among potential volunteers, the willingness of the community to participate in the trial, and strong political commitment at both national and institutional levels.

In 1995, the World Health Organization (WHO) and, later, the US-Centers for Disease Control and Prevention (CDC) initiated support for the Bangkok Metropolitan Administration (BMA) cohort study, which was conducted in 15 narcotic treatment clinics in Bangkok. A total of 3,643 injecting drug users (IDUs) were screened and 1,209 were enrolled into this study. The HIV incidence rate was found to be 5.8% per person-year and subtype E strains accounted for 79% of infections. This study demonstrated a high willingness of the IDUs to participate in the trial as well as high follow-up rate after joining [1].

Concurrent with the development of the BMA cohort, a Phase I/II evaluation of the safety and immunogenicity of a rgp120/subtype B, monovalent (AIDSVAX® MN) vaccine was conducted between 1995-1996. This was followed by another phase I/II trial of the AIDSVAX® B/E vaccine in 1998-99 [2]. Based on both the encouraging immunological responses and safety profile of the vaccine, together with the overall success cohort preparation [1,3], the decision was made to advance to a phase III efficacy trial among 2,500 IDUs in Bangkok. This advancement proceeded in concert with continuous consultation between the investigator, sponsors, and the Thai Technical Subcommittee on HIV Vaccines.

Phase III efficacy trial of AIDSVAX® B/E in Bangkok Thailand

The study was approved by the Technical Subcommittee in March 1999. It was a randomized, double blind placebo controlled trial designed to assess the protective efficacy of a rgp120 B/E candidate vaccine. Volunteer screening and recruitment were conducted between March 1999 and August 2000 among injecting drug users (IDUs) attending 17
narcotic treatment clinics operated by the BMA. The inclusion criteria were: IDU of either sex who possessed Thai National Identification, aged 20-60 years, negative HIV tests at screening and baseline, history of intravenous drug use in the previous 12 months, and who were able to understand the study (by passing a comprehension questionnaire twice) and able to give written informed consent. Pregnant and lactating women were excluded from the study. During each visit, volunteers were educated about how to reduce the risk of HIV infection. Risks behavior and social harm assessment questionnaires were administered every six months.

The study vaccine contained two rgp120/HIV-1 envelope antigens one derived from a subtype B virus and the other derived from a subtype E virus. Both the candidate vaccine and placebo were administered through intramuscular injections at months 0, 1, 6, 12, 18, 24 and 30. In addition to HIV tests, at each visit, adverse events and possible social harms were assessed. HIV-1 testing was preformed during each follow-up visit. For those volunteers who seroconverted to HIV during the study, plasma HIV-1 RNA and CD4/CD8 counts were determined at <1, 1, 2, 4, 8, 12, 16, 20 and 24 months after diagnosis of HIV infection.

**Results**

From March 1999 to August 2000, a total of 4,943 IDUs were screened and 2,546 eligible, consenting IDUs were enrolled. The median age was 26 years (range 20-59), 93.4% were male and 67.3% had at least secondary education. At baseline, 92.4% of the participants were injecting heroin (the remainder were taking stimulants or tranquilizers on a regular basis). Of these, 61.3% were on methadone detoxification and 20.9% were taking methadone maintenance [4]. The reasons for participation were: wanting to know HIV information (96.5%), altruistic reasons (95.8%), wanting to test for HIV infection (95.6%), and wanting to have a physical examination (94.5%) [4].

The candidate vaccine was found to be safe and well-tolerated. The most commonly reported side effect was tenderness and soreness at the injection site. Severe adverse events were reported among 414 volunteers but none were attributed to receipt of the vaccine [5]. The overall vaccination compliance rate was 97.6%. A total of 102 volunteers died during the follow-up period. The most common causes of death were: drug overdose 38 (37.3%), sepsis 17 (16.7%), and accidental injury 12 (11.8%).
HIV infection occurred in 106 (8.4%) vaccine recipients and 105 (8.3%) placebo recipients. The overall annual HIV incidence rate was 3.4% per person-years. There was little change in incidence by the 6-month time period. There was no significant difference between the vaccine and the placebo recipients who became infected with regards to level of viremia, CD4 counts, onset and clinical course of AIDS-defining conditions or time of initiation of antiretroviral therapy. It was concluded that there was no protective efficacy of the candidate vaccine with regards to the study’s primary outcome assessment [5].

During the first 12 months of follow-up, the high risk behaviors of injecting drugs declined from 93.8 to 66.5%, and needle sharing declined from 31.0 to 11.7%. These changes remained stable for the remainder of follow-up. Overall, social harm events, such as discrimination and loss of opportunity, were infrequent. Over the study period, 39 events were reported by 37 volunteers. All were of minimal-to-moderate impact. The vast majority (33) were related to the volunteers’ personal relationships. All social harm events were resolved [5].

Challenges in conducting an efficacy study with injecting drug users

IDUs are a challenging group for any research, especially for a project that requires 3 years of follow-up. The main issues we struggled with were:

- Establishing the logistical and organizational structure required to successfully complete such a study in this population
- Harmonization of the work of multiple collaborators with different backgrounds and coming from different institutions
- Establishment, training and maintenance of high quality teams able to conduct such a study using the highest international standards
- Design of a recruitment process that ensures true voluntary participation of a group whose activities outside the clinic often violate the law
- Maintaining the quality of the trial and the interest and spirit of both the participants’ and the staff during a 3 to 4-year trial period

To ensure the quality of the trial and to obtain and maintain support from all necessary authorities, an advisory board was established by the principal investigator (PI). Members of the board...
included the Deputy Governor of Bangkok (Dr. Praphan Kitisilp), the President of Mahidol University (Prof. Pornchai Matangkasombut), the former Permanent Secretary of the Ministry of Public Health (Dr. Paichit Pawabutr), and a representative from VaxGen Inc. (Prof. Sricharoen Migasena). The trial was run by six coordinators under the leadership of the PI, as shown in the Diagram 1.

Diagram 1. Administrative structure of the BVEG
Throughout the trial, there were weekly meetings of the key coordinators, laboratory representatives and the PI. At these meetings, problems were discussed and solved. Updates on the progress of the trial were provided every month to members of the advisory board, to key players and to the relevant national authorities.

Review and approval process

The protocol was reviewed and approved by various institutional ethical review boards, including those from Mahidol University, BMA, CDC, Thai Ministry of Public Health and the Technical Subcommittee under the National AIDS Commission, in consultation with UNAIDS and the US FDA. As a final step, the protocol was submitted to the Director General of the Department of Disease Control (DDC) for final approval [6].

Setting up a good clinical practice (GCP) clinical team

Conducting a Phase III trial under GCP is a challenge. Conducting one involving IDUs in a less developed country is an even greater challenge. For this study, we took advantage of the Vaccine Trial Center (VTC) of Mahidol University which had considerable experience in conducting phase I and II trials of different candidate vaccines. To its existing infrastructure, we added several new components to bring it up to the new international regulatory standards. For example, we added one research nurse to co-ordinate activities and to perform the detailed clinical research work in close coordination with physician-Director of each of the 17 BMA clinics (or his/her designees). Next we added a layer of internal monitoring by assigning four physician supervisors from the VTC to oversee the clinical responsibilities - Dr. Punnee Pitisuttithum (the GCP coordinator), Professor Emeritus Pavan Suntharasama, Professor Emeritus Swangjai Pungpak, Dr. Valai Bussaratid and one senior research co-ordinator, Associate Professor Benjaluck Phonrat. All staff were extensively trained on current GCP standards, details of the protocol, Standard Operating Procedures (SOP), use of a counseling manual, how to record the source documents and on how to extract data onto the Case Report Forms (CRF). Such training was not difficult, since most of the staff had participated in the previous phase I/II studies.
During the 3.5 years of the study, the clinical team held weekly meetings. During these meetings, the nurse co-ordinators reported all the activities that occurred during in the past week at each clinic to the team members, and advice and recommendations were made on ways to solve the multiple issues that arose during the trial. Higher level policy issues were referred to the weekly meetings of the key coordinators.

**Counseling team**

There were teams of three social workers and a psychologist at each of 17 BMA narcotics treatment clinics. These teams provided counseling to: 1) reduce drug use, or to encourage drug abstinence; 2) to avoid harmful injection and sex-related risk behavior; and 3) to encourage HIV risk reduction in general.

The guidelines for HIV risk reduction counseling in the trial were developed based on the CDC risk reduction counseling guidelines and the handbook for pretest-post-test counseling published by the Drug Treatment and Prevention Division of BMA, in 1991.

**Pre-trial run-in period**

In each of the participating clinics, counselors were trained how to provide education and counseling and to respond to specific questions. In addition, the research nurses were trained on each step of the clinical activities as required by the SOPs. Before being assigned to a clinic each nurse was evaluated by the physicians. This ensured that the correct procedures were practiced in a standardized way across clinics. To ensure standardization, two to three rounds of practice runs were conducted before starting the trial.

**Trial phase**

The trial was initiated in March 1999. To ensure that all staff was in good practice before the full-scale launching in May 1999, the clinics opened in sequence.
Recruitment activities

The 17 BMA narcotic treatment clinics achieved the target enrollment of approximately 200 participants per month for the initial 6 months. However, it declined somewhat thereafter (Graph 1).

Graph 1. Recruitment mechanisms leading to successful screening and enrollment of 2,545 injecting drug users in the AIDSVAX® B/E HIV vaccine trial in Bangkok, Thailand, March 1999 through August 2000.

Number Screened and enrolled by quarter Jan. 1999-Sept. 2000

From Vanichseni et al. (2004), AIDS 18(2): 311-316

To complete full enrollment, several additional recruitment strategies were employed. These included: 1) opening of additional recruitment sites, such as suburban health clinics; 2) establishing and expanding mobile clinics; 3) extending clinic working hours; and 4) placing advertisement messages in the mass media (TV, radio, posters, etc.). Finally, to enlarge the profile of the study within the IDU community itself, volunteers were encouraged to contact friends who might be interested in joining the study. This became known as the “friend-refers-friend program”. These recruitment mechanisms are summarized in Table 1.
Informed consent process

Each participant was educated about all aspects of the study through the combined use of video, booklet flipchart, and group and individual discussions. To ensure that all prospective trial volunteers understood the presentations, a comprehension questionnaire consisting of 20 true/false questions, including required must-know questions, was used. Volunteers “passed” by getting 80% marks, including all the questions considered as “must know”, such as what the vaccine is, confidentiality issues, right to withdraw, etc.

Risk reduction counseling

Participants were given risk-reduction education in groups or individually. Risk reduction counseling has been in regular practice at the clinics since 1989. Advice was given to stop drug use. Indeed, if an individual was able to quit using drugs, he/she was encouraged to share the achievement with friends. If, despite counseling, injection continued, advice was given to change the route of administration, e.g., from injection to inhalation or ingestion. If that was not possible, then it was recommended to change to a new needle and syringe for each injection.

Table 1. Recruitment mechanisms leading to successful screening and enrollment of 2,545 injection drug users in the AIDSVAX® B/E HIV vaccine trial in Bangkok, Thailand, March 1999 to August 2000.

<table>
<thead>
<tr>
<th>Recruitment Mechanisms</th>
<th>Number of IDU enrolled</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruiting attendees of drug treatment clinics</td>
<td>1,105</td>
<td>43.4</td>
</tr>
<tr>
<td>Recruiting referrals from IDU referral program*</td>
<td>519</td>
<td>20.4</td>
</tr>
<tr>
<td>Recruiting preparatory cohort study participants</td>
<td>374</td>
<td>14.7</td>
</tr>
<tr>
<td>Recruiting suburban health clinic attendees</td>
<td>240</td>
<td>9.4</td>
</tr>
<tr>
<td>Extending drug treatment clinic</td>
<td>89</td>
<td>3.5</td>
</tr>
<tr>
<td>Using mobile van clinics</td>
<td>72</td>
<td>2.8</td>
</tr>
<tr>
<td>Disseminating mass media information messages (TV, radio, poster or flyer)</td>
<td>19</td>
<td>0.8</td>
</tr>
<tr>
<td>Other</td>
<td>127</td>
<td>5.0</td>
</tr>
</tbody>
</table>

*enrolled injecting drug users referring other injecting drug users to Bangkok Metropolitan Administration drug treatment clinics for screening and possible enrollment. (Vanichseni et al. (2004), AIDS 18(2): 311-316)
Many of clinic clients could do that. If not, they were advised to clean the equipment with bleach which was provided free by the clinic. Condoms were also provided free of charge at each clinic. Since incarceration leads to a higher risk of HIV infection [1,7] all counsellors led group discussions to help the volunteers obey the laws. To prevent drug overdose after release, volunteers were advised that, if they were arrested, they should reduce their drug dose after being discharge from prison.

Retention activities

Every participant was provided with a project identity card and clinic appointment dates. During the trial, two postcards containing the addresses of the clinic were provided to each participant. Whenever they had to leave home, were hospitalized, left for another province, or went to prison, they were requested to mail the postcard to the clinic to advise the staff of their new or temporary address and telephone number.

About 60% of the volunteers came for every appointed visit, on time and without staff’s effort. Telephone and/or letter reminders were made to the others. With time, mobile teams were strengthened to do more home visits. Home visits were routine for the counselors at the clinics even before the study began. To ensure that such visits were acceptable to the volunteers, such approval was included in the consent form. Such approval included both home and incarceration visits. For incarceration visits, such follow-up, required the mobile team to go to a variety of places including the provincial prison, provincial treatment centers or military camps.

Treatment and care [8]

BMA provided free comprehensive medical care for any HIV infected clinic attendees. This included counseling and education, screening for tuberculosis and other opportunistic infections (OI), monitoring of CD4 counts and antiretroviral therapy. Out of the 209 IDUs found to be HIV-infected during the pre-trial screening 15 were found to have active tuberculosis (by clinical examination and chest x-ray) and received Directly Observed Therapy-short course (DOTs). The remaining 180 cases who had no active tuberculosis received isoniazid
prophylaxis according to then BMA HIV treatment guidelines. Eleven participants refused or did not require INH prophylaxis.

As the BMA was the venue for the study, BMA guidelines were used to guide HIV-specific therapy. For example, the BMA guidelines recommended cotrimoxazole weekly for OI prophylaxis when CD4 count is less than 200 cells/µL. A total of 39 HIV-infected individuals at screening had CD4 counts less than 200 cells/µL, out of which 30 (77%) took cotrimoxazole regularly. The remaining 9 refused or stopped treatment due to side effects or were loss to follow-up. Antiretroviral therapy was also provided according to the BMA guidelines. Table 2 summarizes antiretroviral therapy outcomes.

Table 2. Outcome of antiretroviral therapy (ART) among seroconverted IDU.

<table>
<thead>
<tr>
<th>Antiretroviral therapy</th>
<th>Initial guideline (1998)</th>
<th>New guideline (October 2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants qualified for ART</td>
<td>79</td>
<td>18</td>
</tr>
<tr>
<td>On ART</td>
<td>34 (43%)</td>
<td>10 (55.6%)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>11 (13.9%)*</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Stopped because of side effects</td>
<td>4 (5%)</td>
<td>3 (16.7%)</td>
</tr>
<tr>
<td>Died</td>
<td>7 (8.9%)</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>CD4&gt;200 and decided to stop</td>
<td>23 (20%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*includes participants who refused treatment.

As part of a government insurance scheme, the project provided health insurance to all participants during the trial period. Even with such insurance, compliance to antiretroviral therapy was a challenge. Adverse events were one of the factors contributing to poor compliance. Interestingly, compliance improved with incarceration, as treatment was administered by prison staff.

Community relation club (CRC)

The concept of Community Advisory Boards (CAB) was a challenge with injecting drug users as no organization existed that could well work with us. After the study was launched, a Community Relation Club (CRC) was established that included parents, community leaders and IDUs (both HIV negative/positive and female/male). A total
of 14 bi-monthly meetings were held. The major issues discussed during the meetings included study confidentiality, study benefits to participants, community risk behavior changes and access to antiretrovirals and OI prophylaxis for HIV infected participants [9]. New information relevant to the trial, such as the results from the related study in western hemisphere, was also provided to the club members for further distribution to friends and their families.

Lessons learned

Review and approval processes

A wide variety of Institutional Review Boards (IRB) or Ethics Committees (EC) reviewed this study. Often, the members of these groups had very broad professional experience dealing with IDUs and incarceration. These experts provided assistance and constructive advice regarding both the design and management of the study. On the other hand, with such a multi-stage review and approval process, the time consumed was long. In the end, it took about one year to gain full approval. However, recognizing that this was the first time in history that an HIV vaccine efficacy trial was to be carried out in a developing country among IDUs, the reasons for the delay seemed acceptable.

Team Preparation

Initially, little emphasis was placed on writing detailed counseling notes. At the time, more emphasis was placed on counseling methodology and proper filling out of CRFs. As a result, it was difficult to monitor counseling activities during the initial stages of the trial. This weakness was realized with time and corrective actions were taken.

Recruitment and Retention

It was initially expected that a high proportion of the volunteers recruited for the preparatory cohort would join the phase III trial. However only 347 (14.7%) of these volunteers eventually joined the phase III trial. This was probably due to the delay in trial approval, during which time the volunteers either lost their interest, changed their route of drug use (such as the oral route), or shifted to other drugs (like medazolam and/or amphetamine). An immense effort by a truly devoted staff was required to achieve a high retention rate, (approximately 90%) in this study. Since most of the staffs were women, sometimes
this created difficulties for the visits outside the clinic. According to Thai customs, women should go to places in groups of at least two. This led to considerable difficulties when making jail visits.

**Trial Conduct**

The conduct of the trial complied with GCP guidelines. This was mainly achieved through multiple factors: good team efforts, great leadership and supervision from the top, the hard work of all levels of staff, and the training of nurses, counselors, and other team members. Other major contributing factors for success were the regular supervision and monitoring by staff from the VTC and VaxGen, Inc.

The independent Data and Safety Monitory Board (DSMB) evaluated safety issues throughout the trial. In addition, a WHO advisory team and the counseling monitoring team evaluated the counseling and education techniques used by the staff during the trial. Constructive advice from these groups contributed to improving counseling skills among the staff. The study team managed to establish good working relationships with all collaborators (government authorities, advisory committees and participants) and sponsors, which contributed to the successful completion of the trial.

**Risk Reduction Counseling**

An excellent effect of risk-reduction counseling was documented during the first 12 months of follow-up. During this time, high risk injection behaviors decreased from 93.8 to 66.5%, and sharing of needles reduced from 31.0 to 11.7%. Despite continued intensive counseling, these changes remained stable for the rest of the follow-up period. Importantly, despite initial concerns that volunteering for a preventive vaccine study might increase risk-taking behaviours, we could detect no evidence of increased risk during the study.

**Treatment and Care of Participants**

Some participants expected that the clinics would provide free treatment and care of every medical event that occurred during their participation in the trial. Sometimes it was difficult to deal with these high expectations. But, fortunately, the local self-administered BMA government system was able to provide free medical treatment over and above that which could be provided by the drug treatment clinics.
Antiretroviral compliance is a challenge when treating IDUs. The staff had to reinforce the need for antiretroviral drug compliance at every visit. Sometimes a clinic staff member had to accompany participants to the hospital to see the doctor who would explain the importance of compliance.

Administration

The success of this study required full participation by all members of the collaborative team. The PI set the standard by recognizing the importance of each partner. This was a very important factor in holding all of the partners together. Meetings among the higher authorities and collaborators occurred monthly to update everyone about the trial. These meetings were important to convey the sense to all staff, including that in the field, that the trial was receiving full support from all levels.

There were weekly meetings among key coordinators, laboratory representatives and the PI. This was a key factor in moving things along quickly. Between-meeting communication by phone was also important in case of urgency.

As this study plowed new ground at every step, everyone had to "think outside of the box". Since this type of research activity needs quick actions and solutions, stiff bureaucracy had to be avoided. Having an open mind was the key to ensuring that all the necessary things were done to make this endeavor a success.

Each collaborator had opportunities to present his/her work in various national and international scientific meetings throughout the 4-year period. On the average up to six scientific abstracts were submitted annually to scientific conferences, and these were presented as the work of the entire BVEG team. These activities were strengthened and supported by staff from VaxGen, Inc.

An International Advisory Board which consisted of Dr. José Esparza from WHO-UNAIDS (now with the Bill & Melinda Gates Foundation), Dr. Xu Zhi-Yi from the International Vaccine Institute in the Republic of Korea, and Prof. Roel A. Coutinho, from the Health Department in Amsterdam, Netherlands, was established. With their broad experience in many vaccine trials and IDU studies, they provided very fruitful advice at various stages of the trial. Special areas of advice included how to increase recruitment, or follow participants who were incarcerated while keeping within the standards of good ethical
practices. Advice was also given on how to deal with the impact of the results of the North American VaxGen trial on the Thai trial, especially if the candidate vaccine showed no efficacy. In addition, recommendations from a WHO-UNAIDS Ethical Review Team (led by Dr. Ruth Macklin) resulted in improvements regarding how best to maintain participant’s confidentiality while communicating between the project and other government institutes. The WHO-UNAIDS Review Team also recommended the use of triple antiretroviral regimen as a treatment of choice for the HIV infected participants in late 2001.

Discussion

On the whole, good coordination, strong determination and leadership, excellent team work and devotion of both staff and participants led to the ultimate the success of this trial. One of us was asked in a meeting “What should be done to improve such a trial if we have a chance to conduct another trial in the future?” More community engagement was our answer. It was difficult to have community involvement, especially in 1999. The concepts of community engagement and community advisory boards were new at that time in Thailand. And it proved to be a real challenge with IDUs. Injecting drug use is illegal, and IDUs tend to live isolated and secretively. Too much publicity would have not been good for the volunteers, since they would then be recognized as IDUs.

Finally, we would like to thank all the volunteers and our staff for bringing this trial to a successful outcome.
References


The Rayong-Chonburi Community Phase III HIV Vaccine Trial

Supachai Rerks-Ngarm
Punnee Pitisuttithum
Dwip Kitayaporn
Chirasak Khamboonruang
Sorachai Nitayapan
Arthur E. Brown
Deborah Birx
Jerome H. Kim
Prayura Kunasol

Background

In 2000, a Phase I/II trial was conducted to assess the safety and immunogenicity of ALVAC-HIV (vCP1521) priming with two doses of AIDSVAX™ B/E boosting in HIV-negative Thai adults. Both candidate vaccines matched local subtypes prevalent in Thailand. The prime-boost vaccination with ALVAC-HIV (vCP1521) and AIDSVAX™ B/E appeared to be safe and well-tolerated among the participants; moreover, it induced both cellular and humoral HIV-specific immune responses. Therefore, in 2003, the vaccine combination was found to be an appropriate candidate for advancement to phase III evaluation.

The phase III trial is a community based, multi-center, randomized, double-blind placebo-control study, involving 16,000 eligible volunteers between the ages of 20-30 years. The primary objective is to determine whether immunization with ALVAC-HIV (vCP1521) boosted by AIDSVAX™ B/E gp120 protects Thai volunteers from HIV infection. The secondary objective is to determine the effect of vaccination on the steady-state phase of viremia and CD4+ after intercurrent infection by powering to detect 0.3 log viral load difference in the context of primary outcome equipoise. All study participants receive ALVAC HIV or placebo priming at 0,4,12, and 24 weeks.
Boosting doses of AIDSVAX® B/E or placebo are given at 12 and 24 weeks [1,2]. Female volunteers are screened for pregnancy prior to enrolment, and those found positive are excluded. The enrolment period is approximately one year [1].

To comply with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice (ICH-GCP), research ethics, and to ensure comprehensibility among Thai volunteers, the informed consent form was drafted first in the Thai language and then translated into English. The informed consent process involved group or individual discussions, questions and answers, booklets and video presentations. All volunteers who provided informed consent after passing a comprehension test are enrolled into the study [3].

Rayong and Chonburi provinces were chosen as the study sites (Chapter 6, Community Cohorts in Rayong and Chonburi). A total of seven district hospitals, one sexually transmitted infection (STI) clinic and over 40 health centers have been reinforced and selected for screening and vaccination sites [1]. The study is being conducted under two separate protocols-RV148 for screening and RV 144 for enrolment. The total follow-up time is three years. After the six-month vaccination regimen is completed, follow-up is schedule at six-monthly intervals. Immediate vaccination related reactions are evaluated within the 72-hour post-vaccination period. Subsequent assessment of vaccine- or placebo-related adverse events and HIV risk behaviors is carried out at each vaccination visit and at the six-month follow-up visits. HIV testing is conducted at 24 weeks and at each six-month follow-up visit. Standard pre- and post-test counseling is performed before and after HIV testing, respectively. Blood for plasma is collected and stored at baseline, 24, 26 weeks, and every six months during the follow-up period. Peripheral blood mononuclear cells (PBMCs) are collected and stored at baseline, 6, 12, and 42 weeks [1].

The safety profile of this study is monitored by an International Data and Safety Monitoring Board (DSMB) consisting of members from Mahidol University, Chulalongkorn University, and other academic institutes in the U.S.A., and is chaired by Prof. Walter R. Dowdle from the Task Force for Child Survival and Development. The board conducts safety reviews every six months [1]. Furthermore, a pharmaco-vigilance committee has been established to monitor safety [4]. As at the end of November 2005, 16,093 volunteers had been screened of whom 11,603 enrolled in the study.
Challenges in conducting a community trial

- Determining the optimum structure for dealing with a large, complex trial involving 16,000 participants.
- Maintaining the political commitment and interest of various administrators and collaborators.
- Coordinating and harmonizing various levels of administrators within the Ministry along with the various collaborators to work as a team, to move the project forward quickly, efficiently, effectively, and finally make the project successful.
- Recruiting and retaining all participants for a 3-4 year period in the trial.
- Engaging the community in the trial area (Chonburi and Rayong), conducting community education and raising awareness of the community about the AIDS epidemic and the need for a preventive HIV vaccine (since the trial involves a large number of participants).
- Matching the anticipated workload with the appropriate number of personnel: for example, to screen close to 25,000 participants for enrollment, to prepare and give approximately one hundred thousand injections during the trial (approximately 60-80 participants per day per clinic at eight clinical sites), to follow, to record and report the safety profile of each participant and to provide education and counseling, including risk reduction education, for a 3-4 year period.
- Determining where and how to store and manage approximately one hundred thousand vaccine vials both upon arrival and at the clinical sites. How the vaccines are to be transported and maintained at the proper temperature at the sites. What the emergency plan should be if the temperature is not maintained. Lastly, how these vaccines are tracked and what the inventory system should be.
- Determining how to handle and store at least 80,000 specimens over a 3-4 year period with good inventory and tracking systems, what are the QA and QC tests for each laboratory assay to be used, especially end-point laboratory testing (HIV testing).
- Determining how to deal with the massive data generated, and their appropriate QA and QC systems.
Protocol Development and Approval

The draft protocol had been presented in a scientific forum prior to its review process and was submitted for review to all relevant Institutional Review Boards (IRBs) and other concerned authorities. International agencies, such as WHO/UNAIDS, were also involved. Then, the final version of the protocol was submitted for official approval by the IRB and Institutional Ethical Committee (IEC) [1,2]. This process took nearly one year to complete.

Administrative Structure

The structure is complex, involving all of the required components and activities (Diagram 1).

Diagram 1. The simplified structure of the phase III community trial.

PCMO = Provincial chief medical officers, SI = Senior Investigator, VDC = Vaccine Distribution Center
A core staff meeting is held monthly. These meetings include provincial chief medical officers (PCMO), hospital director, chief, district health officers, nurse coordinators from both provinces, collaborators and sponsor representatives. There are also weekly meetings of the collaborators, consultants and PI responsible for recruitment, clinical, laboratory and data management staff and sponsor representatives.

Infrastructure strengthening and capacity-building

Some of the existing government facilities were modified and renovated for the study. For example, the Health Centers were modified for volunteer screening and a District Hospital was modified for clinical activities. In addition, an existing EPI vaccine storage facility was modified to serve as the Vaccine Storage and Vaccine Distribution Center for the project. A 30-bed hospital building of the Health Department was renovated for use as Trial Registry and Repository Center. A retrovirology laboratory of the Armed Forces Research Institute of Medical Sciences (AFRIMS), Royal Thai Army, is used as the central laboratory, and the Data Management Unit at the Faculty of Tropical Medicine, Mahidol University is used for data processing and primary analyses.

1. Field Site Selection

According to the existing healthcare delivery system, district hospitals are responsible for the medical care services in every district, and health centers are responsible for primary care services at the sub-district level. For this study, the clinical activities are performed at eight district hospitals in four districts from each province (Chonburi and Rayong). Screening activities occur at the surrounding 5-10 health centers. Altogether, there are 47 screening sites, 40 health centers, 7 district hospitals, and 1 sexually transmitted disease clinic, which was upgraded into another clinical site.

An 10 beds hospital building in the Health Promotion Center in Chonburi was renovated into a Trial Registry and Repository Center (TRRC), to process and store all specimens in the trial, including transportation of specimens to and from the clinics, and to and from AFRIMS lab for anti-HIV assays in Bangkok.

An existing Expanded Program on Immunization cold room was renovated to secure the trial vaccine as the Vaccine Distribution
Center. The temperature monitors were improved to ensure optimal temperature for the trial vaccine and placebo. A back-up generator is serviced to maintain temperature in case of power failure. The vaccine transport vans were refurbished to ensure temperature control during transport to eight clinics.

2. Recruitment Teams

Recruitment teams were established, consisting of health volunteers who were trained by the project. Community volunteers were also recruited and trained in order to assist in community education and mobilization. Several community education teams were established to raise AIDS and project awareness among the community. The non-governmental organization (NGO) network is also involved with the community outreach team, as shown in the Diagram 2. The district outreach teams, which are composed of village health volunteers and community leaders, implement all community-related activities, liaison and provide a communication network that links the community with the district team [Personal communication]. Posters and flyers were among the tools used to educate the community team [2].

Diagram 2. Community engagement and activities in Rayong and Chonburi provinces.
3. Screening Teams

The screening teams consist of two counselors at the 42 health centers surrounding eight clinical sites. All were trained in GCP, the screening protocol, and Standard Operating Procedures.

4. Clinical Team

The clinical team takes overall responsibility for the clinical part of the study, starting from the informed consent process, through vaccination, to recording and reporting of safety profiles. Based on activities involving 16,000 participants, five to six full-time Clinical Research Coordinators (CRCs), two Nurse Pharmacists (NPs) and three Research Assistants (RAs) are needed. The Vaccine Senior Investigator (VSI) has been appointed. Together with the VSI, there are five core staff members who are medical doctors (MDs). In addition, there are five assistants who are CRCs who supervise the field CRCs and assist the VSI monitor the clinical activities internally (Diagram 1).

At each clinical site, the Hospital Director and/or his designate senior investigator (SI) are responsible for the treatment and care at the respective clinical site. Eight to nine hospital nurses are also involved in providing counseling (pre-, post-test and risk reduction counseling) to volunteers and act as liaisons between the Health Centers and the clinical sites whenever necessary.

The CRCs are responsible for the actual conduct of the study, including the informed consent process, assessing the eligibility criteria of the volunteers, and collecting blood specimens and vaccination. One of the CRCs has been appointed Chief, and she is responsible for the smooth daily workflow process and for reporting the weekly status of the site to the VSI. She also attends weekly meetings at the VTC with the VSI, MDs and VTC CRCs. The two nurse pharmacists (NPs) are responsible for all reconstitution of the study vaccine/placebo when requested by the CRCs, and they must maintain accurate accounts of the vaccine/placebo assigned to their sites. They have also responsible for maintaining the temperature of the refrigerator holding the vaccine/placebo within the protocol requirements (2-8 °C). A generator has also been installed as back-up in case of power failure. This vaccine storage room is only accessed by NPs and sponsor-related personnel and is always locked for security and confidentiality. The NPs are also the only people at the site having access to the volunteer randomization code. They have signed an agreement that they will not discuss randomization...
lists, codes or volunteer assignments. The three Research Assistants (RAs) assist with administrative processes, such as registering the volunteers, scheduling and issuing the study numbers for all volunteers.

All study data are documented in the source document which is bound to the case report forms in one single binder. These binders are kept in a locked container sitting just outside each clinic. Data collected on the CRFs are faxed to the Data Management Unit at the Faculty of Tropical Medicine, Mahidol University, Bangkok, and blood specimens are collected by the sponsor's laboratory.

5. Counseling Team

About 8-12 hospital nurses were trained in counseling (pre- and post-test counseling, risk reduction counseling), AIDS education and GCP.

Trial initiation

The trial was launched soon after final approval in a phased-in manner. Furthermore, the provincial team developed an HIV/AIDS awareness campaign and organized community participation. The first screening began on September 29, 2003, and the first participant was enrolled on October 20, 2003. A site-by-site initiation approach was implemented to ensure high-quality research activities. By February 2004, all sites were activated and were recruiting and enrolling study participants. Recently available statistics, in October 2004, indicate that a total of 11,733 volunteers have been screened and 6,963 have been enrolled in the study [2,4].

Informed consent process

The participants must pass screening comprehension tests before going to the clinical site. At the clinical site, they are shown a short video (about 12 minutes) and are given a copy of the informed consent form (ICF) to follow and read. The video includes important details in the written informed consent. At the end of viewing the video, the CRC again reviews the content of the ICF with the volunteers and answers any questions they may have individually, or in a group. Once questions and answers have been dealt with, the ICF is signed. The CRC allows as much time as necessary for each volunteer to decide before he/she signs the ICF. Discussion of the ICF may be done in groups, but the ICF is always signed individually.
Safety and social impact reporting

At all vaccination visits and subsequent diary card return visits, participants are questioned regarding any adverse events (AE) and/or participation impact events (PIE). A PIE involves any harm that may result from trial participation, whereas adverse events describes medical events only and not social harm events. If a PIE is present, the participant is counseled by the nurse counselor and followed up until resolution.

Adverse events in this study are documented and categorized during encounters with a healthcare provider (physician, nurse, etc.) only. They are documented in the source document and in the Case report forms (CRF). A Serious Adverse Event (SAE) is reported separately on a SAE report form. Any SAE which is related to the study vaccine/placebo is reported within 24 hours and non-related SAE within 7 days. All are followed to resolution. The criteria for reporting SAE are in accord with those specified in the ICH-GCP guidelines.

Trial supervision, monitoring and assessment

Overall progress of the trial in terms of the numbers of interested people, and screened and enrolled participants, are monitored weekly by both field and central core groups. Safety profiles and SOP compliance to the vaccine protocol are monitored internally and reported weekly by the VTC group to detect any safety concerns. The protocol physicians and other technical staff in the central coordinating office visit the field sites, especially health centers, regularly to provide supervision. If any deviation from the SOPs is detected, immediate correction is made to maintain protocol adherence.

Management of HIV infected volunteers in the trial [1]

Study participants who need medical care are referred to MOPH facilities for medical care. Throughout the trial period, the costs of HIV-related medical care, including antiretroviral therapy and laboratory investigation, are provided by the sponsor. After the end of the trial, HIV-infected participants will continue treatment and follow-up under the National Health Insurance Scheme. The management of HIV infection is provided as per the national guidelines for HIV infection
management in Thailand. Non-HIV related disease conditions that are related to the conduct of the study are fully supported by the sponsors; otherwise, participants are referred to the National Health Insurance Scheme. Community members who are found to be HIV-positive at the time of screening are also referred to MOPH health facilities for appropriate medical care.

Lessons learned

Since the trial is so big, there have been some difficulties with administrative issues. Coordination between the PI staff and collaborators has been a challenge, especially in the field. Some remedies have been put in place. For example, although PCMOs and hospital directors are not directly responsible to the Department of Disease Control, closer oversight has been required to avoid or deal with problems. Supervision has been facilitated by establishing administrative tours by the key staff and/or collaborators under the leadership of the PI. In addition, specific issues are addressed at the monthly core staff meetings. Working in a sincere environment and the harmonization of various teams are key factors for success.

Site preparation

As discussed above, site preparation has required massive infrastructure strengthening and renovation of existing structures. This took longer than initially planned. Furthermore, extensive capacity building through training of various levels of staff in GCP, SOP, protocol, etc., were conducted to assure the required standards were achieved and maintained [2,4].

Recruitment process

The new concept of involving community groups in education and recruitment is being implemented in this trial. A community education team has been established and trained. No team members had health-related educational backgrounds or were healthcare providers. During the conduct of the trial, it was observed that the educational messages, particularly on vaccine safety, were not clearly conveyed to the population. This created uncertainty among the community and
slowed the recruitment process [2,4]. However, it is difficult to accurately assess the level of understanding among the community. There is always concern that there might be stigmatization of those enrolled in the trial, or there may be a potential increase in risk behavior among the study participants [2].

Informed consent process

The informed consent process, using a video as an educational tool and discussion with staff, is considered successful. One small drawback is that sometimes participants have understood but could not be enrolled because they could not read and write.

Trial conduct

Several training sessions were provided for all staff participating in this study. All training and training materials were prepared in the local language (Thai, in this trial) to allow the research staff to comprehend the content of the subjects.

By closely supervising the start-up of each clinic at the beginning of the trial, the staff gained confidence in performing the required activities. The trial activities are closely monitored and assessed, both by field and central core staff. This enables the team to identify problems as soon as they arise and seek solutions promptly. Refresher and “lessons learnt” sessions are regularly arranged, including courses on advanced GCP and advanced cardiac life support.

In order to match the workload and the availability of participants, the clinics are open in the late evening and weekends. Sometime, CRCs from the other sites with lower numbers of enrolments come to help the high enrolment sites. One group of pharmacist assistants rotates to different clinics to help pharmacists as needed. Team-spirit building and rewards have been essential for team motivation. Morale building, support and understanding among various teams are important. Regular team-building workshops are required.

Community engagement was a key approach to getting community participation and support. The social impact data have
not yet been analyzed, but various kinds of rumors and/or misunderstandings were encountered among the community and the project staff. Therefore, these should not be overlooked or underestimated and should be solved in a timely manner.
References


Data Management for HIV Vaccine Efficacy Trials
Infrastructure Strengthening for Clinical Research in Thailand

Dwip Kitayaporn

Introduction

National Plans for AIDS vaccine research, development, and evaluation were developed in 1992-1993 in Brazil, Rwanda, Thailand, and Uganda, with the assistance of the World Health Organization/Global Programme on AIDS (WHO/GPA) [1]. These National Plans describe national policy procedures for submission, review, approval, and monitoring of research proposals. They also contain specific recommendations for a research agenda to prepare for future HIV vaccine efficacy trials, including virus isolation and characterisation, baseline epidemiology data and cohort development, social and behavioural research and repeat phase I/II trials of candidate vaccines which have already been tested in the country of origin. The Joint United Nations Programme on HIV/AIDS (UNAIDS) provided technical and financial support for the implementation of these activities, including the establishment of cohorts of HIV-negative volunteers in the four countries. The WHO and UNAIDS have also provided continuous advice to national authorities regarding the conduct of HIV research, especially clinical trials [2]. Thailand, after the establishment of its first plan promulgated in 1993 [3], modified it in 1997 [4]. Research and clinical infrastructure, with adequate laboratory and data...
management support, are one of the requirements and could be considered as part of an ethical obligation with regards to the principle of distributive justice [5].

History

The attempt to establish a data management facility at the Faculty of Tropical Medicine, Mahidol University, Vaccine Trial Centre (VTC), for HIV vaccine candidate trials can be dated back to 1995 when the phase I/II study of AIDSVAX® (MN) in Bangkok for injecting drug users (IDUs) [6] was carried out. In those days there was a need to clarify the differences between data management issues and the Data and Safety Monitoring Board (DSMB) because there were many people who were not clear about these two different entities. The former refers to a system organised for the systematic management of data to be used for storage modification, and retrieval of data [7] while the latter refers to a committee responsible for periodically reviewing accumulated data for evidence of adverse or beneficial treatment effects during the trial and for initiating recommendations for modification of a study treatment, including termination of the treatment when appropriate [8]. The clarification took some time before resolution could be made in Thailand.

Building a data management unit in Bangkok really began in July 1995 on a trip to Seattle, WA, U.S.A. At that time, the Thai team learned about the DataFax technology (Clinical DataFax Systems Inc., Hamilton, Ontario, Canada; http://www.datafax.com). DataFax is a fax-based data management system for clinical trials. Since its introduction in 1990, it has been adopted by pharmaceutical companies, contract research organisations, and universities in various continents. Many of these trials have been used in successful submissions to the US Food and Drug Administration for new drug applications. The system was also then used at the Fred Hutchinson Cancer Research Center (http://www.fhcrc.org) in Seattle, WA, U.S.A.; discussions took place as to whether it would be used for vaccine trials. Nearly all of the data management of the earliest phase I/II trial of Bangkok IDUs [6] were done by the sponsors, i.e., Genentech Inc. (South San Francisco, CA, U.S.A.) and the Fred Hutchinson Cancer Research Center team. During those trials the Thai team began to learn about data management issues.
The VTC owes very much to VaxGen Inc. (Brisbane, CA, U.S.A.) for its generosity in technological transfer, and to those involved in the National Plan set-up, in establishing a data management facility at the VTC of the Faculty of Tropical Medicine, Mahidol University. Rounds of negotiations were made with the late Professor Natth Bhamarapravati as to where the premises should be for the facility. As the ambiguity between the DSMB and data management became clearer, and with tremendous input from VaxGen Inc., the VTC facility was established in 1998 at its current location. The set-up had to be done about six months prior to the launch of the AIDSVAX® B/E (VaxGen Inc., Brisbane, CA, U.S.A.) candidate HIV vaccine efficacy trial that enrolled 2,549 IDUs in a randomised placebo controlled trial that began in March 1999. The set-up was done in parallel with the approval processes and raised anxiety as to whether it would be established and operable because of the long duration of the approval process at that time. It was started with an area of 112 square metres on the rooftop of the newly built Anek Prasong Building of the Faculty with a set of six staff with the approximate total costs of about US$ 400,000. By the time when the author left the Faculty in December 2004 the space and the staff number were doubled. The DataFax technology allowed the quality control (QC) and quality assurance (QA) on data management to be more efficient, because the Case Report Forms (CRF) could be transmitted via facsimiles from 17 participating Bangkok Metropolitan Administration drug treatment clinics instead of keypunching the data. The fax optical reader reads the forms, sends the signal through the fax modem, and then data are interfaced onto electronic databases. The process minimises use of paper. Starting from the time when CRF’s are faxed, time spent in data processing is less compared to conventional keypunching methods and QC reports can be rapidly faxed back to clinical sites for corrections. Data correction forms are no longer needed as series of changes can be re-faxed and audit trails are automatically established.

The establishment of the Data Management Unit (DMU) has been historic. It is the first time in Thailand that clinical trial data management for licensing purposes has been accomplished in Thailand in compliance with the Good Clinical Practice (GCP) guidelines [9]. In the first phase III trial of the HIV candidate vaccine, the facility served as a “secondary database” for the “primary database” in Brisbane, CA, U.S.A., and
was linked via the Internet. In the second phase III trial conducted in Thailand, the RV144 (Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120B/E (ADSVAX® B/E) Boosting in HIV-Uninfected Thai Adults), much capacity building was kindly contributed by the Henry Jackson Foundation, and the US Army, to comply with the Code of Federal Regulations (21 CFR Part 11). Because of regulatory requirements for trials of pharmaceutical products for licensure purpose, tremendous efforts and resources are in place to comply with the regulations set by the CFR and the ICH/GCP Guidelines, including facilities, security systems, QA, QC, and training at different levels. These include training on the regulatory requirements, GCP rules, computer system rules, computerised system validation, security systems, etc., to ensure that the trials comply with standards, i.e., ability to create both human-readable and electronic records for which an audit trail could be established. The processes also require that accurate and complete copies of records be kept to allow inspection and review of clinical trial records by regulatory authorities, auditors, and monitors should the candidate vaccines prove efficacious. Moreover, records changes should not obscure previous data and any changes must be traceable to allow verification by authorities. The second trial budget for data management for the five year trial is estimated to be no less than US$3 million and is contributed by the sponsors. These include costs for space rental and renovation, staffing, office facilities, hardware to accommodate test and production environments, software, travelling, training of different levels of staff, etc.. Although the approval of the trial does not explicitly require that the data management system be approved before the trial is launched, but if the product proves to be efficacious then its validation, auditing, and monitoring will become essential. Because there is no law governing investigational new drug/vaccine applications for licensure in Thailand, and because the vaccine candidates could be licensed in the US, the US Code of Federal Regulations was then adhered to.

**Lessons learned**

The set-up demonstrates that a clinical trial in a developing country can provide infrastructural development for the host country. Infrastructures and human resource developments have been developed to comply with international rules and regulations for pharmaceutical
products licensure. Yet, the greater challenge in this case is now to achieve sustainability after the AIDSVAX® and the Prime Boost trials are over. Plans to have the data management infrastructure sustainable are very challenging and will need to be developed. These will depend upon the vision of the many parties involved, e.g., sponsors, academy, administrators, and regulatory agencies. The overall goal to this success, therefore, is to foster such technological transfers in an environment that encourages appropriate, mutually beneficial, long-term, and productive ties among these parties.
References


CHAPTER 7

FROM "GUINEA PIGS" TO "GUINEA PIGS:" COMMUNITY AWARENESS AND RESPONSE TO AIDS VACCINE RESEARCH AND DEVELOPMENT IN THAILAND
From Guinea Pigs to guinea pigs: Community Awareness and Response to AIDS Vaccine Research and Development in Thailand.

Nusara Thaitawat

Fourteen years on and the headlines on the front pages of Thai newspapers still shout “guinea pigs” whenever an article on AIDS vaccine research is published. Odd one might say!? Isn’t Thailand that developing country somewhere in Southeast Asia with an impressive record of 10 phases I and II trials, and two large-scale Phase III trials: one was completed two years ago, and the other, currently in its final stage of enrolling a record 16,000 volunteers, is not only the world’s largest community-based trial but also the only one that is currently taking place?

As someone who has been involved in the coverage of AIDS vaccine research as a journalist since 1991 when a British publication shocked Thailand with an article on the US Army’s plans to use Thai soldiers as subjects to test a candidate AIDS vaccine, a project which was still “classified” at home; [1] and now on the other side of the fence, working as the communications manager of the ongoing phase III trial, I’ve witnessed the evolution of how the Thai media has covered AIDS vaccine research, and how the public has responded over the years. This chapter is about the Thai media’s successes and difficulties in covering AIDS vaccine research and why there exists such a huge gap between the specialized knowledge of Thailand’s AIDS vaccine researchers, and the seemingly un-curable “guinea pig syndrome” of the every day Thai.
There are four issues which I wish to address:

- What the National Plan for HIV/AIDS Vaccine Development stipulates about communications and community participation?
- What are the policies on communications and community participation of the various AIDS vaccine trials since 1991?
- How does the community see its role in AIDS vaccine research?
- And, Why is this “guinea pig syndrome” (seemingly) un-cur-able?

The National plan for HIV/AIDS vaccine development

Drafted at the initiation of the World Health Organization after Thailand was identified among 14 countries as a potential site for AIDS vaccine research, Thailand’s National Plan for HIV/AIDS Vaccine Development was officially launched in early 1993. Critically acclaimed for laying the foundation for all aspects of vaccine research which eventually secured Thailand’s position at the forefront of the global effort to find an AIDS vaccine, the plan addresses it all, except one important area: communications and community participation. Chapter 3 entitled “Communications and Public Information” of the National Plan is very short:

Given that AIDS vaccine research could easily cause confusion and strong emotions in society, the Technical Sub-Committee (of the National AIDS Commission) shall develop a communications and public information strategy with the research teams, vaccine manufacturers, and the Department of Communicable Disease Control ¹ (of the Ministry of Public Health), with the aim to:

- Providing the public valid information on AIDS vaccine research, especially on progress made in Thailand;
- Responding to false claims and correcting possible misinformation; and
- Supporting the conduct of AIDS vaccine research by creating an enabling environment.

The strategy shall target different groups in society.

¹ The Department of Communicable Disease Control was restructured into the Department of Disease Control, effective 2003 under the Thaksin government’s civil service reforms.
namely the general public, the medical and scientific
community, politicians, policy makers, the media, non-profit
organizations, and the private sector. Due consideration
shall be given to any impact the communication strategy
could have on public goods and internationally.2

While national plans are generally not expected to lay down the
specifics, the above two paragraphs and three bullets certainly lack the
spirit of multi-sectoralism and partnership with the community, and is
telling of the thinking of the time: paternalistic and very researcher-
centered. Professor Emeritus Dr. Prasert Tongcharoen, Thailand’s
foremost virologist from the Department of Microbiology at Faculty of
Medicine Siriraj Hospital, Mahidol University and the first chair of the
Technical Sub-committee recalled that there was no notion then about
communications and community participation as are known today,
“only PR”, he said. “We were focusing on how to have a vaccine as
soon as possible, the rate of infection was alarming… actually we were
considering efficacy trials rather than phases I and II. It was only later
when we got more data on HIV having several strains that we had to
make it compulsory to do repeat phase I and II trials in Thailand,” he
recalled.3

Dr. Prayura Kunasol, former Director- General of the Department
of Communicable Disease Control who was part of the team which
drafted the plan, pointed out that one social scientist was involved in
the drafting process.4 Following much debate over the direction of the
chapter, it was finally decided to include the three basic elements of
communications: inform, correct misinformation, and create
understanding and public support; and leave the wording as general as
possible to allow flexibility to address the complexity of each specific
case of “confusion and strong emotions in society.”

The approach seemed right then given the intense reaction
which the British publication, The Economist had caused in 1991, around
the time drafting of the National Plan was starting. In breaking the news
of a US planned AIDS vaccine trial in Thailand, the publication quoted a

2 Unofficial translation by the author, prompted by comparing the “draft”
English text posted on the official website of the Bureau of AIDS, TB and
STD, Department of Disease Control, http://aidsthai.org which does not
correspondent to the Thai version in its entirety.
3 Interviews with the author.
4 Interviews with the author.
US government official as saying: “Thai Army recruits would make a good trial group. Following them up is easy and army discipline being what is, they are unlikely to object. Since Thai recruits get infected at a relatively high rate, a trial that gave a vaccine to one group and a placebo to another, and then gave all concerned the same sort of counseling, check-ups and treatment, should be able to produce answers fairly quickly.” The Thai Army spokesperson responded by dismissing the planned trial as “unlikely.” He said: “Thai soldiers are not guinea pigs.”[2]

The first piece of news about AIDS vaccine research in Thailand could not have been less auspicious in a country which believes strongly in the right positioning of the stars to launch any major undertaking. The papers and networks devoured the story for several weeks, clearly enjoying the confrontation between US and Thai officials and the outpouring of emotions of AIDS and rights activists, and while being totally confused in the limited data and understanding Thai scientists and health authorities had on what exactly the trial was about.

Unfortunately, this incident sealed the fate of future news coverage and the relationship between the Thai media, AIDS vaccine researchers, and health authorities. The Thai media and its news consumers, with their limited understanding of human research easily became stuck with the concept of “guinea pigs,” and AIDS vaccine researchers and health authorities were overwhelmed with the seemingly uncontrollable feelings of activists, the un-professionalism of the media, and lack of appreciation of the general public of the significance of an AIDS vaccine for Thailand at the time when over 100,000 people were being infected each year.

Thus quiet is best. And thus flexibility was given to the powers that be, the Technical Sub-committee, the research teams, vaccine manufacturers, and the Department of Communicable Disease Control, as to what constitutes “valid” information and how to provide it; what is “misinformation” and how to correct it; and what is “an enabling environment” for AIDS vaccine research, and how to create it.

The Policies on communications and community participation of the various AIDS vaccine trials since 1991

Often we hear AIDS vaccine researchers ask the questions: “how would community influential react,” and “how would the media cover our trial” when planning communications and community
participation. While the hoped-for answers are of course “the trial is good for the community,” “the community wants an AIDS vaccine; we, researchers and health authorities are responding to a community need,” and “becoming a volunteer is a good thing,” there is that apprehension and reluctance deep inside: “do we really have to deal with the community and the media?”

All the 12 trials have been mostly faithful to Chapter 3. The policies on communications and community participation were dictated by the researchers and their sponsors with the endorsement of the Technical Sub-committee, and adapted as situations dictated, swinging from high to low profile. The rationale was simple: high profile was intended to push a particular agenda, and low profile to ensure the peace and security of being left alone by AIDS and rights activists, and the media to do their work. But did the key investigators of each trial get what they wished for? Most of those interviewed by the author have claimed affirmative, more or less.

For example, prior to the launch of the HIV-1 MN Synthetic Peptide trial in early 1990s, its research team had worked closely with the media, NGOs and other stakeholders to push the Ministry of Public Health and other concerned authorities to speed up their work in establishing hitherto non-existing regulations governing AIDS vaccine research in Thailand. The team managed to stir public opinion on the immediate need for an AIDS vaccine and how slow the authorities had been. When the trial began, the media was given high access, even to volunteers as they were vaccinated. This trial and its principal investigator, Dr. Praphan Phanuphak, however controversial he may be among his peers, is remembered by the media and NGOs as a most progressive medical researcher in pushing for AIDS vaccine research to stop the disease as soon as possible, the most accessible and most willing to speak layman’s language when talking about the subject.

1 The Plan for HIV/AIDS Vaccine Development of 1993 though identified only the Technical Sub-committee as having authority over strategies of communications and community participation, it later included the Ethical Committee of the Ministry of Public Health, the respective Institutional Review Boards (IRBs) of the institutions which are collaborating in the trial, and the IRBs of sponsors, namely the US Food and Drug Administration, the US National Institutes of Health, or the Human Subjects Research Review Board of the US Army.

6 The investigators asked for anonymity.

7 Thailand’s first trial involved 30 volunteers. Immunization began June 1994.
The trial is remembered as the most transparent, and had demonstrated that volunteers are not guinea pigs, but ordinary and educated people were participating.[3]

As for the other phases I and II trials: “They were small, 30-300 volunteers who came from a specific group, so there was no need to publicize the trial to the general public.” Educational materials were produced, including video presentations, brochures, flyers, posters, and radio spots for use in target groups. The mass media was invited to publicize the launch of the trial but never for follow up on progress made, and for the trial’s results which were reserved for international AIDS vaccine conferences and English language medical journals. The belief is that the media was not able to understand, would misreport and cause public confusion.

This approach was applied to Thailand’s first phase III efficacy trial which involved over 2,500 volunteers who were recovering injecting drug users (IDUs) in Bangkok. The investigators maintained that they have strictly followed internationally recognized ethical principles in creating understanding of the trial, obtaining informed consent, counseling, and retaining volunteers over three years, but the setting of the trial—the volunteers being IDUs and the clinical sites being drug rehabilitation clinics and educational material having been designed to bring out “the hero in IDUs,” “a chance to correct the past and do something good for their country”—was just too unconvincing. AIDS and rights advocates suspected “some degree of coercion Thai-style” was applied and that the high retention rate of 97% was mainly due to the volunteers having to follow up on their methadone treatment. The trial’s investigators insisted that the informed consent process was validated by neutral parties in and outside of Thailand, and that many of the IDUs approached, had declined to volunteer and this did not in any way affect their relationship with the health officials and thus their continued treatment at the rehabilitation centers which acted as clinical sites for the trial. At the AIDS conferences in Barcelona in 2002 and in Bangkok in 2004 questions were asked about the ethical conduct of the trial. It appears that the debate will not end easily as more people become interested in human trials, gained some knowledge and become more vocal.

8 The Thai word is kreng jai, it puts people in a situation of having to agree to do something out of consideration of seniority, dependency, respect, etc. There is no English equivalent.
The on-going phase III trial in Chonburi and Rayong provinces to involve 16,000 volunteers, aged 18-30 raised many eyebrows in also opting for a low profile approach to communications and community participation. The two key arguments are that the existing health system of the Ministry of Public Health which reaches the smallest villages throughout the country has an established pool of volunteers and community supporters that can be tapped; and that quiet will allow the successful enrollment of volunteers without inviting controversy. Others disagree, they maintained that mass media campaigns and intensive community outreach activities aimed to raise awareness of HIV/AIDS, create understanding of AIDS vaccine research including the role and responsibility of volunteering and the rights of volunteers, would ensure that the volunteers comply, strengthen community support for the trial in the long term, and prepare all concerned of the efficacy results and access to the vaccine. As this trial is still on going, time will provide the evidence-based answers to these arguments.

In the meantime, the proposed phases I and II trial by the Thai Red Cross Society, Chulalongkorn University and a consortium of Australian universities and entities have breathed fresh air into the field. Unlike all other past trials, researchers in Thailand and Australia have made serious efforts to engage all stakeholders in the planning and execution of the trial. Some of the key investigators are the same as the HIV-1 MN Synthetic Peptide trial and can easily build on the positive image that they have left with the media, and AIDS and rights advocates. Preliminary results of their engagement activities have shown that almost all stakeholders have little background on AIDS vaccine research 14 years on. They also do not know why and how they should get involved. The Thai-Australian team, together with Thai and Australian NGOs are continuing their efforts nonetheless. The research team has agreed that a representative of the community, a neutral clinical researcher, and other stakeholders will be part of the drafting of the

---

9 Officially known as the Prime-Boost HIV Vaccine Phase III Trial, it is spearheaded by the Department of Disease Control, Ministry of Public Health, in collaboration with the Faculty of Tropical Medicine, Mahidol University, the Armed Forces Research Institute of Medical Sciences, Thai and US Components; Sanofi-Pasteur; and VaxGen Inc. It is sponsored by the US Military HIV Research Program, and the US National Institute of Allergy and Infectious Diseases.

10 Final draft of the protocol is pending safety results from same trial in Australia.
protocol. A set of activities have also been initiated to form a Community Advisory Board (CAB). Could this signify the maturity of Thailand’s AIDS vaccine research in embracing multi-sectoralism? Only time can tell but a precedent has been set for future AIDS vaccine trails in Thailand.

How does the community see its role in AIDS vaccine research?

Community participation in AIDS vaccine research remains a new concept in Thailand, having been consciously left behind by AIDS vaccine researchers and health authorities. Mr. Nimit Thien-Udom, Director of the AIDS Access Foundation (ACCESS), and the current Director of the Thai NGOs Coalition on AIDS (TNCA) accepts that the responsibility to know about AIDS vaccine research does not rest solely with AIDS vaccine researchers and health authorities, “but they have an important role to play by making the subject and themselves accessible.” He recalled that though he has been involved in AIDS awareness for a long time, all information about AIDS vaccine research he and colleagues obtained had come from foreign NGOs attending the same international conferences outside Thailand. Thai NGOs, though numbering several hundreds and operating throughout the country, have closely followed the policies of the Ministry of Public Health in combating HIV/AIDS with the objectives to strengthen them and ensure accountability of health authorities and the protection of those infected and affected by the disease. In the early days, they had focused on prevention and awareness then moved on to care and treatment. “We spent a lot of time working on various strategies, building on our experience in prevention, care and treatment. Now the situation has stabilized and we can turn our attention to vaccine research,” he said.

The TNCA, together with the Network of People Living with HIV/AIDS (TNP+) held what they termed “Vaccine 101” in early

---

11 The AIDS Access Foundation (ACCESS) is Thailand’s early non-profit organizations, which launched the first phone counseling service.
12 The Thai NGO Coalition on AIDS (TNCA) is a national umbrella organization of AIDS NGOs from all over Thailand. It has over 300 members to date.
13 Interviews with the author.
14 The Network of People Living with HIV/AIDS (TNP+) is also a national umbrella organization of NGOs, Community-Based Organizations (CBOs) and other groupings of people living with HIV/AIDS. It has some 300 members nationwide.
2003 when the on-going Prime-Boost trial was developing its community engagement strategy. The rationale was that if they were to constructively contribute to pushing for the earliest availability of an AIDS vaccine for Thailand, they had to know the A to Z of AIDS vaccine research. The event, which benefited from Dr. Prasert’s lecture, signified a step forward for Thai NGOs who in the past had focused their energies in “shouting and yelling” for the rights of volunteers based on the pre-conception that AIDS vaccine researchers and health authorities could not be trusted, based on previous experience. “Vaccine 101” also initiated brainstorming on the various possible contributions which NGOs, with their connections to the grassroots and their innovatively simple ways of communicating about HIV/AIDS to the layman, could make in the Prime-Boost and Thai-Australian trials. It was concluded that all stakeholders and the community would have to start from “zero.”

The report on Media Situation Analysis and Audience Research on Public Opinions towards AIDS Vaccine Trials which was commissioned by the Communications Working Group, Technical Sub-Technical Committee, confirmed that there was no knowledge about AIDS vaccine research and no idea how the community could contribute, not even in those areas such as Bangkok and Chiang Mai, where previous trials and cohort studies had been conducted. There was however the fear that people would be used as guinea pigs by the researchers and their foreign sponsors. This fear is believed to originate in and is perpetuated in popular cultures, through movies and books on human guinea pigs, and the sensational “guinea pigs” headlines of the mass media.

The Thai press is diversified. How each publication or news agency interpreted its responsibility: some adhered to the universal principles of “inform and educate” and “serve as a watch dog” for the public through news coverage, analysis and commentaries; others saw themselves as opinion leaders and aimed to influence public thinking; while some were in the business of selling news. Each media organization employed reporters from varied backgrounds according to their respective self-defined responsibility. Health is not seen as “hard news” unlike politics or military affairs, and so mostly young inexperienced reporters would be assigned to this beat as a stepping stone to other beats. Some do stay but most go on to other beats after a few years and even to date, there are few professional health reporters in the main stream press.
Why is this “guinea pig syndrome” (seemingly) un-cur-able?

Thailand’s AIDS vaccine research is dominated by a small group of people who had initiated it over a decade ago. Now in their early 70s, they have been mentoring their own students, in their early 50s who in turn have young medical doctors, in their early 30s as part of their teams. While certainly their own knowledge and experience, accumulated over the years are being passed on, unfortunately so are some of the biases, especially in communications and community participation. The on-going phase III trial in Chonburi and Rayong provinces can only underline the long-standing biases dating from the early days of the epidemic in the country: AIDS and rights activists are “trouble makers,” the media “superficial and sensational,” and the general public “not well educated enough to understand.” The paternalistic approach to community relations: doctor-to-patient, very much remains the key strategy to recruitment of volunteers. This is even though the US sponsors have provided unprecedented financial and technical support for communications and community participation which had offered the best hope so far to systematically bridge the gap between the world of AIDS vaccine researchers and health authorities, and those of the media, AIDS and rights activists, and the community.

The situation as is gives little hope for addressing the “guinea pig syndrome” of the every day Thai. The gap between Thai AIDS vaccine researchers and health authorities, and the general public is expected to deepen even more as collaborating institutions in the Prime-Boost trial work hard to recruit and maintain over 3 years such a large number volunteers. The Thai-Australian trial did set a precedent but is too small to be the prime mover for chance in the Thai medical community.

The National Plan is currently being reviewed. Albeit strong opposition from some of the original members of the working group, a multi-sectoral team including NGOs, rights activists, and communication experts, has been formed to review the plan clause by clause. It is hoped that amendments can be completed within 2005.
References


3. The report on Media Situation Analysis and Audience Research on Public Opinions towards AIDS Vaccine trials was commissioned by the Communications Working Group, under the Technical Sub-committee in 2004.