A JOINT CLINICAL RESEARCH CENTER IN THAILAND: ROLE IN HIV VACCINE DEVELOPMENT

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Abstract. In 1992 the Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand, collaborated with the Phramongkutklao Army Medical Center to set up the Joint Clinical Research Center (JCRC). The purpose of the Center is to conduct clinical research in support of HIV vaccine development and testing. To date, eight HIV vaccine-related research protocols have been conducted at the JCRC, involving 1,668 volunteers. The JCRC has been, and continues to be, a key site for the transfer of clinical trial expertise to new sites at universities, government clinics and hospitals in Thailand and other countries. Overall rates of follow-up have been excellent, while protocol violations and data clarification errors have been minimal.

INTRODUCTION

Though 93% of the world's burden of preventable disease mortality occurs in developing countries (Commission on Health Research for Development, 1990), too little research funding is targeted towards them, creating a dangerous funding shortfall (Global Forum for Health Research, 2000). A necessary strategy for controlling the global spread of infectious agents is the building of research and clinical capacity in developing countries (National Intelligence Council, 2000). As a matter of principle, all countries, especially those with high burdens of disease, should have access to the most effective tools to control their health problems and develop their research capacities.

Investigators face tremendous obstacles including scientific isolation, insufficient technical training and research tools, lack of updated scientific information, limited financial, material, and inadequate human resources. In order to build up scientific capacity, monitor and control disease, and promote health, research on locally relevant issues must be supported and sustainable partnerships created to facilitate these efforts (Harris and Tanner, 2000). We report on a long-term partnership between Thailand and the United States of America in the field of HIV vaccine trials.

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The views and opinions herein represent those of the authors and not necessarily those of the US and Royal Thai Armies.

MATERIAL AND METHODS

Background

The Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand, traces its origin to the year 1958 when a group of scientists from the United States and Thailand established the South East Asian Treaty Organization (SEATO) Cholera Research Laboratory. Although initially instructed to conduct scientific research on various aspects of the cholera epidemic, the laboratory's mission was expanded in 1961 to include research on other tropical diseases at which time it was renamed the SEATO Medical Research Laboratory. The

Laboratory became the AFRIMS upon dissolution of SEATO in 1977, and today it operates as a joint Thai/American military medical research venture. It is comprised of US and Royal Thai Army (RTA) components. Overall command rests with a Royal Thai Army Medical Department officer of flag rank. The U.S. component functions as a special foreign activity of the Walter Reed Army Institute of Research (WRAIR) in Washington, DC, and of the US Army Medical Research and Materiel Command (USAMRMC) (AFRIMS, 2001).

Thailand was one of the four countries that were identified in the early 1990s by the World Health Organization as potential HIV vaccine evaluation sites (Heyward *et al*, 1996). It was recognized that Thailand had an optimal set of circumstances for carrying out vaccine trials. The scientific and logistical infrastructures were solid and there was already a strong national commitment to recognizing and combating the developing epidemic. At the same time, there was a rapidly increasing incidence of HIV associated with viral strains of relatively narrow diversity.

A US component Department of Retrovirology was established at AFRIMS in 1991-92 (McNeil, 2001). The first project was a Thai-US collaboration collecting HIV prevalence and incidence data on the 60,000 recruits who were screened for HIV annually.

In mid-1992, personnel were hired and trained to begin preparations for Phase I and II HIV vaccine trials. The US military staff was augmented by US and Thai civilians hired by the Henry M Jackson Foundation for the Advancement of Military Medicine (HMJF). Standard Operating Procedures (SOP) and forms were shared by WRAIR, modified to meet local conditions in Bangkok, and used as the basis for the initial clinical studies.

At the end of 1992, the Department of Psychiatry at Phramongkutklao Hospital (PMKH) provided the AFRIMS HIV Research Program with two rooms in their outpatient department (OPD): these were renovated for use as a research clinic. The name Joint Clinical Research Center (JCRC) was chosen; this did not include a reference to HIV or vaccines because of the sensitivity surrounding HIV at that time. The *Joint* refers to the collaboration between AFRIMS Thai and US Components, PMKH, WRAIR, and the HMJF.

The JCRC submitted the first vaccine trial protocols for review at a time when Thailand was in the process of writing its National Plan for HIV/AIDS Vaccine Development and Evaluation, which included guidelines for the review of HIV research proposals (Ministry of Public Health of Thailand, 1993). These AFRIMS protocols were among the first to enter the review system and may have been catalysts for setting in place some of the national review procedures.

Collaborations

Late in 1994, the Research Institute of Health Sciences (RIHES) at Chiang Mai University initiated collaboration with the HIV Research Program, AFRIMS, to form the ARVEG (AFRIMS-RIHES Vaccine Evaluation Group). In 1997, two Mahidol University sites joined the collaboration, Siriraj Hospital and the Vaccine Trial Centre within the Faculty of Tropical Medicine. The four-site collaboration was named the Thai AIDS Vaccine Evaluation Group (TAVEG). The JCRC has played an important role in the transfer of clinical trial expertise to new sites, helping to build capacity in these academic centers. The JCRC has also facilitated exchanges of investigators between Thailand and other developing countries interested in HIV vaccine development.

Staff and training

The clinical staff of the JCRC staff have had extensive bi-lingual training in Good Clinical Practices, research methods, HIV test counseling, behavioral risk assessment and intervention, as well as in vaccinology, immunology, data management, information technology, and protocol-specific SOP training, all of which is regularly updated. The vaccine trial nurses and the clinic physicians have been certified in Basic Life Support and Advanced Cardiac Life Support. Staff turnover has been low. The current core team of 7 nurses, 2 research assistants and

a coordinator have an average of 8.4 years experience with the JCRC research program.

RESULTS

Research activities and services

The research activities and clinical services offered by the JCRC have been designed, implemented and revised over many years. This process has created the expertise and experience to conduct phase I and II clinical evaluation of HIV vaccines and to provide the basis for interpretation of phase III results through the study of adult Thais infected with locally circulating HIV. Collaboration and informal interaction with other departments at AFRIMS and other institutes in Thailand and abroad have enhanced the exchange of information and the refinement of clinical research methods.

Natural history studies

In 1992, a study of the natural history of HIV infection in both prevalent and incident cases was initiated. The incident cases (newly infected cases whose approximate date of seroconversion was known) were recruited from the follow-up study of army recruits and from other incidence studies conducted in several cohorts by AFRIMS-Ministry of Public Health collaborations. The prevalent cases (dates of infection not known) have been mainly referred from the PMKH Infectious Disease Clinic. In all, 840 prevalent cases and 177 incident cases were enrolled. Subjects were evaluated by a study physician for their clinical status. Laboratory tests, including CD4 T-cell count, were routinely done and genotyping by PCR and RNA quantitation added as they became available. Several publications and abstracts have resulted from this study (Lynch *et al*, 1998; Brown *et al*, 2000; de Souza *et al*, 2000; McCutchan *et al*, 2000; Chuenchitra *et al*, 2001; Tovanabutra *et al*, 2001; Trichavaroj *et al*, 2001). Some of the significant findings include: the first identification of a CRF01_AE/B recombinant of HIV-1 (Tovanabutra *et al*, 2001); the demonstration of cross-clade CTL responses (Lynch *et al*; 1998); the increasing, but still relatively narrow viral diversity in seroconverters from 1992-1996 (McCutchan *et al*, 2000); and the demonstration of relatively increased natural killer (NK) function in Thais (de Souza *et al*, 2000).

Another study entitled 'Evaluation of the mucosal virology and immunology of HIV-1 in Thailand' was undertaken to assess characteristics of HIV-1 in mucosal compartments. To date, 68 HIV-uninfected (including 21 HIV vaccine recipients), and 100 HIV-infected volunteers have been enrolled. Specimens collected include blood, urine, naso-pharyngeal washes, endo-cervical secretions, vaginal washes, and semen. Recruitment and specimen collection have been remarkably successful in spite of presumed cultural barriers that may have caused difficulty. Both male and female nurses have explained the semen and gynecologic specimen collection procedure to volunteers; there appears to be uniform volunteer willingness to participate, regardless of sex. (Buapunth *et al*, 2001). Published findings have included the detection of HIV-1 RNA in nasopharyngeal washes, which is the first time this has been demonstrated for any subtype of HIV (de Souza *et al*, 2001b). Pap smears are provided to female volunteers as a service: to date, one case of cervical dysplasia has been discovered.

Vaccine trials

HIV vaccine trials have been the main thrust of the research effort of the HIV Research Program at AFRIMS. Five Phase I/II vaccine protocols (with a total of 713 enrollees) have been conducted under the multi-site program, four having used the JCRC as a clinical site (Table 1). The trials have been conducted under US Food and Drug Administration (FDA) Investigational New Drug applications with import permits from the Thai FDA. Scientific and ethical approvals have been obtained from institutional and national review boards in Thailand, and the Thai and US Army Medical Departments. International teams from the trial sponsors have performed external monitoring, and have found that the

Table 1
HIV vaccine trials conducted by the Thai AIDS Vaccine Evaluation Group (TAVEG).

Beginning of enrollment	Vaccine	Manufacturer	Sites	Number randomized
August 1995	A phase I trial of Biocine HIV SF2 gp120/MF59, subtype B vaccine in seronegative Thai volunteers (RV99)	Chiron Biocine	JCRC RIHES	27 27 Total: 54
November 1997	Phase I/II double blind, placebo-controlled study of the Chiron Biocine® HIV Thai E gp120/MF59 vaccine administered alone or combined with the Chiron Biocine® HIV SF2 gp120 antigen in healthy HIV-seronegative Thai adults (RV114)	Chiron Biocine	JCRC RIHES VTC Siriraj	93 98 99 93 Total: 383
January 2000	ALVAC-HIV (vCP1521) priming with either oligomeric gp160 THO23/LAI-DID or Chiron HIV Thai E (CM235) gp120 [+/- SF2 gp120] boost (RV132)	Aventis Pasteur and Chiron Vaccines	RIHES Siriraj	66 67 Total: 133
March 2000	ALVAC-HIV (vCP1521) priming with VaxGen gp 120 B/E (AIDSVAX® B/E) boost (RV135)	Aventis Pasteur and VaxGen	JCRC VTC	66 62 Total: 128
November 2000	Booster injections with higher dose gp120/MF59 subtype E antigen in RV114 volunteers previously immunized (RV114A)	Chiron Vaccines	JCRC VTC	12 12 Total: 24

quality of the data generated at the JCRC and other TAVEG sites has been exemplary. Table 2 summarizes the error rate in the Case Report Forms (errors made per 10,000 data points collected) for one of the ongoing vaccine protocols. The overall error rate at JCRC in the trial has been 0.68 errors per 10,000 monitored data points collected. The completion rate (enrolled volunteers who complete the protocol, Table 3) in the three vaccine trials has been 96%, 98% and 97%. Staff were careful to ensure that visits took place within the window periods specified in the protocols (Triampon, 2001). If there were occasions when the volunteer could not meet the scheduled window, the sponsor was informed and an exception requested to continue with protocol visits. This has occurred only 11 times in over 1600 volunteer visits, generating a compliance rate that exceeded 99% across the trials.

The vaccine protocols have contributed to the body of safety and immunogenicity data on various products (Chuenchitra *et al*, 1997; de Souza *et al*, 1997, 2001a; Loomis-Price *et al*, 2001; Nitayaphan *et al*, 1996, 2000, 2001; Pitisuttithum *et al*, 2000; Polonis *et al* 2001). Plans are currently underway to proceed to a Phase III field efficacy trial using a prime-boost vaccine combination from one of the three combinations evaluated in 2000-2001 by the TAVEG. The JCRC staff will play a key role in the transfer of clinical trial capacity to the field sites in the phase III trial, which will include about 16,000 adult volunteers from the general community.

Screening for vaccine trials

As preparations for vaccine trials were being made it became apparent that there would be value in having in place a concurrent process

Table 2
Data error rate at JCRC for a prime-boost vaccine clinical trial, up to March 2001.

Data form title	Data points per page	Pages analyzed	Data points analyzed	Errors detected	Error rate (errors detected in 10,000 points analyzed)
Medical history	14	16	224	0	0
Demography	10	67	670	0	0
Eligibility criteria	12	66	792	0	0
Vaccine administration	15	216	3,240	1	3.09
Post injection reaction	178	432	38,448	1	0.26
Safety laboratory	39	394	15,366	2	1.30
Medications	27	4	108	0	0
Adverse event	24	9	216	0	0
Termination	31	3	93	0	0
Form review	7	3	21	0	0
Total		1,210	59,178	4	0.68

Table 3
Number of visits: follow up rates, compliance (JCRC site only).

Vaccine protocols initiated	RV99	RV114	RV135
Number randomized	27	93	66
Number completed	26	91	64
Subjects lost to follow-up	1[a]	2[b]	2[c]
Trial completion rate	96%	98%	97%
Total number of visits	277	731	648
Visits outside of acceptable window per protocol	2	6	3
Protocol compliance rate (visits within window)	99.3%	99.2%	99.5%

[a] Incarcerated.
[b] 1 dropped due to family concerns about the trial; 1 moved upcountry.
[c] 1 death, unrelated to vaccine trial; 1 dropped due to psychiatric condition (depression).

to allow screening of potential volunteers for upcoming vaccine trials via a separate protocol. The screening would take place during the review and approval process period of the vaccine protocol, so that a pool of eligible volunteers would be ready for consent and enrollment. The collection of data that could be used for refinement of future vaccine trials in terms of inclusion criteria, recruitment targets, catchment areas, etc. was a secondary objective of the protocol.

To date, the protocol has been used to screen 1,155 volunteers over three episodes of screening for enrollment into four HIV vaccine trials at four different TAVEG sites in Thailand (Table 4). Motivations for volunteering have been analyzed and described (Chinaworapong *et al*, 1996, 2001; Jenkins *et al*, 1995, 1998). One of the early lessons learned was that the word 'volunteer' (in Thai) has a somewhat different meaning than intended by the researchers. During the first round of advertisements, many people called asking for jobs.

Low-risk, HIV-uninfected volunteers for

Table 4
Proportion of screened subjects according to vaccine site and protocol, TAVEG sites.

Site	Protocol	No. enrolled in screening protocol	No. randomized in vaccine trial	No. screened per vaccine enrollee
JCRC	RV99	58	27	2.1
	RV114	132	93	1.4
	RV135	95	66	1.4
RIHES	RV99	49	27	1.8
	RV114	205	98	2.1
	RV132	147	66	2.2
VTC	RV114	151	99	1.5
	RV135	90	62	1.5
Siriraj	RV114	123	93	1.3
	RV132	105	67	1.6

Table 5
Example of trial recruitment figures for an HIV vaccine clinical trial.

Booth	Interested	Uncertain	Not interested	Screened	Enrolled
Thai Red Cross Fair	143	277	123	11	9
Blood donation site	109	81	18	9	8
Monk Universities	214	205	52	36	27
Airline office	2	9	15	0	0
Poultry processing factory	89	51	20	1	1
Insurance company	15	31	17	0	0
Army Institute of Pathology	10	1	1	0	0
Navy Base	21	11	4	11	3
Word of mouth					
AFRIMS staff	NA	NA	NA	14	15
Previous volunteer	NA	NA	NA	32	25
TV and News	NA	NA	NA	9	4
Other	NA	NA	NA	20	0
Total	593[a]	666[b]	250[c]	132[d]	93[e]

e/d = 70%; e/a = 16%; e/a+b = 7%; d/a = 22%.
NA: No data available.

vaccine studies have been recruited from the community. The recruitment effort has targeted blood donors, monks (both at temples and at monk universities), naval officers, corporate staff, factory workers, office personnel, attendees at Red Cross Fairs, attendees at scientific conferences, staff at PMKH and AFRIMS, and word-of-mouth from previous volunteers (Table 5). The person-to-person approach was found to be a very efficient method of recruitment. It seemed that confidence was increased among participants by talking to each other, and learning from the experience of former volunteers that participation was safe (Morgan *et al*, 1996).

Behavioral research

A component of every vaccine trial conducted in the JCRC has been ancillary behav-

ioral studies. Volunteers are given a series of questionnaires at baseline and throughout the trial to assess areas such as:

- current and historical risk behavior (for purposes of exclusion from enrollment and monitoring behavioral change as a result of participation in the trial)
- knowledge and attitudes about HIV and vaccines
- psychiatric or social problems that may preclude participation in the trial or require intervention during the trial
- difficulties and perceptions of social discrimination that may have occurred during the trial.

These factors have been analyzed and reported by TAVEG behavioral scientists (Jenkins *et al*, 1996; Thapinta *et al*, 1999).

Before enrolling in a TAVEG vaccine trial, a volunteer is required to successfully pass a Test of Understanding. This is a nurse-administered instrument that tests the volunteer's understanding of both HIV vaccines in general and the specifics of the upcoming clinical protocol. The test is also used as a tool for volunteer education.

Counseling and education

JCRC staff have undergone extensive training in counseling and topics of health education. Topics include HIV pre- and post-test counseling, family counseling, stress counseling, and sexuality issues.

The JCRC staff provide these types of counseling to both HIV-positive and HIV-negative volunteers in the various studies. In addition, they are responsible for providing education about the research protocols, background information on HIV, vaccines, health and sexuality, and for administering the informed consent and Test of Understanding at the initial study visit.

The staff have produced a range of educational materials *eg* computer presentations, brochures, newsletters, videos, and visual aids. These materials are used to facilitate recruitment and retention in the trials, and for general dissemination of information about HIV vaccine research.

The JCRC have transferred this counseling expertise to other sites within the TAVEG and other departments within AFRIMS.

Quality assurance, monitoring and audits

Quality assurance (QA) procedures are in place to ensure the integrity of all data. As each data form is completed, a second staff member checks it for completeness, and signs it. All corrections are made according to the Good Clinical Practices guidelines; all data are double-entered and audit trails upheld. A barcoded identification card ensures a secure linkage between the subjects, their records and their vaccine assignments within the trial.

All research performed at the JCRC must be approved by both the US Army and the Royal Thai Army regulatory processes. HIV vaccine trials are also reviewed by the Ethical Committee of the Thai Ministry of Public Health, the National AIDS Commission's Subcommittee on HIV Vaccine Trials, and the Institutional Review Boards of each collaborating academic site. Before any vaccine trial is initiated, the research sites conduct a Readiness Workshop for the Subcommittee, which showcases the Standard Operating Procedures, clinic forms, training, laboratory readiness – in short, all of the preparation that is required for the undertaking.

The AFRIMS QA Coordinator conducts a pre-implementation review of all regulatory documents, which includes the certification of the consent forms and their translations. External monitoring of the HIV vaccine trials is conducted jointly with the sponsor: thus far, this has been the vaccine manufacturer(s) or the WRAIR. Data management is handled by the sponsor with in-country participation.

Laboratory quality assurance

The AFRIMS Department of Retrovirology and Division of Research has implemented a rigorous Quality Assurance (QA) program to ensure compliance with Good Clinical and

Laboratory Practices. The QA Program program adheres to standards described in the National Committee for Clinical Laboratory Standards Guidelines (NCCLS) and participates in the proficiency panel testing program of the College of American Pathologists (CAP). CAP accreditation was achieved in September 2002. This is the first clinical laboratory in Thailand to receive this accreditation.

DISCUSSION

The building of scientific capacity in developing countries is urgently needed to improve health worldwide and curb the global spread of the HIV epidemic (Harris and Tanner, 2000). By giving scientists the skills and materials needed, these nations can be empowered to take charge of their own development and health status and participate as genuine partners in global medical research: the successful experience of the JCRC, the quality and sustainability of the services offered, and the data generated, testify that this can be done. Some lessons can also be learned from the JCRC experience. Strong support at the highest national level, along with an open attitude to international collaboration, and a strong national ethical plan, are all key elements for the creation of a supportive environment for HIV vaccine and prevention research. An equal and balanced partnership is another essential component and can take time to establish.

It is important to consider the research priorities with prime relevance to the country, to share responsibilities, and strengthen the knowledge and skills of professional counterparts. Research and training should then be linked to public health action (Costello and Zumla, 2000). All the studies conducted at the JCRC have prevention counseling and education as an adjunct. The quality of the research and the services offered are constantly monitored and, where possible, improved through staff training: the correlate is that long-term political commitment and financial and technical support become essential requirements. Fighting HIV/AIDS is a multi-dimensional endeavor, and requires a number of sectors to participate technically and financially in the effort.

Conclusion

The successful establishment of a clinical research unit in a developing country results from many factors, the chief of which is a dedicated team of staff that features high motivation for learning and adaptation to new methodologies, low turnover, and regular training. The well-established logistic and scientific infrastructures in Thailand, the excellent collaboration between the US and Royal Thai Army Medical Departments, Mahidol and Chiang Mai Universities together with a long-term commitment by the US Military HIV Research Program have been crucial elements in the JCRC success.

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