Recruitment, screening and characteristics of injection drug users participating in the AIDSVAX® B/E HIV vaccine trial, Bangkok, Thailand

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Objectives: To describe recruitment, screening and baseline characteristics of injection drug users (IDU) participating in a phase III HIV vaccine (AIDSVAX® B/E; VaxGen, USA) trial and to compare enrollment characteristics between trial participants and 1209 IDU from a 1995–1998 vaccine trial preparatory cohort for changes that might impact trial design assumptions.

Methods: Enrollment for both studies was conducted at Bangkok narcotic treatment clinics, where a standardized questionnaire was administered on demographics, risk behavior and incarceration history over the previous 6 months.

Results: During 1999–2000, 4943 IDU were screened for enrollment; successful sources of recruitment included clinic attendees (43.4%), an IDU referral program (20.4%) and preparatory cohort participants (14.7%). Of those screened, 1689 (34%) were HIV seropositive (HIV subtype B 23.6%; subtype E 76.4%). Of the 2545 enrolled, 93.4% were male. Compared with cohort IDU, trial IDU were younger (mean age: 28.8 versus 31.3 years), better educated (secondary level or higher: 67.2% versus 58.7%), and less likely to inject drugs daily (39.4% versus 90.4%); they were more likely to have been incarcerated (78.4% versus 65.7%), have recently injected stimulants (14.8% versus 5.8%) and tranquilizers (11.5% versus 2.3%), and obtained needles/syringes from a source other than a pharmacist (7.2% versus 3.9%) (all $P \leqslant 0.003$).

Conclusions: IDU at high risk for HIV have been successfully enrolled in the AIDSVAX® B/E efficacy trial. Only minor epidemiologic differences were found at enrollment between trial and preparatory cohort IDU. The latter has proven critical in guiding trial design; results are expected in late 2003.

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Introduction

Phase III vaccine efficacy trials have traditionally been conducted in populations at highest risk for infection. This is done to increase trial efficiency and to test the vaccine in populations likely to be targeted for immunization after licensing. For HIV vaccines, this strategy has been challenged as many of those at highest risk [injection drug users (IDU), commercial sex workers, and men who have sex with men] may not want to be identified because of concerns about stigmatization, discrimination, or the illegal nature of their activities. In addition, such persons may choose not to participate because of lack of trust in the sponsoring institution, the long-term commitment requested or other trial requirements.

The Thai HIV epidemic among IDU began in 1988, when prevalence rose from $< 1\%$ to $> 40\%$ [1]. In 1991, an HIV vaccine development program was initiated to support establishing vaccine preparatory cohorts and to develop the infrastructure and technical capacity to conduct large-scale HIV vaccine efficacy trials [2,3]. In response, the Royal Thai Government's National Plan for HIV/AIDS included a vaccine development and evaluation component [4]. From 1995 to 1998, an HIV vaccine preparatory cohort study of 1209 IDU was conducted to determine the feasibility of performing a phase III trial in this group. This cohort revealed an annual HIV incidence rate of 5.8/100 person-years, high follow-up rates ($> 70\%$ at 36 months) [5] and willingness of IDU to participate in HIV vaccine trials [6]; it also defined the clinical course of HIV infection in this population [7,8]. In addition, an HIV subtype distribution of 20.8% B and 79.2% E (circulating recombinant form 01_AE) was found [9,10]. Based on these findings, a recombinant gp120 vaccine was developed composed of antigens from HIV subtype B (MN) and subtype E (A244) (AIDSVAX® B/E, VaxGen, Brisbane, California, USA) [11,12]. A 1998 phase I/II trial of this vaccine showed it to be immunogenic and safe [13]. In 1999, a phase III trial to evaluate the safety and efficacy of the AIDSVAX® B/E vaccine was initiated.

This paper describes the vaccine trial's recruitment methods, screening and enrollment, and the baseline characteristics of participants. It compares these with those of preparatory cohort participants to look for any changing epidemiological factors that might impact trial design assumptions.

Methods

Trial design

This is a randomized, double-blinded, placebo-controlled trial. Enrolled volunteers were randomly assigned to receive either AIDSVAX® B/E vaccine or placebo (1:1 ratio) at months 0, 1 and 6, with boosters at months 12, 18, 24 and 30. Assuming a 4% annual HIV incidence rate in 2500 IDU over 3 years, the trial is designed to detect vaccine efficacy with a lower-bound 95% confidence interval (CI) of 30% (point estimate 67%). The primary endpoint was HIV infection measured by enzyme-linked immunoassay (EIA) and Western blot and the secondary endpoint was mitigation of disease measured by viral load and CD4 cell count. At enrollment and every 6 months thereafter, standardized questionnaires were administered, and an HIV test was performed. HIV-infected participants were followed-up every 4 months and receive care according to Bangkok Metropolitan Administration (BMA) treatment guidelines, which now include three antiretroviral drugs for a CD4 cell count $< 200 \times 10^6$ cells/l or for symptomatic infection [14].

Study setting

The Bangkok Vaccine Evaluation Group, a collaboration of the BMA, Mahidol University, Thailand Ministry of Public Health (MOPH)–US Centers for Disease Control and Prevention (CDC) Collaboration, and VaxGen, initiated this trial in March 1999. The trial is conducted in 17 BMA narcotic clinics where approximately 8000 IDU receive methadone treatment.

Community outreach

In Bangkok, IDU have limited representation by non-governmental or community-based organizations. In November 1998, a community advisory committee was established to address ethical and other concerns. Focus groups were held among IDU attending narcotic clinics to identify ways to foster mutual trust and understanding. In March 1999, the committee was expanded to include past IDU, HIV-infected persons and community leaders.

Recruitment

IDU attending narcotic clinics were informed of the trial. Various recruitment techniques were used including TV and radio announcements, a telephone hotline, posters and flyers. BMA clinic staff were available to provide detailed information about the trial and answer questions. IDU screened for enrollment received 350 Thai baht (approximately US $8.30) for their travel and time.

Screening and enrollment

IDU known to be HIV seropositive were not screened for enrollment. Eligibility criteria included completion of informed consent, possession of a Thai national identification card, age 20–60 years, availability for 3 years' follow-up, history of injection drug use in the previous year, and willingness to receive HIV counseling and testing. IDU screening seropositive (Genetic System HIV1/HIV2 EIA, Sanofi Pasteur Diagnostics,

Genetic Systems Corporation, Washington, USA; confirmatory Western blot, NOVAPATH HIV-1 Immunoblot, Biorad Laboratories, California, USA) were excluded from enrollment; HIV subtype distribution among these screening specimens was determined by V3 loop peptide EIA [15].

Trained counselors provided further HIV education to remaining eligible IDU during individual and group sessions, with assistance of audiovisual and written materials. In addition, these potential participants were tested to assess comprehension of trial concepts [16,17], including: (i) vaccine-induced antibody may cause a false-positive HIV antibody test; (ii) the HIV vaccine may lead to faster disease progression in those who become HIV infected; (iii) volunteers will not know whether they received vaccine or placebo; and (iv) it is not known whether the vaccine provides protection. To pass the test, volunteers had to respond correctly to 80% of true–false questions and to several critical concepts. They were allowed two attempts. Those who passed provided a medical history and received a physical examination to ensure they satisfied medical criteria. Healthy, consenting HIV-seronegative IDU were enrolled.

Education and counselling

Comprehensive education and risk behavior counseling were provided at every study visit, as described elsewhere in this issue [18].

Ethical approval

The trial protocol was approved by Thailand's National AIDS Committee; the Ethical Review Committee of the Thailand MOPH; the Institutional Review Boards of Mahidol University, BMA, and CDC; the US Office for Human Research Protection; the US Food and Drug Administration; and UNAIDS, Geneva, Switzerland.

Preparatory cohort study

The methods and characteristics of the preparatory cohort enrolled in 1995 and 1996, and followed through 1998 are published elsewhere [5,19].

Statistics

Cohort and trial participant enrollment characteristics were compared using chi-square or Fisher's exact test for categorical variables and the *t* test or Wilcoxon rank sum test for continuous variables. Adjusted odds ratios and 95% confidence intervals were estimated using multiple logistic regression; factors significant ($P < 0.1$) on univariate analyses were retained in the model.

Results

From March 1999 to August 2000, 4943 IDU were screened for enrollment. Their median age was 26 years (range, 20–59); 94.3% were male and 1689 (34.2%) were HIV seropositive. Of 1496 HIV-seropositive specimens, HIV-1 subtype could be determined for 1380 (92.2%); of these, 325 (23.6%) were subtype B and 1055 (76.4%) were subtype E. HIV-1 subtype could not be determined for 116 (7.8%) because of no or dual reactivity. HIV infection (70.6%) was the most common reason for not being enrolled, followed by unwillingness to participate (7.4%) and inability to show a Thai national identification card (categories not mutually exclusive).

Enrollment declined from 203 persons in May 1999 to 92 persons in October 1999. Activities to increase enrollment included TV and radio announcements, a telephone hotline, posters and flyers (September 1999); extended clinic hours (November 1999); recruitment through an IDU referral program; and screening at mobile and suburban clinics (March 2000). During the final 10 months of enrollment, an average of 156 persons were enrolled per month (Fig. 1). Complete enrollment of 2545 IDU was achieved on 31 August, 2000.

The most common sources for vaccine trial recruitment were BMA narcotic clinics (43.4%), an IDU referral program (20.4%) and preparatory cohort participants (14.7%) (Table 1). The principal motivations included HIV testing (95.6%), a physical examination (94.5%), HIV information (96.5%) and altruistic reasons [e.g., stop spread of HIV (95.8%)]; 71.7% thought being

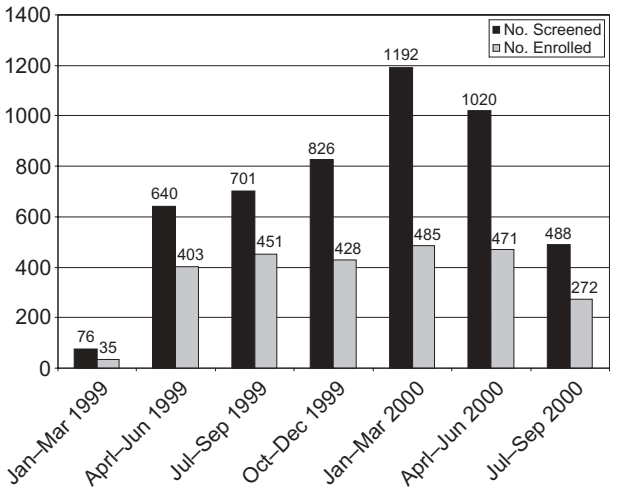

Fig. 1. Number of injection drug users screened and enrolled in the AIDSVAX® B/E HIV vaccine trial in Bangkok, Thailand, by quarter, from January 1999 to September 2000.

Table 1. Recruitment mechanisms leading to successful screening and enrollment of 2545 injection drug users in the AIDSVAX® B/E HIV vaccine trial in Bangkok, Thailand, March 1999 to August 2000.

Recruitment mechanism used	Number	Percentage
Recruiting attendees of drug treatment clinics	1105	43.4
Recruiting referrals from injection drug users referral program[a]	519	20.4
Recruiting preparatory cohort study participants	374	14.7
Recruiting suburban health clinic attendees	240	9.4
Extending drug treatment clinic hours	89	3.5
Using mobile van clinics	72	2.8
Disseminating media information messages (TV, radio, poster or flyer)	19	0.8
Other	127	5.0

[a]Enrolled injection drug users referring other injection drug users to Bangkok Metropolitan Administration drug treatment clinics for screening and possible enrollment.

reimbursed for their time and travel was an incentive to participate.

Of the 2545 IDU enrolled, the median age was 26.0 years (range, 20–59), 93.4% were male, and 94.9% had completed at least primary education; there were no differences in median age or gender at screening between enrolled IDU and HIV-seronegative IDU not enrolled (25.5 years; 93.3% male). During the 6 months prior to enrollment, 2351 (92.4%) had injected heroin, 376 (14.8%) stimulants, and 292 (11.5%) tranquilizers; 936 (39.4%) injected daily, 776 (32.7%) at least weekly but less than daily, and 664 (27.9%) less than weekly (Table 2). For those injecting, 171 (7.2%) obtained needles from a source other than a pharmacist, and 789 (33.0%) shared injection equipment at least once. In

Table 2. Results of univariate and multivariate analysis comparing baseline demographic characteristics, drug use, and sexual behaviors of injections drugs users participating in the BMA HIV vaccine trial preparatory cohort and the AIDSVAX® B/E vaccine trial, Bangkok, Thailand.

Factor	BMA[a] [No.[b] (%)]	AIDSVAX® B/E[c] [No.[b] (%)]	OR[d] (95% CI)	*P* value	Adjusted OR[d] (95% CI)	*P* value
Total number	1209	2545				
Mean age (per 1 year increase)	31.3	28.8	0.96 (0.95–0.97)	< 0.0001	0.95 (0.94–0.96)	< 0.0001
Education						
Junior or lower level	499 (41.3)	834 (32.8)	0.7 (0.6–0.9)		0.7 (0.5–0.9)	
Secondary	483 (40.0)	1177 (46.2)	1.0 (0.8–1.2)		0.9 (0.7–1.1)	
Vocational or higher level	226 (18.7)	534 (21.0)	1.0	< 0.0001	1.0	< 0.0001
Ever been in jail/prison						
Yes	794 (65.7)	1996 (78.4)	1.9 (1.6–2.2)		2.0 (1.6–2.4)	
No	415 (34.3)	549 (21.6)	1.0	< 0.0001	1.0	< 0.0001
Injected stimulants in the past 6 months						
Yes	70 (5.8)	376 (14.8)	2.8 (2.2–3.7)		2.5 (1.8–3.4)	
No	1139 (94.2)	2169 (85.2)	1.0	< 0.0001	1.0	< 0.0001
Injected tranquilizer/hypnotic in the past 6 months						
Yes	28 (2.3)	292 (11.5)	5.5 (3.7–8.1)		4.7 (3.1–7.4)	
No	1181 (97.7)	2253 (88.5)	1.0	< 0.0001	1.0	< 0.0001
Frequency of any injection in the past 6 months[e]						
Less than once a week	53 (4.6)	664 (27.9)	1.0		1.0	
Weekly	58 (5.0)	776 (32.7)	1.1 (0.7–1.6)		1.0 (0.6–1.4)	
Daily	1042 (90.4)	936 (39.4)	0.1 (0.05–0.1)	< 0.0001	0.1 (0.04–0.08)	< 0.0001
Obtained needles/syringes from anyone other than pharmacist/chemist						
Yes	45 (3.9)	171 (7.2)	1.9 (1.4–2.7)		1.8 (1.2–2.7)	
No	1121 (96.1)	2215 (92.8)	1.0	0.0001	1.0	0.003
Any sexual intercourse with primary partner in the past 6 months						
Yes	656 (55.2)	1693 (66.8)	0.6 (0.5–0.7)		0.6 (0.5–0.8)	
No	533 (44.8)	842 (33.2)	1.0	< 0.0001	1.0	< 0.0001
Any sexual intercourse with casual partner(s) in the past 6 months						
Yes	1052 (88.6)	2190 (86.3)	1.2 (1.0 –1.5)		0.9 (0.7–1.3)	
No	136 (11.4)	348 (13.7)	1.0	0.06	1.0	0.9

BMA, Bangkok Metropolitan Administration; OR, odds ratio; CI, confidence interval.
[a]The 1995–1998 BMA HIV vaccine preparatory cohort.[b]Denominators may vary because of missing values.[c]The AIDSVAX® B/E HIV vaccine efficacy trial conducted by the Bangkok Vaccine Evaluation Group.[d]AIDSVAX® B/E versus BMA HIV vaccine trial preparatory cohort, predicting AIDSVAX® B/E group.[e]Because of collinearity, the frequency of any injection was evaluated instead of history of heroin, stimulant or tranquilizer/hypnotic injection, because frequency of injection is a more precise indicator of risk.

the previous 6 months, 82.2% had received methadone treatment [18]. A history of ever having been incarcerated (jail or prison) was reported by 1996 (78.4%), and 446 (17.5%) had been incarcerated at least once in the previous 6 months; of these, 58 (13.0%) injected drugs while incarcerated.

The median number of sex partners in the 6 months prior to enrollment was 1.0, and 860 (33.8%) were living with a heterosexual partner; of these, 19.7% reported sexual intercourse less than once a month and 20.8% used condoms with this partner. For the 348 IDU who reported having sex with a casual partner, condom use was common (46.0% always, 16.4% irregular, 37.6% never). Sharing needles/syringes with a sexual partner was reported by 82 (3.2%) participants, and having sex with a person of the same sex was reported by 23 (0.9%) participants.

Significant univariate comparisons between trial and cohort IDU are found in Table 2. Multivariable analysis showed vaccine trial IDU to be younger, better educated, less likely to inject daily, and less likely to have sex with their live-in sexual partners than the preparatory cohort IDU (all $P \leqslant 0.0001$) (Table 2). Trial IDU were more likely to have a history of incarceration, obtain needles and syringes from a source other than a pharmacist, more than twice as likely to inject stimulants, and nearly five times as likely to inject tranquilizers (all $P \leqslant 0.003$).

Discussion

The world's first HIV vaccine efficacy trial in a developing country has been successfully initiated in Bangkok, Thailand. In designing the vaccine trial, it was important to be conservative in estimating HIV incidence. Because we anticipated that the intensive education, counseling and interventions unrelated to vaccine would reduce risk behavior, we assumed a 4% incidence of HIV infection for vaccine trial participants based on an incidence of 6% from the 1995–1998 preparatory cohort [5].

Traditional modes of trial recruitment such as media messages, flyers and posters were not effective tools, accounting for only 0.8% of those who enrolled. Most recruitment contacts occurred in BMA narcotic clinics, followed by IDU referral programs and through previous cohort participation, demonstrating an atmosphere of trust between BMA staff and IDU and the importance of IDU involvement in trial preparation. Similar to other HIV vaccine trials, among men who have sex with men in the United States [20], altruism was a prominent motivation, cited by 95.8% of IDU. Other motivations such as HIV testing, physical examinations and HIV information were important and should be considered in the design of vaccine trials among IDU.

The finding that 32.4% of IDU screened for enrollment were HIV seropositive highlights the urgent need for an effective HIV vaccine in this population. At the time of enrollment, HIV-seronegative IDU reported high-risk behaviors strongly associated with HIV transmission. Although incarcerated IDU were not recruited or enrolled into the trial, participants who became incarcerated during follow-up were retained [18]. Because incarceration may be associated with incident HIV infection through multiple pathways [21], risk-behavior counseling was intensified during follow-up with incarcerated volunteers. Reports of frequently injecting drugs and sharing needles while incarcerated indicate that recruitment efforts to identify high-risk IDU have been successful. However, they also point out the need for intensive risk-reduction counseling, together with free condoms and bleach at every study visit. Trial participants do not report problems obtaining sterile needles and syringes, as they are cheap and widely available. Risk-behavior trends are being evaluated throughout the trial, and education/counseling procedures are being modified when necessary [18].

The finding that trial volunteers were younger, better educated and injected drugs less frequently than cohort IDU suggests, on the one hand, that IDU choosing to participate in a vaccine trial may be more informed about risks for HIV infection and more motivated to enroll. On the other hand, trial participants were more likely to inject tranquilizers and hypnotics, indicating that drug use habits may be changing because of decreasing availability and increasing price for heroin [18]. Although some characteristics between preparatory cohort and trial participants did differ, these differences do not appear to affect the statistical power, trial design or ability to determine definitively the protective efficacy of the AIDSVAX® B/E vaccine.

In HIV vaccine trial preparations, determination of HIV subtype(s) of incident strains is important to ensure a reasonable match between vaccine and circulating viruses [22]. The explosive HIV epidemic among Bangkok IDU in 1988 was almost solely with subtype B [1]. Subsequent cross-sectional studies in the early 1990s suggested a change from subtype B to subtype E [19,23,24]. Throughout the 1995–1998 preparatory cohort period, the proportion of HIV subtypes among incident infections was stable (~20% B and ~80% E) [5,9]. The HIV subtype distribution among IDU testing positive at trial screening (~25% B and ~75% E) supports the use of bivalent AIDSVAX® B/E in this population.

The 1995–1998 preparatory cohort study was essential

for the design and conduct of the vaccine efficacy trial. This cohort helped to determine long-term incidence trends and what would be an adequate trial population size for sufficient statistical power to evaluate vaccine efficacy. In addition, the preparatory cohort showed the willingness of IDU to participate, the distribution of circulating HIV subtypes and the appropriate antigens for inclusion in the vaccine; it also strengthened the public health and research institution capacity to conduct this trial in Thailand. Finally, although the efficacy of AIDSVAX® B/E is still yet to be determined, this trial has clearly demonstrated that IDU at high risk for HIV can be enrolled in sufficient numbers in a large-scale field trial. Final trial results are expected in late 2003.

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