CHAPTER 6
Developing Cohorts for Phase III Trials of Candidate HIV Vaccines

Chiang Mai Community Cohort

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Introduction

In 1992, the Research Institute for Health Sciences (RIHES), Chiang Mai University, Chiang Mai, Thailand was granted an award by the U.S. National Institutes of Health to participate in the international collaborative study entitled "Preparation for AIDS Vaccine Evaluation" or "PAVE" project [1,2]. The overall goal of the PAVE initiative was to establish research sites in Thailand, India, Rwanda, Malawi, Uganda, Zimbabwe and Kenya. The primary objective was to develop suitable prospective cohorts for possible HIV vaccine trials and other HIV prevention studies. All were joint collaborative projects between American and foreign universities. The Thai PAVE project was one of seven international collaborative studies in the PAVE initiative. It was a joint collaborative study of the Office of Disease Prevention and Control, Region 10, Chiang Mai (formerly Office of Communicable Disease Control Region 10), Department of Disease Control (formerly Department of Communicable Disease Control), the Thai Ministry of Public Health and the Department of Epidemiology at Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University (formerly School of Hygiene and Public Health).

The Thai PAVE project was funded in October, 1992 for an initial two-year period. The primary objective of the Thai PAVE was to document HIV incidence of various cohorts in northern Thailand that could be appropriate for enrollment in future HIV vaccine trials [2]. Cohort development began in November, 1992 and volunteer enrollment started in March, 1993. During the first year, a total of 2,708 high-risk HIV seronegative adults drawn from four different populations in six provinces of northern Thailand were enrolled in four cohorts. These cohorts included female commercial sex workers (FCSW), male sexually transmitted disease (STD) clinic users, military conscripts from the Royal Thai Army (RTA) and men recently discharged from RTA service [3].

Cohort of female commercial sex workers

Between March 10, 1993 and May 28, 1993, a total of 1,068 FCSW were screened and subsequently voluntarily enrolled at six STD clinics located in three provinces in northern Thailand. These clinics were operated under supervision of the Office of Disease Prevention and Control, Region 10, Chiang Mai, Ministry of Public Health. At baseline, 409 (38.3%) were HIV seropositive. Of the remaining 659 who were HIV seronegative, 395 (59.9%) agreed to enroll in the follow-up study. Of those enrolled, 175 (44.3%) were brothel-based (so called **"**direct FCSW**"**), and 220 (55.7%) were not brothel-based, working at other sex establishments where they performed other services in addition to sex (so called **"**indirect FCSW**"**). A total of 335 (84.6%) FCSW were seen at the first 3-month follow-up and 289 (73.0%) returned at the second 6-month follow-up. At six months, the follow-up rates were higher in indirect FCSW (85.2%) than among direct FCSW (58.5%). At the second follow-up, 19 FCSW who had seroconverted to HIV were detected: 15 were direct FCSW and four were indirect FCSW. The incidence of HIV infection was 8.2/100 person-years, 29/100 person-years among direct FCSW and 4/100 person-years among indirect FCSW (Table 1) [3]. At 18 months (the third and final 6-month follow-up), a total of 29 seroconverters were detected: 17 were direct FCSW and 12 were indirect FCSW. The incidence was calculated at 7.38/100 person-years. The follow-up rate had decreased to 43.9% (Figure 1) [4-5].

Table 1. Prevalence and incidence of HIV infection and compliance with follow-Up in selected populations in northern Thailand, 1993

Population	No. screened	HIV^{+} (%)	HIV^{-} (%)	Enrolled (%)	F' Up[a] No. (%)	Seroconverters Annual HIV Incidence
Female Commercial Sex Workers	1,068	409 (38.3%)	659 (61.7%)	395 (59.9%)	289 (73.2%)	19 (8.2%)[b]
Male STD Clinic Patients	1,031	164 (15.9%)	867 (84.1%)	264 (30.4%)	259 (98.1%)	7 (4.0%)
Royal Thai Army Conscripts	866	108 (12.5%)	758 (87.5%)	679 (89.6%)	679 (89.6%)	4 (1.2%)[c]
Discharged Royal Thai Army Conscripts	556	74 (13.3%)	482 (86.7%)	380 (68.3%)	360 (94%) (311 HIV neg, 49 HIV pos)	4 (5.1%)

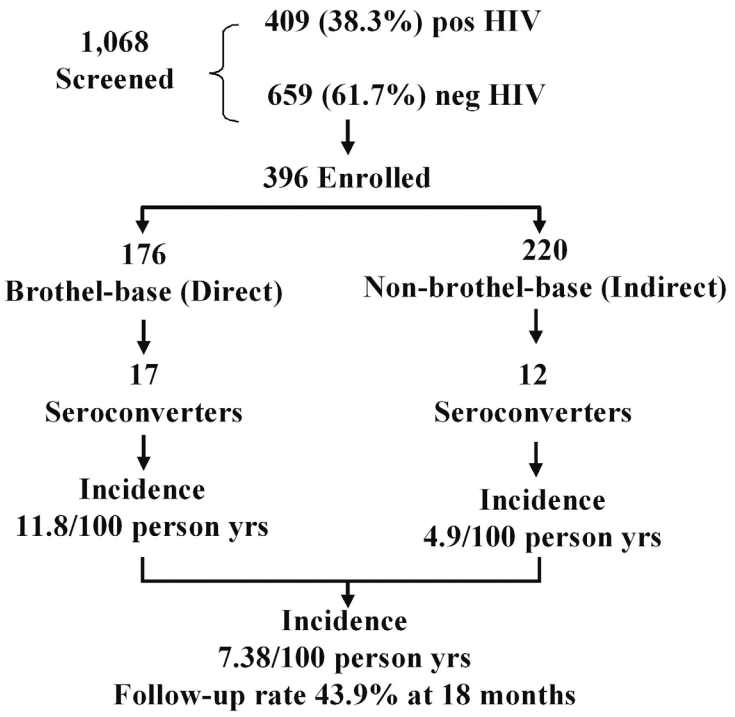
[a] F' Up = Follow-up

[b] HIV incidence = 14.7/100 person-semesters,i.e., 29/100 person-years among direct CSWs; and 2.0/100 person-semesters, i.e., 4/100 person years among indirect CSWs.

[c] 4 HIV seroconverters at 6-month follow-up; HIV incidence in RTA cohorts 1 and 2 enrolled in May 1991 and November 1991 were 98 seroconverters in 3,098.66 years of follow-up or 3.2/100 person-years.

After: Nelson, K.E., Beyrer, C., Natpratan,C., Eiumtrakul, S., Celentano, D.D. and Khamboonruang, C. (1994). Preparatory Studies for Possible HIV Vaccine Trials in Northern Thailand. AIDS Res Hum Retrovirus.19 (Suppl 2): S243-S246.

Figure 1. Summary of prevalence and incidence of HIV infection, and follow-up rates of female commercial sex worker cohort (1992-1995) (n = 396)



After: Khamboonruang, C. (2001). Experience in cohort development for HIV vaccine trials and experience in conducting preventive HIV vaccine rials in northern Thailand. HVTNInternational Working Group Workshop. Rio de Janeiro, Brazil. March 15-17, 2001. Oral presentation

Cohorts of sexually transmitted disease clinic users

In the male sexually transmitted disease (STD) clinic user cohort, 1,031 patients agreed to HIV serological testing. Of those tested, 164 (15.9%) were HIV seropositive at baseline and the remaining 867 were offered enrollment in the prospective follow-up study. Of those offered enrollment, 264 (30.4%) agreed to participate in the study. Three 6-month follow-ups were carried out. In the first follow-up appointment, 259 (98.1%) volunteers returned to the clinic and 249 (94.3%) came back for the second appointment. Seven seroconverters in 175.25 person-years of follow-up were identified with an incidence of 4.0/100 person-years (Table 1) [3]. At 18 months or the third (and last) follow-up, an additional single seroconverter was identified. The incidence was calculated as 2.5/100 person-years. Follow-up rate had reduced to 82% (Table 2) [4-5].

From 1995 to 1997, a similar cohort was developed. Both male and female sexually transmitted disease (STD) clinic users and Anonymous HIV Testing Clinic (ATC) attendees agreed to participate in the follow-up study. A renewal grant award of PAVE to HIV Network for Prevention Trials (HIVNET) and the Walter Reed Army Institute of Research (WRAIR) supported this study. A total of 1,995 volunteers (1,219 males and 776 females) were screened: 371 (18.6%) volunteers [130 (13.8%) males and 47 (8.4%) females] were HIV seropositive and 1,642 (81.4%) [811 (86.2%) males and 413 (91.6%) females] were seronegative at baseline. A total of 1,501 (941 males and 560 females) seronegative attendees agreed to participate in the follow-up study. Follow-up was carried out at six month intervals during a period ranging from 2 to 27 months. The results revealed that 20 seroconverters, 7 males and 13 females, were identified. The incidence was calculated as 0.87/100 person-years: 0.48/100 person-years in males and 1.54/100 person-years in females. The follow-up rate ranged from 80-82% in males and was 82% in females, respectively (Table 2) [4-5].

Table 2. Prevalence and incidence of HIV infection among High-Risk cohorts in northern Thailand

Cohort	Screened No.	Enrolled No. (%)	HIV Positive No. (%)	HIV Negative No. (%)	F/U[a] Duration (months)	F/U Rate (%)	New HIV/ yr. No.(%)
Male STD Clinic Users (1992-1995)	1,031	264 (30.4)	164 (15.9)	867 (84.1)	18	82.0	3 (2.5)
STD/ATC[b] Users: Male & Female (1995-1997)	1,995	1,501 (66)	571 (18.6)	1,624 (81.4)	2-27	20	(0.87)
Male	1,219	941 (41)	130 (15.8)8	11 (86.2)	80-82	7	(0.48)
Female	776	560 (25)	47 (8.4)	413 (91.6)	82.0	13	(1.54)
Factory Workers	499	499 (22)	15 (2.40)	484 (97.6)	6	70.0	5 (2.06)
Male (1998)	106	106 (5)	7 (6.60)	99 (93.4)	6	68.9	2 (4.08)
Female	393	393 (17)	5 (1.27)	388 (98.8)	6	88.3	3 (1.54)
Total	4,595	2,660					

[a] F/U = Follow-up
[b] ATC = Anonymous HIV Testing Clinic

After: Khamboonruang, C. (2001). Experience in cohort development for HIV vaccine trials and experience in conducting preventive HIV vaccine trials in northern Thailand. HVTN International Working Group Workshop. Rio de Janeiro, Brazil. March 15-17, 2001. Oral presentation

Cohorts of military conscripts

Prior to our discussion about the military cohort, the Royal Thai Army's conscription system should be briefly described. The Royal Thai Army commences induction of Thai young men (aged 21) by lottery method during the first two weeks of April each year. Of those who are inducted, half of the conscripts will be assigned to bases in early May and the remaining half in early November. They will be heavily trained during the first two months and then remain in the service for two years. Then, they will be discharged and serve as retired officers until the age of 45. Therefore, military conscripts are an ideal population for an HIV epidemiological study because of the large sample size, accessibility for study, and because of the random selection method used — i.e. the data could be generalized to the young male population in Thailand.

For the Thai PAVE initiative study, two military conscript cohorts, one inducted in May 1993 and another in November 1993, were included in the follow-up study. Although HIV serological screening among RTA conscripts at baseline is required as a routine by the Army, subsequent follow-up testing requires patient consent. Therefore, the seroprevalence and risk behavior history at baseline is representative of 21-year-old men in northern Thailand.

In May 1993, 869 men were conscripted and 107 (12.3%) were found to be HIV positive at baseline (Table 3) [4]. After six months in the service (November 1993), they were asked to follow-up at Paramedical Corps clinic at their original base of assignment. A total of 778 conscripts (89.8%) came back for follow-up. Only 679 subjects had complete data. There were four seroconverters with a calculated annual incidence of 1.2/100 person-years (Table 1) [3]. At the last follow-up or 24 months in the service, follow-up rate declined to 77.40% with the incidence of 0.9/100 person-years (Table 3) [4]. Among 798 men conscripted into the RTA in November 1993, 92 (11.5 %) were infected with HIV at baseline (Table 3) [4]. All agreed to participate in the follow-up study. There were 7 seroconverters identified at the last 18- to 24-month follow-up visits with the annual incidence of 0.1/100 person-years (Table 3) [4]. The follow-up rate was calculated at 78.5% (Table 3) [4]. It would be worth mentioning that intensive "peer education," focused on reducing alcohol use and brothel patronage including condom use skills, was undertaken in this cohort [5]. If data obtained from both cohorts (n = 1,669) was combined for analysis,

the results revealed that 1,549 (93%) men had at least one visit. The follow-up rates at six month intervals for a duration of 24 months were 90%, 83%, 77%, and 77%, respectively, with the overall incidence rate of 0.55/100 person-years [7].

Table 3. Prevalence and incidence of HIV infection among 21-year-old young men in northern Thailand from 1991 to 1998

Cohort (DD/MM/YY)		Tested No.	HIV Positive No.(%)	F/U[a] No.	F/U Rates[b] (%)	Incidence (/100 P-Y[c])
RTA-1	(01/05/91)	935	97 (10.4)	838	78.0	3.4
RTA-2	(01/11/91)	888	111 (12.5)	777	76.0	3.2
RTA-3	(01/05/93)	869	107 (12.3)	866	77.4	0.9
RTA-4[d]	(01/11/93)	798	92 (11.5)	800	78.5	0.1
	(01/05/94)	-	(8.5)[e]	-	-	-
	(01/11/94)	-	(9.3)[e]	-	-	-
RTA-5	(01/05/95)	821	55 (6.7)	821	71.9	0.2
RTA-6	(01/05/96)	820	38 (4.6)	820	-	-
RTA-7	(01/05/96)	835	45 (5.4)	835	-	-
RTA-8	(01/05/98)	682	16 (2.4)	-	-	-
Total		6,648				

[a] F/U = Follow-up
[b] Follow-up duration for all cohorts: 18-24 months
[c] P-Y = Person-Year
[d] Intensive behavioral intervention was undertaken with this cohort
[e] Data was obtained from the Army Institute of Pathology, Royal Thai Army

After: Khamboonruang, C. (2001). Experience in cohort development for HIV vaccine trials and experience in conducting preventive HIV vaccine trials in northern Thailand. HVTN International Working Group Workshop. Rio de Janeiro, Brazil. March 15-17, 2001. Oral presentation.

In April 1993, 556 conscripts, prior to their discharge from two years of military service, were solicited to participate in the follow-up study. Of those offered enrollment, 380 (68.3%) accepted to join the study and 360 (94%) men returned to the Paramedical Corps clinic at their original base of assignment for interview and HIV testing. They were seen at the clinic at 3-, 9- and 15-month visits. At baseline, prior to discharge, 311 (86.4%) men were HIV serological negative and 49 (13.6%) conscripts were HIV positive. At the 3-month visit, 4 of the 311 (1.3%) men who were seronegative at discharge converted to HIV positive, for an annual incidence of 5.1/100 person-years (Table 1) [3]. At the 15-month visit, 3 more seroconverters were identified and contributed a total of 345.9 person-years at risk of new HIV infection and an HIV incidence rate of 2.02/100 person-years (Table 4) [4]. In addition, 185 conscripts who were discharged from the service in 2,000 were enrolled for the HIV natural history study for a long-term follow-up (5.1 years). There were three seroconversions for an incidence of 3 per 970 person-years, or 0.31/100 person years (Table 4) [4].

Table 4. Summary of incidence of HIV infection in Thai young men after discharged fromMilitary service (1991-1999)

Cohort	Identified	Enrolled	Time F/U[a]	Sero-converters	Incidence (per 100 P-Y[b])
Ex-service 1991-1994	551	380	15 mos. (3,459 P-Y)	7	2.02
Ex-service 1998-2000	232	185	5.1 yrs. (970 P-Y)	3	0.31

[a] F/U = Follow-up
[b] P-Y = person-year

After: Khamboonruang, C. (2001). Experience in cohort development for HIV vaccine trials and experience in conducting preventive HIV vaccine trials in northern Thailand. HVTN International Working Group Workshop. Rio de Janeiro, Brazil. March 15-17, 2001. Oral presentation.

One of the secondary objectives of PAVE was to assess the willingness of volunteers in the cohorts to participate in potential future HIV vaccine efficacy trials. Approximately one year after their original recruitment, the four cohorts underwent a cross-sectional survey using face-to-face interviews to determine their willingness to join a vaccine trial. Complete information was obtained from 54.3% (n=215) of the original FCSW cohorts, 83% (n=219) of STD clinic users, 87% (n = 1,453) of conscripts and 77% (n=293) of discharged conscripts. Across the cohorts, approximately 25% of subjects would definitely join the trial if asked and an additional 38% would accept an AIDS vaccine if they were convinced it would be safe and effective. Important barriers to participation included concerns with discrimination (16-45%), short- (37-60%) and long-term (30-55%) vaccine side-effects, fear of disability and death (36-58%) and beliefs that partners would refuse to have sex (24-49%) [8]. Attitudes toward vaccines were summarized in (Table 5.)

Table 5. Interests in HIV vaccine trial participation of FCSWs, STD clinic users, RTA and Ex-RTA cohorts

Questions	%			
	FCSW (n=215)	STD (n=219)	RTA (n=1,453)	Ex-RTA (n=293)
Definitely would join an AIDS vaccine trial	24.7	24.2	24.7	29.0
Definitely would refuse to join an AIDS vaccine trial*	0.9	2.3	10.9	4.1
Would definitely take a proven safe and effective AIDS vaccine*	38.1	51.1	52.2	40.6
Aware that vaccines can prevent infection	61.4	67.1	72.7	68.9
An effective AIDS vaccine could prevent future HIV infections*	76.3	73.1	84.2	84.0
Vaccine-induced HIV + would be discriminated*	27.9	16.4	45.4	43.7
Concerned about immediate vaccine side-effects*	46.5	37	58.2	59.7
Concerned about long-term side-effects*	29.8	31.5	55.2	53.2
Fear of permanent injury or death*	36.3	38.8	58.3	55.3
Partner would refuse to have sex*	23.7	28.8	49.4	43.0

* $p < 0.001$, based on χ^2 test with 3 degrees of freedom.
FCSW = Female commercial sex workers
STD = Sexually transmitted disease clinic attendances
RTA = Royal Thai Army conscripts.

After: Khamboonruang, C. (2001). Experience in cohort development for HIV vaccine trials and experience in conducting preventive HIV vaccine trials in northern Thailand. HVTN International Working Group Workshop. Rio de Janeiro, Brazil. March 15-17, 2001. Oral presentation.

Cohort of factory workers

In 1994, the Research Institute for Health Sciences (RIHES), Chiang Mai University was granted an award from the WHO Global Program on AIDS (GPA) to conduct a feasibility study of establishing northern Thai factory workers as a cohort of potential volunteers for HIV vaccine trials. The study area was located in Lamphun province, adjacent to Chiang Mai. The province is home to the Northern Industrial Estate, an enterprise organization of the Thai Ministry of Industry where over 500 factories are located. Many of the workers live in company housing, but as many as 5,000 live in private housing (e.g. dormitories) around the Estate. The majority of workers were from Lamphun and other northern provinces. During that period of time, the HIV/AIDS epidemic in this region of Thailand was at its peak. Stigmatization and discrimination were serious social problems. Factory worker recruitment was unsuccessful due to uncoordinated assistance from owners and managers. Therefore, workers were offered enrollment in the follow-up study by using a **"**door-to-door**"** recruitment strategy by a mobile team of nurses and counseling staff from the Lamphun Provincial Health Office. No names were used, only subject identifiers, ensuring anonymity. The study was comprised of four visits: a baseline visit, post-test counseling and HIV test result report (4-6 weeks later), 6-month follow-up visit after the baseline, and post-test counseling and HIV test result report visit shortly thereafter. A total of 106 (21.2%) men and 393 (78.8%) women were enrolled. The median age was 22 years and the mean 23.4 years (range 15 to 50 years). The majority of workers (69.4%) were never married. A total of 12 out of the 499 workers were seropositive (confirmed by Western Blot) for an overall HIV prevalence of 2.4%. HIV status varied significantly by sex: prevalence in males was 7 of 106 (6.6%) and for females was 5of 393 (1.3%), OR = 5.49 (95% CI = 1.51, 20.39). A total of 420 of 499 (84.4%) returned for follow-up at 6 months. Retention varied significantly by sex: 73 of 106 (68.9%) men came back for follow-up compared to 347 of 393 (88.3%) women, Relative risk (RR) = 1.21 (95% CI = 1.07, 1.37). There were 5 Western Blot-confirmed seroconverters for an incidence of 5 per 242 person years, or 2.1/100 person years. The HIV seroconversion rate did not significantly differ by sex. Among men, there were 2 new infections among 99 baseline seronegatives for an incidence of 4.1/100 person years. Among 388 uninfected women at

baseline, there were 3 seroconversions for an incidence of 3 per 195 person years, or 1.5/100 person years. When workers were asked about their interests in long term follow up (three years), only 8.6% said yes, 26.2% said no and 65.2% were unsure (Table 2) [9].

Community studies of HIV incidence and prevalence in northern Thailand

Following vigorous prevention efforts undertaken during an explosive epidemic of HIV-1 in the early 1990's, national sentinel surveillance data revealed that both prevalence and incidence of the infection in most of the high-risk cohorts (e.g. FCSW, STD clinic users, and military) were declining. Meanwhile, a trend of the HIV epidemic shifting towards the general population was reported [10,11]. From this observation, a collaborative study to investigate the prevalence and incidence rate of HIV-1 among general communities in northern Thailand was conducted from 1998 to 2001. The collaborators in this study included the RIHES, the Office of Disease Control, Region 10, Chiang Mai, Department of Disease Control, the Thai Ministry of Public Health, the Armed Force Research Institute for Medical Sciences (AFRIMS), the US Army Medical Component (USAMC) and the Johns Hopkins Bloomberg School of Public Health. The Walter Reed Army Institute for Research (WRAIR) and the Henry M. Jackson Foundation for the Advancement of Military Medicine supported this study [4,12, 13]. The objectives of the study were as follows: (1) to measure HIV prevalence and incidence, social mobility and interest in HIV vaccine trial participation among adults who lived in HIV high-risk communities; (2) to identify appropriate communities for targeted cohort development to support HIV efficacy trial in the future and (3) to evaluate level of community interest and support in HIV vaccine trial participation.

Peri-urban communities around Chiang Mai and Lamphun city were selected (Figure 2). These communities had shown from the Thai PAVE studies [3] and the national sentinel surveillance [10, 11] that they had the highest rates of HIV infection in Thailand during the peak of the Thai epidemic in 1991-1995. A "Health Fair" approach was used as a strategy for volunteer enrollment and 6-month follow-up (Figure 3) [12]. Outreach programs were carried out by well-trained local health staff, community leaders, and village health volunteers. Their responsibility was to disseminate information in communities through public forums.

Interested volunteers were enrolled in the project by completing a consent form and self-administered demographic questionnaire. Then, potential volunteers were scheduled to attend the health fair organized at local Buddhist temples or primary schools. At the health fair, they were informed about the project once more and questions were answered. Then, volunteers proceeded to: pre-test counseling about HIV, collection of stool samples (if available) for intestinal parasites, blood draw for HIV and syphilis, and mini-chest x-ray. To protect volunteers' rights and confidentiality, they returned for private, individual post-test counseling and test results at local health centers 3-4 weeks later. Referral and/or treatment of identified health problems were provided free of charge at appropriate health care centers of the Ministry of Public Health. The above described process was repeated in six months for the follow-up study.

Figure 2. Map of Chiang Mai and Lamphun province. Study sites for community cohort development during 1998-2000

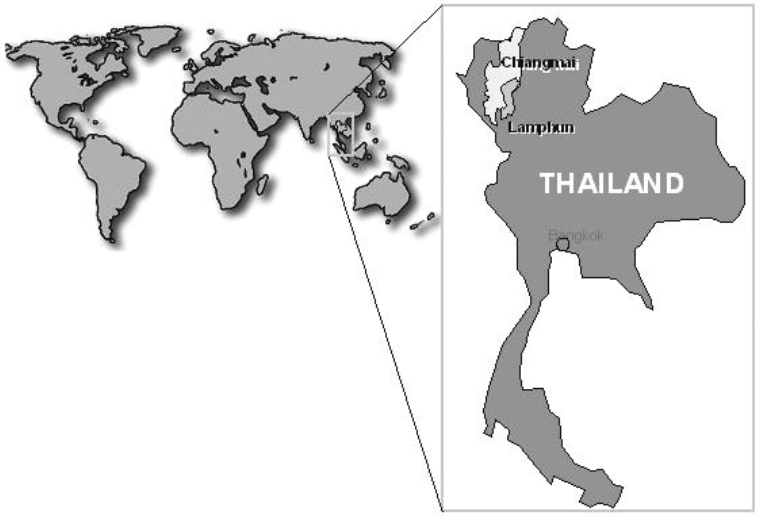
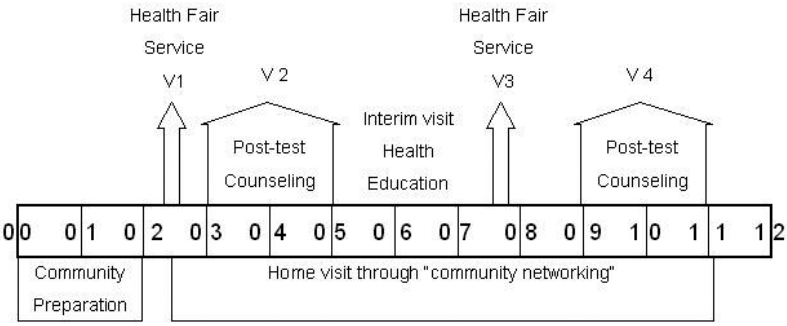


Figure 3. Flow Diagram of community cohort enrollment and follow-up



After: Natpratan, C., Borwornsin, S., Srirak, N., et al. (2000). Community-based HIV vaccine trial preparation in northern Thailand, 1998-1999: A health fair enrollment approach. The 18th Annual Health Sciences Meeting, Research Institute for Health Sciences (RIHES), Chiang MaiUniversity, Chiang Mai, Thailand, June 8, 2000. Poster presentation, Abstract p.47.

A total of 6,812 volunteers were enrolled during 1998-2000: 2,274 in 1998 (Cohort A), 2,259 in 1999 (Cohort B), and 2,279 in 2000 (Cohort C). The age range among the three cohorts was 20-35 years old, except in Cohort A that extended to 45 years. Female subjects all outnumbered males. The numbers of male/female subjects were 880/1,394 in Cohort A, 932/1,327 in Cohort B and 852/1,427 in Cohort C, respectively. At baseline, a total of 160 of 6,812 subjects (2.3%) were HIV positive: 80 of 2,664 (3.0%) were men and 80 of 4,148 (1.92) were women. In Cohort A, 45 of 2,274 (2.0%) volunteers were HIV seropositve, 23 of 880 (2.6%) were male volunteers and 22 of 1,394 (1.6%) were females. In Cohort B, 65 of 2,259 (2.9%) subjects had positive HIV serology; of those positive subjects, 40 of 932 (4.3%) were men and 25 of 1,327 (1.9%) were women. In Cohort C, 50 of 2,279 (2.2%) enrollees had positive HIV serology; of those positive enrollees, 17 of 857 (2.0%) were males and 33 of 1,427 (2.3%) were females (Table 6,7) [4].

At 6-month follow-up, two seroconverters were detected in 1,105.7 person-years of follow-up in Cohort A for a calculated incidence of 0.18/100 person-years. No seroconverter was detected in Cohort B. Two seroconverters were observed in 1,030.5 person-years of follow-up in Cohort C, with a calculated incidence of 0.19/100 person-years. Overall in these two cohorts (A and B), there were four seroconverters among volunteers who were seronegative at baseline during 2,136.2

person-years of follow-up. Thus, the incidence of 0.16/100 person-years was calculated (Table 6) (Unpublished data).

An assessment of volunteers' willingness to participate in future vaccine trials was also carried out. In Cohort A, a cross-sectional survey to determine their willingness to join the trial was conducted at the 6-month follow-up visit. Approximately 33% of volunteers would definitely join an HIV trial and about 37% would definitely refuse. Their reasons for not joining a trial included: don't like injections, not sure about vaccine safety and fear of getting AIDS from vaccination (Table 8) [4]. Consistencies for willingness to participate in a vaccine trial were analyzed across three cohorts at baseline and at 6-month follow-up. The results focused on two simple choices: [1] "I would definitely want to join a vaccine trial" and [2] "I would definitely not join." Those who were willing to join a trial totaled 30.2% (624 of 2,065 respondents) versus 51.4% (1,141 of 2,065 respondents) for the latter (Table 9) [4].

Table 6. Summary of HIV prevalence and incidence rates and retention rates of community cohorts (1998-2000)

Descriptions	Cohort A (1998) Age: 20-45 yrs.	Cohort B (1999) Age: 20-35 yrs.	Cohort C (2000) Age: 20-35 yrs.	Total
1. No.HIV tested volunteers	2,274	2,259	2,279	6,812
Male	880	932	852	2,664
Female	1,394	1,327	1,427	4,148
2. No.HIV Positive (%)	45 (2.0)	65 (2.9)	50 (2.2)	160 (2.3)
Male	23 (2.6)	40 (4.3)	17 (2.0)	80 (3.0)
Female	22 (1.6)	25 (1.9)	33 (2.3)	80 (1.9)
P value	0.08	0.001	0.62	0.004
3. No.seroconvert	2	0	2	4
Male	1	0	0	1
Female	1	0	2	3
4. Incidence (/100 P-Y)	0.18	0	0.19	0.16
5. Retention rates				
No.enroll / No.FU	2,274/2,178	2,259/2,086	2,279/2,204	6,812/6,368
(%)	(95.8)	(92.3)	(92.3)	(93.0)

P-Y = Person-year
FU = Follow up

Table 7. Summary of prevalence and incidence of HIV infection and retention rates among community cohorts, 1998-2000 (Cohorts A-C) (Age 20-35 years)

Year	No. enrolled	No. 6-Mo F/U[a]	Retention Rate (%)	HIV Prevalence (%)	HIV incidence (/100 P-Y[b])
1998	2,274	2,178	95.8	2.0 (1.6-2.6)	0.18
1999	2,259	2,086	92.3	2.9 (1.9-4.3)	0.00
2000	2,279	2,204	92.3	2.2 (0.7-4.6)	0.19
Total	6,812	6,368	93.0	2.3	0.16

[a] F/U = Follow-up
[b] P-Y = Person-Year

After: Khamboonruang, C. (2001). Experience in cohort development for HIV vaccine trials and experience in conducting preventive HIV vaccine trials in northern Thailand. HVTN International Working Group Workshop. Rio de Janeiro, Brazil.March 1517, 2001. Oral presentation.

Table 8. Interests in HIV vaccine trial participation, community cohort C (1998) (Interviewed during the last follow-up visit or V4)

Question	Doi Saket N = 1,135	Hang Dong / San Pa Tong N = 1,085	P value
- Definitely would join and AIDS vaccine trail	402 (35.4)	334 (30.8)	0.02
- Definitely would refuse to join an AIDS vaccine trail	406 (35.8)	422 (38.9)	0.02
- Why? If you would not join.			
Don't like injections	76 (15.6)	77 (15.4)	1.0
Not sure of safety	320 (65.8)	314 (62.8)	0.4
Afraid of getting AIDS from the vaccine	125 (25.7)	118 (23.6)	0.5
Desired incentive, if you join an AIDS vaccine trial [Number(%)answeringyes]			
Money	89 (13.7)	99 (17.1)	0.1
Health insurance	281 (43.4)	252 (43.4)	1.0
Life insurance	208 (32.1)	186 (32.1)	1.0
Recognition for altruism	250 (38.6)	178 (30.7)	0.005
No incentive	81 (12.5)	111 (19.1)	0.002

After: Khamboonruang, C. (2001). Experience in cohort development for HIV vaccine trials and experience in conducting preventive HIV vaccine trials in northern Thailand. HVTN International Working Group Workshop. Rio de Janeiro, Brazil. March 15-17, 2001.Oral presentation.

Table 9. Interests in HIV vaccine trial participation, community cohort A-C (1998-2000)

V2 Interview	V4 Interview	same answer at V2 and V4 N (%)	% Total
I would definitely want to join	I would definitely want to join	624 (30.2)	13.6
Very likely	Very likely	(1.0)	0.4
Somewhat likely	Somewhat likely	280 (13.6)	6.1
Total		924 (44.8)	20.1
Definitely would not join	Definitely would not join	1,062 (51.4)	23.2
Not likely	Not likely	(3.8)	1.7
Total		1,141 (55.2)	24.9
Grand Total		2,065 (100.0)	45.0

V2 = visit 2
V4 = visit 4

After: Khamboonruang, C. (2001). Experience in cohort development for HIV vaccine trials and experience in conducting preventive HIV vaccine trials in northern Thailand. HVTN International Working Group Workshop. Rio de Janeiro, Brazil. March 15-17, 2001. Oral presentation.

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The Bangkok Metropolitan Administration (BMA) Cohort of Injection Drug Users (IDUs)

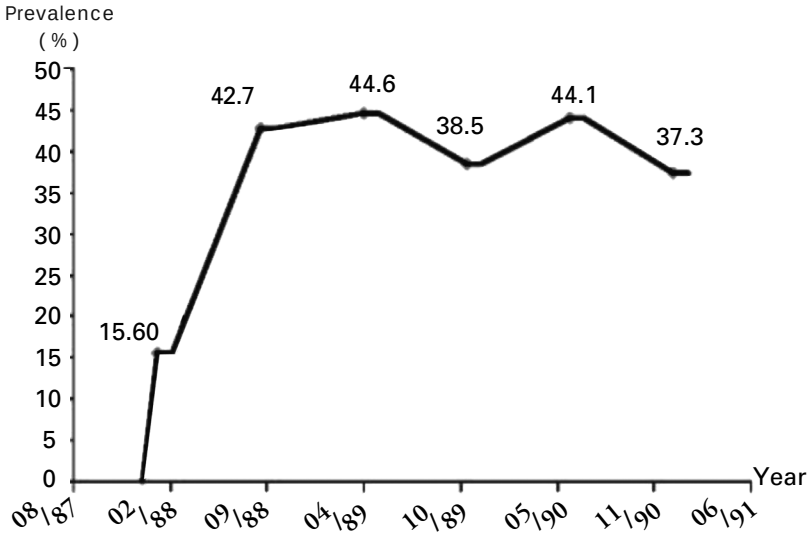
Suphak Vanichseni
Dwip Kitayaporn
Timothy D. Mastro

A Challenge for Thai public health: control of HIV/AIDS among injecting drug users (IDUs) in Bangkok

The establishment of and prospective follow-up of cohorts of persons at high risk for HIV infection are essential steps to assess the feasibility of preventive HIV vaccine efficacy trials [1,2]. In Thailand, two national plans, from 1993 and 1997, defined prospective cohort studies as essential components leading to HIV vaccine efficacy trials as part of Thailand's national effort to develop and evaluate HIV vaccines [3,4]. The basis for the concept of developing a cohort of IDUs for epidemiologic evaluation leading to HIV vaccine trials began in 1988 when the Bangkok Metropolitan Administration (BMA) Drug Treatment and Prevention Division documented an explosive epidemic of HIV-1 infection among IDUs attending BMA drug treatment clinics [5]. The BMA had initiated an outpatient methadone programme for heroin users in 1980. In this programme, drug users were able to voluntarily enrol in a 45-day methadone detoxification programme administered at BMA clinics free of charge. HIV surveillance of these IDUs showed a sharp increase in HIV seroconversion in 1988 (Figure 1). In response to this epidemic, the BMA launched a multifaceted HIV prevention programme for IDUs. The programme included a city-wide information

and education campaign that delivered HIV prevention messages and materials. Drug users also received HIV risk reduction counselling and bleach was provided to clean injection equipment. In addition, in 1989, a pilot methadone maintenance (as compared to detoxification) programme was started. To better assess the burden of the drug use and the related HIV-1 problem, it was deemed necessary in 1991 to estimate the total number of IDUs in Bangkok and the number of these that were HIV-1 infected. A two-sample (drug users in treatment programmes and drug users in police station jails) capture-recapture study was conducted [5]. This study yielded an estimate of 36,600 opiate users and approximately 12,000 HIV-infected IDUs in Bangkok in 1991. Two additional retrospective studies of drug users in treatment programmes in Bangkok estimated HIV-1 incidence of about 10 to 12 per 100 person-years in the early 1990s [7,8]. Although HIV-1 incidence rates had decreased since the late 1980s, they remained unacceptably high.

Figure1. HIV seroprevalence among IDUs under treatment in 17 Bangkok drug treatment clinics



Source : Drug Abuse Prevention and Treatment Division, BMA

Bangkok, with a large population of IDUs at high risk for HIV-1 infection, together with an extensive network of outpatient drug treatment clinics operated by the BMA, offered a potential setting in which to conduct a large-scale HIV-1 vaccine efficacy trial. In the early to mid-1990s, approximately 8,000 illicit drug users sought treatment in the BMA system each year; about 70% injected drugs and almost all used heroin. Methadone substitution therapy has been offered since 1980 along with extensive HIV prevention efforts since the late 1980s. In addition, data from a small BMA pilot cohort study of 152 recently HIV-infected IDUs showed a one-year retention rate of 78% [9]. Furthermore, early HIV-1 molecular epidemiologic data indicated that these high risk Bangkok IDUs were predominantly infected with HIV-1 subtype B strains [10,11] which were similar to the HIV-1 strains found in North America and Europe that had been used in the formulation of the then available candidate HIV-1 vaccines. The 17 BMA drug treatment clinics had well-established infrastructures; each clinic was generally staffed with a physician, three nurses, three social workers, and a psychologist. In 1994, this situation led drug treatment officials to approach the BMA Deputy Governor (Dr. Chaiyan Kampanatsanyakorn at the time) for support for the establishment of a cohort study of IDUs. This resulted in a collaborative effort to begin an IDU cohort study among scientists from the BMA, the World Health Organization's Global Programme on AIDS, Faculty of Medicine Siriraj Hospital of Mahidol University, and the Thailand MOPH-US CDC Collaboration (TUC, formerly known as the "HIV/AIDS Collaboration" a joint activity of the US Centers for Disease Control and Prevention [CDC] and the Thai Ministry of Public Health). This cohort study was conducted to determine the feasibility of conducting an HIV-1 vaccine efficacy trial among IDUs in Bangkok by assessing successful follow-up rates, HIV-1 incidence rates and the genetic characterisation of infecting HIV strains [12,13]. The recruitment, enrolment and follow-up of more than 1,000 volunteer IDUs posed a special challenge for the staff of the BMA clinics, as they were more experienced in public health practices than in research.

What did we learn from this IDU cohort?

1. Recruitment

In the early 1990s, there were about 8,000 drug users who attended 17 BMA narcotic clinics annually. Volunteers who were not known to be HIV infected were recruited from the clinics. During the first phase of enrolment, 82.5% of those approached were willing to participate in the cohort study [12]. Thus, it appeared that cohort enrolment in this environment was possible. During 1995-96, a total of 3,643 IDUs were screened for enrolment [13]. The HIV-1 prevalence in this group was 29.9% and 1,209 HIV-seronegative IDUs were enrolled for prospective follow-up. Data from a nested substudy explored whether the IDU volunteers were willing to participate in an HIV vaccine efficacy trial. In this study [14], a subset of 193 IDUs previously enrolled in this prospective cohort study was invited to group sessions describing a potential trial. Then they were asked to completed questionnaires assessing their comprehension and willingness to participate. A week later, they completed a follow-up questionnaire that again assessed comprehension and willingness to participate, as well as barriers to and positive motives for participation in a possible vaccine trial, with whom (if anyone) they talked about the information, and whether others thought participation was a good, bad, or neutral idea. At baseline, 51% were definitely willing to participate, and at follow-up 54%; only 3% were not willing to participate at either time. The refusal rate could reflect how well volunteers could make informed decision-making.

2. Retention

As one of the purposes of this feasibility study was to assess retention in preparation for a possible candidate HIV vaccine trial, ethically sound, extensive efforts were made to support IDUs to remain in the cohort study and attend 4-monthly visits. Volunteers proved to be very committed to come for scheduled visits and clinic staff routinely made home-visits to encourage successful follow-up. A special challenge involved incarceration of volunteers as arrest and incarceration were common for this group of IDUs. Before enrolment, incarceration was reported by 66% of participants and 43% during study follow-up [13,15]. Because of this high rate of incarceration, it was important for the success of this cohort study to train BMA staff how to find and contact incarcerated volunteers. Study staff received good co-ordination

and co-operation from the Correction Department of the Ministry of Interior Affair (now Department of Correction, Ministry of Justice), and from the prison officers. Multiple discussions and negotiations took place during the first year of the study to establish procedures that would allow study participants to be followed-up while incarcerated. By the end of the cohort study, every case known to have been incarcerated was visited in the prison by a team of clinic staff to conduct the activities according to the protocol including counselling and preventive measures. We found that the volunteers in prisons were very happy to meet BMA staff, because many of them were not normally visited by anyone. They felt that the BMA staff took good care of them; some even said that staff take better care of them than their mothers!

A special calendar was created for following up volunteers every 4 months for study visits, which included interviews, counselling, and HIV testing. Each clinic was supplied with a set of 5-month calendars for follow-up scheduling; the names of month were changed in rotation and small boxes were made to accommodate name cards for each working day of the week. The clinic staff could then track if the volunteers were not attending the clinics as scheduled. They would contact them or make home visit according to their consent. BMA staff were usually acquainted with their families and the location of their homes because it was their routine work to do home visits for after care in the process of drug treatment. The resulting follow-up rates were satisfactorily high; successful follow-up was obtained for 88.2% at 12 months, 75.9% at 24 months, and 71.2% at 36 months [13].

3. HIV incidence and other epidemiological and biological data

This prospective cohort study of 1,209 HIV-negative IDUs began in 1995 and followed-up participants through the end of 1998. The overall HIV-1 incidence rate was 5.8 (95% confidence interval, 4.8-6.8) per 100 person-years of follow-up and HIV-1 subtypes E (now known as CRF01_AE) and B accounted for 79% and 21% of infections, respectively [13]. During the study, BMA staff provided pre- and post-test counselling for every 4-monthly HIV serologic tests together with health education and distribution of free bleach (to clean syringes and needles) and condoms. Most participants were receiving methadone treatment, either as detoxification or as maintenance. HIV-1 seroconversion was primarily associated with the frequency of heroin injection, the sharing of injection equipment, and incarceration especially with drug injection. Sexual

behaviour was not associated with increased risk for HIV-1. The risk factors for infection with HIV-1 subtypes E and B were similar [13].

This cohort study and a substudy of IDUs who became HIV-infected also allowed for the genetic characterisation of the infecting HIV-1 subtype B and E strains [16]. This information led to the design of the VaxGen AIDSVAX® B/E product (VaxGen Inc., Brisbane, CA, U.S.A.) that was subsequently tested in this population. This study also allowed for a comparison of infection with HIV-1 subtypes B and E. Median HIV-1 RNA levels at the earliest time within 3 months of seroconversion were more than three times higher for persons infected with subtype E than subtype B (63,100 versus 18,050 copies/ml, p=0.001) but this difference decreased over time [17]. Another study on genetic analysis of incident HIV-1 strains among injection drug users in Bangkok showed evidence for multiple transmission clusters during a period of high incidence from July 1996 through 1997 [18]. It was hypothesised that higher viral loads could potentially contribute to faster disease progression and increased infectiousness or transmissibility to subsequent contacts during the period of high incidence observed in this study [19]. From this cohort, participants with high HIV-1 RNA levels and low CD4 cell counts, close to the time of seroconversion, were more likely to experience early immunologic progression. Approximately one quarter of seroconverters reached the surrogate immunologic endpoint within 18 months of their first positive visit and before starting anti-retroviral therapy [20]. It was also observed that unprotected sex with casual partners was associated with amphetamine use [21]. Another sub-study, using samples from IDUs who were screened prior to their enrolment into this cohort, demonstrated an estimated annual incidence of 17.3%/year (95% CI, 12.8-24.2%/year) compared with 9.0%/year (95% CI, 6.7-11.9%/year) measured from the prospective cohort during the same period [22]. This may be because persons screened from a cross-sectional sampling probably have higher risk for HIV than selected uninfected individuals who chose to participate and received risk reduction counselling in a longitudinal cohort study.

Finally, we observed that HIV risk behaviour dropped substantially among IDUs who remained in the study and received regular counselling. However, despite this drop in risky behaviour, HIV-1 incidence remained at an unacceptably high level [23]. Consequently, a safe and effective HIV-1 vaccine would provide a much-needed additional preventive modality for this high-risk population. The

1995-1998 BMA IDU cohort study provided essential information and a vital learning experience for scientists and public health officials in Bangkok and those working in HIV vaccine trials. This effort led to the developing world's first HIV vaccine efficacy trial, initiated in this IDU clinic setting in 1999.

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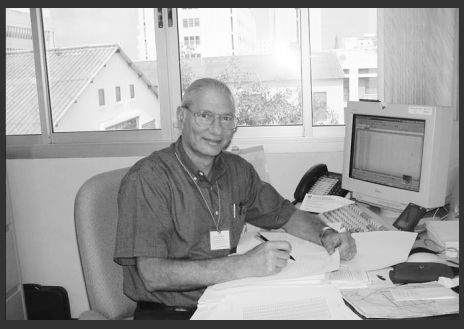

Community Cohorts in Rayong and Chonburi

Michael W. Benenson

Introduction

Phase III (preventive) HIV vaccine trials in Thailand had been in the planning since the early 1990s. There were several attempts to identify potential populations in which a large-scale vaccine trial could be conducted. This section will discuss two cohorts that were evaluated in Rayong and Chonburi Provinces. Challenges in identifying a suitable cohort are discussed.

A cohort that is chosen for a phase III vaccine trial should consist of a sample that comes from a larger population that can support the requirement for the estimated sample size needed for the subsequent vaccine trial. The larger population should have the same desired characteristics of the cohort so that the results obtained in the cohort will relate accurately to the entire vaccine trial population. Once volunteers are enrolled in a vaccine trial, the success of the trial will depend on the incidence of new infections and the retention of volunteers in the study. To ensure retention, the cohort and the population it is derived from, should be stable, with little movement out of the study area. There should be enough new HIV infections occurring in the cohort during the period of observation so that the subsequent vaccine trial can be accomplished with a practical sample

size. Enough new HIV infections must occur to be able to demonstrate the difference between the infection rates in the vaccine group compared to the placebo group.

Background

In the early 1990s, Thailand was one of four countries identified by WHO as potential sites for future HIV vaccine trials. Since that time, Thailand has been at the forefront of HIV vaccine evaluation. Several vaccine companies have manufactured vaccine candidates specifically designed for the clade E virus that is the prevalent subtype in Thailand. The outstanding medical infrastructure, the world-class research community, and the narrow genetic diversity of the HIV strains circulating in Thailand were all in favor of Thailand to support a phase III vaccine trial. The rate of infection in Thailand rose dramatically in theearly 1990's, but fortunately the rate responded remarkably to public education and the 100% condom campaign. The rates of both sexually transmitted diseases (STDs) and HIV decreased dramatically [1-4]. This has been good news for public health, but it has made the identification of a potential cohort for an HIV vaccine trial more difficult. For example, initially Royal Thai Army (RTA) recruits were considered as a possible cohort. But a three-year study of recruits showed low incidence and disappointing follow-up. The 2-year enlistment of RTA recruits would make a trial that lasted more than two years very difficult to manage, and there is also a concern about ethical considerations and true informed consent in a hierarchical organization like the military. Subsequently, commercial sex workers were considered. They have a high rate of HIV infection but, again, there was concern about follow-up over a multi-year study. A recent study to look at persons attending STD clinics in Thailand was also disappointing [5]. There were no infections among the women attendees and the rate in the men was fairly low. Based on the observed HIV-1 incidence, HIV vaccine efficacy trials in such populations would have to be larger than previously planned. The HIV incidencein this group accurately reflected the decrease in the number of STD cases that were being seen in the government clinics. Other cohorts were explored by groups working in Chiang Mai (Chapter 6, Chiang Mai Community Cohort).

The efficacy of a vaccine may well be modified by the route, and infecting dose. For this reason it was decided to determine the

feasibility of doing a phase III trial in a large general community cohort where the transmission and demographics would be representative of the general population. The Thai Ministry of Public Health (MOPH) develops surveillance data on a number of different groups including direct and "indirect" sex workers, attendees at STD clinics, antenatal women, blood banks, and military conscripts. It was clear from this data that the area to the southeast of Bangkok was continuing to have fairly high prevalence rates. As a result, Sattahip District of Chonburi Province, and Mueang District of Rayong Province were chosen as sites for cohort development because of their potential higher HIV incidences as well as the excellent infrastructure and support anticipated.

Experience

Two cohorts were developed and evaluated on the eastern seaboard of Thailand—one in Chonburi and the other in Rayong [6-8]. The study areas were approximately 2.5 hrs. southeast of Bangkok.

Preparation

1) Facilities. The cohort studies were centered in the MOPH's Community Health Centers. These are located throughout the provinces (there are over 90 health centers in Rayong Province). The health centers provide primary care to surrounding villages, with a staff of 3-5 nurses and health technicians. During the cohort development, all procedures except laboratory testing were conducted in the health centers.

Counseling work areas providing a level of privacy were established in the health centers, and supplies and equipment consisting of desks and chairs, lockable file cabinets, blood drawing equipment, table top centrifuges, blood pressure cuffs, SOP manuals, pre-printed labels, and volunteer document binders were provided.

2) Personnel-Manpower consisted of the MOPH personnel working in the community health centers. They received a salary supplement based on the number of volunteers they enrolled and followed. The staff received training on HIV and AIDS, basic and advanced counseling courses, Standard Operating Procedure (SOP) training, and informal Good Clinical Practice (GCP) training provided by the monitors that reviewed the documents on a regular basis.

General description

The procedures for the two cohorts were essentially identical except for the populations recruited and the length of follow-up. After obtaining signed, informed consent, participants were enrolled into the study. Participants completed a self-administered behavioral questionnaire and a questionnaire on knowledge and attitudes about HIV/AIDS. Pre-test counseling was performed before venous blood was obtained for HIV, hepatitis B, and syphilis testing. Those that were hepatitis B naïve were offered the three dose hepatitis B vaccine series. Participants returned in two weeks to receive post-test counseling, to learn the results of their testing, and to receive an appointment to return in 6 months for repeat counseling, testing, and risk reduction education. At 12 months in Rayong, and 18 months in Chonburi the volunteers were brought back for a final visit, similar to the previous visits, but at this visit they also completed a questionnaire about interest and likelihood of participating in a possible future phase III HIV vaccine trial.

Description of the Rayong cohort

1,002 women between the ages of 20 and 45 attending family planning clinics in the Mueang district of Rayong Province, Thailand, were recruited and enrolled into the study. Women attending family planning clinics were chosen because it was thought that the follow-up rate would be reasonably high in this group since they would be returning periodically for birth control. The volunteers were recruited, enrolled, and followed at 6-months and one year. Potential volunteers were recruited from three family planning clinics (Tapong, Nernprah, and Pae) in Rayong Province between February and August 1998. Women were eligible to enroll in the study if they signed informed consent, were older than 20 years of age (the age of majority in Thailand), were Thai citizens, could read Thai, and planned to reside in the area for at least a year.

Results of the initial Rayong cohort

At enrollment, 39 of the women were already HIV-1 infected (3.9%). Factors related to being HIV-1 sero-positive were: being younger,

being married for less than 5 years, having 2 or more sexual partners, being HbsAg positive, and perceiving a high risk of acquiring HIV infection. During the 12-month follow-up period two incident HIV infections were identified for an incidence rate of 0.22/100 person years. The two incident cases were 22 and 25 years of age. The follow-up rate over the 12-month period was acceptable: 92% of the sero-negative women seen at enrollment were seen again at the 6-month visit and 90% were seen at the 12-month visit; 89% were seen at both the 6 and 12-month visits. The follow-up rate was lower in the younger women and decreased over time.

Second Rayong cohort

The low incident rate in the initial Rayong study (just described) and the fact that the incident cases were of a younger age prompted the enrollment of a second cohort comprised only of younger women. This cohort consisted of women between the ages of 20 and 30 recruited between September and November 1999 to be followed for 12 months. Two hundred and sixty five of the women that were in the initial cohort and were under the age of 30 agreed to be continued in this new cohort. In addition, 850 new volunteers were recruited and enrolled. The majority of these new volunteers (538) came from the three health centers from the initial cohort. Another three hundred twelve volunteers were referred from three **"**satellite**"** health centers, one located close to these health centers. The study design was identical to that of the initial cohort.

Results from the second Rayong cohort

At study entry, there were 34 HIV-1 infected persons among the 850 newly enrolled volunteers. This prevalence rate (4%) was essentially identical to that in the initial cohort. In this cohort, again, having two or more sexual partners, a perceived high risk of HIV, and evidence of exposure to hepatitis B virus, were related to being HIV infected. There was one incident infection among the 850 new volunteers and there were three incident infections among the 265 women from the initial cohort. Overall the incidence rate in the volunteers in this second cohort was 0.39 / 100 person years of follow-up.

HIV sub-types

Sera from the volunteers with pre-existing HIV infection were tested to determine the subtype of the infecting virus. Subtype B accounted for 18% of the HIV-1 infections in the initial cohort while the rest were subtype E. In the second cohort 10% were B and 3% were B/E, again the remainder were subtype E. The 6 incident infections (the 2 from the initial cohort and 4 from the extended cohort) were also tested for subtype. Five were subtype E while the other was untypeable.

Description of the Chonburi Cohort

Potential volunteers were recruited from the general community by the local health center staff, using flyers, public address systems, and word of mouth.

Fifteen hundred volunteers between the ages of 20 and 45 from two communities (Chong Samaesan and Phlutaluang) in Sattahip District, Chonburi Province, Thailand, were recruited and enrolled into the study beginning in March 1999. Procedures were identical to those described for Rayong, except the follow-up period was 18 months. Experience in the Rayong Cohort and cohort studies in Chiang Mai suggested that the incidence would be lower than originally expected, and most of the newly infected persons would be in the younger age group. For these reasons an additional 1,000 volunteers between the ages of 20 and 30 years of age were recruited from two additional communities, Taothan in July, and Bang Sare in September 1999.

Results Chonburi community cohort

In total, 2,500 volunteers from the general community were enrolled. At enrollment, 121 of the volunteers were already HIV-1 infected. The overall prevalence was 4.8%, varying from 3.8% to 7.0% in the four communities. There were a number of factors related to being HIV-1 sero-positive. Multivariate analysis indicated three significant factors for males: history of IV drug use (Odd ratio (OR) = 18.41, 95% CI 8.50-39.92), positive syphilis serology (OR = 4.72, 95% CI 1.45-15.35), and having an unskilled or temporary occupation (OR= 2.86, 95% CI 1.61-5.05). Among females, being married less than 5 years (OR = 5.59, 95% CI 2.40-12.99) and having more than two

sexual partners (OR = 2.17, 95% CI 1.06-4.44) were found to be significant factors associated with being HIV sero-positive.

During the study 17 individuals sero-converted giving an overall rate of 0.5/100 person-years of follow-up. The incidence was highest in the age category 25-29 years (0.98/100 person-years), lowest in those over 30 years of age (0.22/100 person-years), and intermediate in those 20-24 years of age (0.37/100 person-years). Seven of the infections occurred in the first 6-month follow-up period (0.66/100 person-years), nine between the 6 and 12-month visit (0.95 /100 person-years), and one between the 12 and 18-month visit (0.11/100 person-years). There were 15 incident infections among those under the age of 30, an incidence of 0.68/100 person-years with a 95% confidence interval of 0.34 to 1.02/100 person-years.

Follow-up

Overall follow-up was 88% at the 6-month visit, 85% at the 12-month visit and 80% at the 18-month visit in the initial cohort, while the rest were subtype E. Follow-up varied by community. The most common reason for loss to follow-up (more than 50%) was the fact that the volunteers had moved (either their house or work place) and could not be contacted.

HIV sub-types

Ninety-three percent (99/107) of the prevalent cases where the virus could be subtyped were infected with subtype E. Six percent were subtype B and two percent were dually reactive. In the second cohort 10% were B and 3% were B/E, again the remainder were subtype E. All incidentinfections that were subtyped were found to be caused by subtype E. These results are similar to what has been seen in other areas of Thailand - a vast preponderance of subtype E with fewer subtype B infections. Further characterization of the subtypes has been done with more sophisticated techniques and the results have been reported in a number of presentations and papers [9-11].

Conclusions

Cohorts from the Rayong Family planning clinic had an adequate follow-up rate but the HIV incidence was low. It was felt that there was a selection bias in that women attending a family planning clinic might be different than the general population regarding their concern about their own health and their relationship with their partner. The constant HIV prevalence of 4% over the period between the screenings of the two cohorts suggests that HIV was continuing to circulate in the community.

In the Chonburi community cohort the follow-up rate was marginal, but it was felt that in an intervention study the follow-up rate would be higher. The follow-up rate varied by community and was highest in the most isolated community. The follow-up rate can clearly be improved by better screening of potential volunteers and establishing better contact information and mechanisms for tracking volunteers. The incidence rate, especially in those volunteers under that age of 30, was sufficient to support a phase III trial but the trial would require a fairly large sample size. Sixty percent of the volunteers seen at the final visit stated that they would definitely (39%) or very likely (21%) participate in a future phase III vaccine trial. The staff also expressed eagerness to participate in a future phase III vaccine trial.

Lessons learned

1. Maintaining the cohort. Since the results of the cohort study are to be used to determine the feasibility of doing a phase III trial, it is important that the results are related temporally to the beginning of the trial. In Thailand where the incidence has been dropping fairly consistently for the last decade, this is of prime importance. The cohort should be kept intact and followed longer than originally planned if the follow-on vaccine trial is delayed (vaccine not ready, protocol approval time extended, etc.).

2. Stability of the cohort. The cohort should be fairly stable regarding out migration. The area chosen had a number of industrial estates and there was positive inward migration anticipated. Even with this, approximately 50% of the loss to follow-up was related to volunteers moving from the province. There should also be political stability. There was some support for a vaccine trial in the southern

provinces of Thailand. However, in retrospect, we realize that the political unrest would have made working in those southern provinces both very difficult and dangerous.

3. Logistic considerations. It was very useful to have the cohort in an area that is reasonably easy to support logistically. The transportation infrastructure in the area of the cohorts was steadily improved during the cohort development and is presently outstanding. The nearness to Bangkok and the road network made it easy to support the study sites.

4. Mimicking the anticipated vaccine trial. The cohort procedures were designed to be as similar as possible to the procedures likely to be done in a subsequent vaccine trial. A test of understanding should have been incorporated into the study design of the cohort. This would have given an idea of the difficulty of getting the population under consideration to understand and pass such a test. The hepatitis B vaccine was used as a surrogate to see how volunteers would return for a series of vaccinations. At the time of the cohort development, hepatitis B was a concern in the communities so it was difficult to determine how the compliance with the hepatitis B vaccine would correlate with vaccinations in a subsequent HIV vaccine trial.

5. Health Centers. The MOPH's health center infrastructure proved to be an efficient and expandable framework for recruiting and following volunteers. Using the health centers as the primary location for recruitment, enrollment, and follow-up proved to be very useful. These clinics are designed to support a number of villages and provide the primary health care for most of the population. The staff are known and well respected in the communities. There are also village health volunteers, each usually responsible for ten households that support the activities of the community health center. This is a group of individuals that are likely to be very important in future vaccine trials in a community setting.

6. Satellite clinics. The use of satellite clinics to recruit potential volunteers was an important method of increasing the number of potential volunteers. Since the age range was fairly restricted, there was concern about the number of potential volunteers in the study area. The three satellite clinics recruited additional volunteers, thus expanding the catchment area, and also provided additional staff to the original health centers.

7. Staff compensation. There was a per volunteer supplemental compensation plan for the staff. This was clear and unambiguous for the staff. Financial issues are a potential problem and a clear understanding by the staff about the compensation is essential to prevent financial issues from becoming a problem to the study. Supplies and reimbursement was done as smoothly and quickly as possible and was never an issue.

8. Participation in a vaccine trial. A questionnaire was given to the volunteers to determine their likelihood of participating in a subsequent vaccine trial. It is important that the volunteers know and understand what the possible requirements are for the subsequent vaccine trial so they can give an accurate response to questions about their future participation.

9. Similarity of study design. The study designs in the Rayong and Chon Buri cohorts were essentially identical, and this allowed easy comparison between the results of the two cohorts. When multiple cohorts are under consideration at the same time it will be helpful to make the study designs as similar as possible.

10. Circulating HIV subtypes. Since the importance and understanding of possible cross-glade protection is unknown, it is important that the HIV subtypes circulating in the community be similar to the subtypes contained in the putative vaccine.

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