Issues in Women's Participation in a Phase III Community HIV Vaccine Trial in Thailand

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Abstract

To assess qualities and outcomes of women participating in a large, community-based HIV vaccine trial, the present study was conducted among female participants of the RV 144 prime-boost trial in Thailand from 2003 to 2009. Qualities of participation refer to complete vaccination, retention, and status change. Outcomes of participation refer to incident rate, adverse event, and participation impact event. A total of 6,334 (38.6%) women participated in the trial, of whom about 50% were classified as low risk and 11% as high risk. About 85% of participants completed four vaccinations and 76% were included in the per-protocol analysis of the on-time vaccination schedule. More women (88%) completed 42 months follow-up compared with men (85%). Women aged 21 and above had more adverse events compared to younger age groups. More women (5%) compared with men (3%) reported participation impact events (PIEs). High-risk women had more PIEs and a higher infection rate compared to the low-risk group. Complete vaccination and retention on last follow-up were more common in married women aged above 21, and being a housewife. Female volunteers showed the same qualities and outcomes of participation as males in the HIV vaccine trial. There was no statistically significant difference in vaccine efficacy between men and women, especially among the high-risk and married women. The study highlighted the important behavioral, social, and cultural issues that could be considered for future HIV vaccine trial designs.

Introduction

INCLUSION OF WOMEN IN CLINICAL trials is important for scientific and ethical reasons. Since the National Institutes of Health (NIH) Revitalization Act of 1993, there has been an increasing number of women in clinical trials.^{1–4} In 1995–1999, the U.S. FDA reported women participants from 42% (1995) to 55% (1998), with no directional trend.⁵ In 2000–2002, FDA reports and summaries of non-gender-specific clinical trials in new drug applications (NDAs) showed that 50% of subjects in trials were female.⁶ In 2006–2009, about 40–60% of non-gender-specific trials enrolled female participants with safety and efficacy gender analyses in 74% of NDAs while 100% of Biologics License Applications (BLAs) had efficacy gender analysis.^{7,8}

There are many challenges in HIV vaccine research and development such as absence of known immune correlates of protection and lack of validated animal models. Clinical trials on promising vaccine candidates require target participants, especially young adults including women and adolescents.⁹ Young adults need to be included in trials as HIV incidence is higher in these groups, and they would benefit the most from an HIV vaccine. Women compared with men are more likely to become infected and to acquire asymptomatic sexually transmitted diseases, which increase the susceptibility to HIV. Some women resort to anal intercourse to prevent pregnancy, which further increases their risk of acquiring HIV.¹⁰ While studies such as the VAX 004 (that tested the efficacy of AIDSVAX rgp120 B/B') Phase III trial and Phambili using the

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MRK Ad5 HIV vaccine suggested that a vaccine might have a different efficacy among male and female subjects, we cannot say the same from STEP, where only one event occurred among women.¹¹ Social and behavioral issues such as lack of empowerment, inability to make a decision without consulting their partners, low educational status, discrimination, pregnancy, and stigma of being labeled as high risk for HIV prevent participation of women.^{12,13}

The prime boost HIV vaccine trial RV144 in Thailand from 2003 to 2009 enrolled 16,402 participants of whom 38.6% were women. Since HIV transmission was generally heterosexual in Thailand, the government wanted to develop a vaccine for the general population. The RV144 trial involved male and female participants of different sociocultural backgrounds from urban and semiurban areas of Thailand. The main objective of this study was to determine the qualities and outcomes of women's participation including their risk behavior and factors associated with compliance to study protocol, retention, pregnancy, as well as safety and efficacy endpoints.

Materials and Methods

Prime-boost HIV preventive vaccine trial (RV144)

The ALVAC HIV vaccine priming and AIDSVAX vaccine boosting efficacy trial published in 2009 was a double blind, placebo-controlled community-based, multisite trial at two Eastern Seaboard provinces of Thailand.¹⁴ From 2003 to 2005, recruitment was conducted through local media (radio and television), booth presentations, community education, and health forums. Each participant signed an informed consent form. There were four immunization visits in the first 6 months of enrollment; follow-up was done every 6 months for 3 years. Participants who reported any adverse events and participation impact events (PIEs) were given risk reduction counseling. Follow-up was done until the event resolves. The health officer may assist by providing brochures/documents or necessary information, if required.

Blood was taken for HIV serology and immune responses. Treatment and care were administered, if necessary. All enrolled women used contraceptive methods in the initial 9 months of enrollment to avoid pregnancy. Institutional review boards in Thailand and the United States approved this study.

Data management and analysis

We collected demographic data on enrollment and each follow-up visit along with data on safety and primary efficacy endpoints. To estimate potential risks for infection and participation impact between the two groups, a behavior risk assessment questionnaire was used on each follow-up visit. For trial integrity, site investigators monitored any participation status change and loss-to-follow-up cases. Age stratification (≤ 20 , 21–25, and ≥ 26) was based on available information on risk potential behavior and infection outcome. The occupation of female participants was classified into four groups based on their social roles and respective potential risk: housewife, student, sex workers including those who worked in the entertainment business, and others. We used self-response questionnaires to assess risk behaviors such as injecting drug use (IDU), risky sexual behaviors, and sexually transmitted disease (STD) at baseline and on scheduled

follow-up. Baseline risk was categorized into three levels: (1) high risk (if study participants considered themselves as high risk or reported high-risk behaviors, e.g., needle sharing, multiple sex partners, sex work, STD symptoms); (2) low risk (if study participants perceived their risk as low, and in the previous 6 months reported 0–1 sex partners and no sex with sex workers, casual partners, same gender partners, HIV-infected partners, IDU partners, or a partner with multiple partners; reported no STD symptoms within 6 months of the study enrollment); and (3) moderate risk (study participants were neither low nor high risk). PIEs were categorized as positive and negative. The positive PIEs include employment/school benefits, personal relationship benefits, positive recognition, and medical and dental care benefits, whereas negative PIEs include problems at employment/school place, problematic personal relationships, discrimination, and health and life insurance problems.

Primary endpoint was diagnostic of HIV infection based on repeat positive results. Infection time was defined as the midpoint between the last negative result and the first positive result. Retention was defined as the time from enrollment until the final visit within the study period.

Pregnancy was not considered a participation outcome, but the percentage of women who became pregnant during the study was important as it may impact the study results scientifically, statistically, and ethically. A urine pregnancy test was performed prior to vaccination and during follow-up. Participants who became pregnant during the study period continued on with all scheduled visits, but were not given further immunizations. The date of current pregnancy was estimated from the self-reported date of the last menstrual period or the date when pregnancy was confirmed. However, many were incomplete due to uncertainties in recall. In this study, missing and incomplete dates of pregnancy were retrospectively estimated from the date of delivery.

In the main study,¹⁴ populations were classified as intent-to-treat (ITT), modified intent-to-treat, and per-protocol. The intent-to-treat population was defined as all study participants randomized to either study arm during the accrual period. The modified intent-to-treat population was the ITT population except for seven HIV-infected subjects. The per-protocol population excluded participants who did not comply with the protocol-defined vaccination schedule, those not fully vaccinated, those who did not receive the correct randomized treatment (active or placebo), or those who were randomized and became infected during the immunization period. The analysis of this study was based mainly on ITT population.

Chi square test was used to compare different parameters between men and women. Changes in behavior on follow-up were determined using generalized estimation equation analysis. The characteristics and outcomes of female participants were analyzed based on their risks using logistic regression and Cox's proportional hazard regression. The analyses were exploratory in nature, and neither multivariate adjustment for confounders nor multiple comparisons were done.

Results

Difference between male and female participants

Among 16,402 enrolled participants, 6,334 (38.62%) were women residing in urban and semiurban communities, of whom about 12% were housewives, 5% were sex workers or

worked in the entertainment business, and about 6% were students. The majority of women (76.6%) classified as others (Table 1) include those who worked as laborers, farmers, government officers, etc. Baseline risk categories showed that about 50% women and 46% men were low risk while 11% women and 25% men were high risk. More women (81%) reported having a sexual partner compared with men (74%) but men tended to have more than one sexual partner (15% men and 4% women). Eleven percent of women had casual sex partners, of whom 42% used a condom. In contrast, about 29% of men had casual sex partners, of whom 25% used a condom.

Participation qualities include complete vaccination, retention, and status change (as shown in Table 2). There was no difference between men and women on participation qualities.

About 76% of both groups were found in the per-protocol analysis of the on-time vaccination schedule. There were decreasing trends in retention in both groups; however, more women (88%) tended to retain and complete 42 months of follow-up compared with men (85%). The number of missed visits during the study also differed between women (17%) and men (21%). About 21% women and men changed their participation status due to varying reasons for each group.

There was no statistically significant difference between men and women in terms of infection regardless of type of analysis of population (Table 3). In the main study,¹⁴ vaccine efficacy for different types of analyzed populations was not different between the two groups. Adverse events (AEs) as a safety indicator showed that women (71%) tended to have

TABLE 1. COMPARISON OF CHARACTERISTICS AND RISK BEHAVIORS BETWEEN MALE AND FEMALE PARTICIPANTS, THAILAND, 2003–2009

Participant characteristics	Male		Female		p-value
	N	(%)	N	(%)	
Total enrollment	10,068	61.38	6,334	38.62	
Age groups					
≤20	2,993	29.13	1,613	25.47	<0.001
21–25	4,573	45.42	2,771	43.75	
≥26	2,562	25.45	1,950	30.79	
Mean (SD)	22.98	(3.35)	23.44	(3.48)	<0.001
Occupation risk groups					
Housewife	3	0.03	779	12.30	<0.001
Student	688	6.83	383	6.05	
Sex worker/entertainment	241	2.39	318	5.02	
Others	9,136	90.74	4,854	76.63	
Marital status					
Single	5,423	53.86	1,272	20.08	<0.001
Married	4,074	40.46	4,206	66.40	
Ever married	571	5.67	856	13.51	
Education					
No formal education	145	1.44	121	1.91	0.001
Primary education	3,480	34.56	2,106	33.25	
Secondary/vocational education	6,327	62.84	3,996	63.09	
Bachelor	116	1.15	111	1.75	
Baseline risk groups					
Low risk	4,662	46.31	3,127	49.37	<0.001
Medium risk	2,875	28.56	1,789	28.24	
High risk	2,531	25.14	1,418	11.39	
Baseline risk behaviors (during 6 months prior to enrollment) ^a					
Being injection drug user (IDU)	182/9,298	1.96	119/5,842	2.04	0.733
Having sexual partner	7,169/9,649	74.30	4,999/6,185	80.82	<0.001
Having >1 sexual partners	1,058/7,169	14.76	183/4,999	3.66	<0.001
Having casual partner	2,694/9,436	28.55	645/5,803	11.11	<0.001
Use condom with casual partner	666/2,694	24.72	270/645	41.86	<0.001
Having sex with sex worker	1,113/9,587	11.61	107/5,795	1.85	<0.001
Use condom with sex worker	56/1,113	5.03	6/107	5.61	0.796
Having same-sex partner	258/9,501	2.72	110/5,904	1.86	0.001
Use condom with same-sex partner	86/258	33.33	83/110	75.45	<0.001
Having HIV-positive partner	175/9,343	1.87	82/5,830	1.41	0.03
Use condom with HIV ⁺ partner	18/175	10.29	11/82	13.41	0.460
Having IDU partner	90/9,486	0.95	47/5,925	0.79	0.317
Use condom with IDU partner	11/90	12.22	7/47	14.89	0.193
Having sexually transmitted disease	229/9,580	2.39	252/5,953	4.23	<0.001
Being incarcerated	339/9,709	3.49	42/6,109	0.69	<0.001
IDU while incarcerated	35/339	10.32	3/42	7.14	0.516

^aBased on complete responses to each question.

TABLE 2. COMPARISON OF PARTICIPATION QUALITIES BETWEEN MALE AND FEMALE PARTICIPANTS, THAILAND, 2003–2009

Participation outcomes	Male		Female		p-value
	N	(%)	N	(%)	
Total enrollment	10,068	61.38	6,334	38.62	
Vaccination completion					
No vaccination	3	0.03	4	0.06	<0.001
1 vaccination	695	6.90	439	6.93	
2 vaccinations	494	4.91	324	5.12	
3 vaccinations	221	2.20	244	3.85	
4 vaccinations	8,655	85.97	5,323	84.04	
Complete 4 vaccinations	8,655	85.97	5,323	84.04	0.001
Complete 4 vaccinations on time (per-protocol)	7,675	76.23	4,867	76.84	0.372
Retention					
Remain in study cohorts					
At month 6	9,741	96.75	6,157	97.21	0.101
At month 12	9,606	95.41	6,080	95.99	0.077
At month 24	9,449	93.85	6,002	94.76	0.016
At month 36	9,232	91.70	5,915	93.38	<0.001
At month 42 (complete 3 years follow-up)	8,577	85.19	5,584	88.16	<0.001
Retention months, mean (SD)	40.84	(9.24)	41.25	(8.56)	0.005
Missed blood drawn follow-up visit(s)					
1 visit	855	8.49	441	6.96	<0.001
2–3 visits	736	7.31	393	6.20	
4–5 visits	429	4.26	192	3.03	
6–7 visits	73	0.73	27	0.43	
Missed at least 1 blood drawn follow-up visit	2,093	20.79	1,053	16.62	<0.001
Participation status change over the course of the study	2,108	20.94	1,352	21.33	0.549
Change participation sites	109	5.17	83	6.14	<0.001
Discontinue immunization	101	4.79	300	22.21	
Discontinue from study before final visit	877	41.60	444	32.79	
Resume follow-up visits after loss to follow-up	1,021	48.43	525	38.86	
Discontinued from immunization/study	978	9.71	744	11.75	<0.001
Primary reasons for discontinuation					
Refused further participation	289	29.55	197	26.48	<0.001
Protocol deviation	8	0.82	2	0.27	
HIV infection	1	0.10	1	0.13	
Experienced adverse reaction	11	1.12	14	1.88	
Required contraindication medication	1	0.10	0	0.00	
Noncompliant to study	67	6.85	40	5.38	
Moved from study areas	57	5.83	29	3.90	
Pregnancy	0	0.00	237	31.85	
Lost-to-follow-up	375	38.34	179	24.06	
Death	136	13.91	24	3.23	
Others	33	3.37	21	2.82	

more AEs than men (66%). Men with AEs had more injury and complications, mostly due to motorcycle accidents (35% men compared to 15% women). As an indicator of social issues, women (5%) reported more PIEs compared to men (3%). Social issues included relationships in family and workplace and unpleasant comments from neighbors/co-workers. Measures were in place to address them, particularly among women (refer to Materials and Methods). Women (85%) had more problematic personal relationships compared to men (75%). In addition, men (8%) reported more problems with employment and education compared to women (6%).

Baseline risk behavior of women participants

Age-stratified analyses of baseline risk behaviors (Table 4) revealed that on enrollment about 2% women of all age

groups were IDUs and about 0.7% had a history of being incarcerated. About 4% of women had more than one sexual partner and 11% had casual partners; more women aged ≥ 26 reported having sex with sex workers (2%). Workers in the sex and entertainment business appeared to have high-risk behavior at baseline: IDUs (2%), more than one partner (32%), casual sex partners (43%), sex with sex workers (16%), and had a history of STDs (10%). Women with different marital status reported divergent risk behaviors. Divorced, separated, and widows tended to have high-risk behavior, of whom 28% had a casual partner, 17.5% had more than one partner, and 6.5% had sex with sex workers. Women with different educational levels also reported diverse risk behaviors with risk behaviors that tended to decrease as educational level increased. In women with no formal education, about 5% were IDUs, 26% had casual sex partners, 5% had more than one sex

TABLE 3. COMPARISON OF PARTICIPATION OUTCOMES BETWEEN MALE AND FEMALE PARTICIPANTS, THAILAND, 2003–2009

Participation outcomes	Male		Female		p-value
	N	(%)	N	(%)	
Total enrollment	10,068	61.38	6,334	38.62	
HIV infection (case/person)					
Total enrollment population	79/10,068	0.78	53/6,334	0.84	0.716
Modified intention-to-treat population	75/10,064	0.75	50/6,331	0.79	0.750
Per-protocol population	53/7,675	0.69	33/4,867	0.68	0.934
HIV incident rate (case/person year)					
Modified intention-to-treat					
Vaccine	32/16,221	0.197	19/10,286	0.185	0.998
Placebo	43/16,179	0.266	31/10,300	0.301	0.403
Per-protocol					
Vaccine	24/11,036	0.217	12/7,088	0.169	0.482
Placebo	29/11,377	0.255	21/7,216	0.291	0.514
Adverse events (AEs)					
Ever experienced at least 1 AE	6,628	65.83	4,472	70.60	<0.001
For those experienced AE, mean (SD)	2.28	(0.02)	2.70	(0.03)	<0.001
Total AEs	15,350		12,345		
Injury and procedural complications	5,386	35.09	1,811	14.67	
Infections and infestations	5,079	33.09	4,589	37.17	
Gastrointestinal disorders	1,317	8.58	1,416	11.47	
Skin and subcutaneous	738	4.81	766	6.20	
Musculoskeletal/tissue disorders	728	4.74	519	4.20	
Participatory impact events (PIEs)					
Ever experienced at least 1 PIE	264	2.62	336	5.30	<0.001
For those experienced AE, mean (SD)	1.10	(0.02)	1.11	(0.02)	0.891
Total PIE events	293		370		
Personal relationship	220	75.09	316	85.41	
Employment/school problem	24	8.19	21	5.68	
Positive recognition	19	6.48	7	1.89	
Discrimination	13	4.44	11	2.97	
Problem related to blood donation	6	2.05	5	1.35	

partner, 3% had sex with sex workers, and 3% were incarcerated. Among women classified as high risk, about 6% were IDUs, 38% had casual sex partners, 15% had more than one sex partner, 7.5% had sex with sex workers, 19% had a history of STDs, and 1% were incarcerated.

Differences in vaccine efficacy among risk groups cannot be determined because of the small sample size of these groups in the RV 144 trial.

Change in risk behavior among women participants

Women aged ≤ 20 did not significantly change their risk behaviors over time except for having less casual partners; those aged 21–25 significantly reduced having a casual partner, having more than one partner, and having sex with sex workers, but were at increased odds for incarceration; and those aged ≥ 26 also had similar decreased sexual risk behaviors but increased incarceration as shown in Table 5. Most of the risk behaviors among women aged ≤ 20 did not significantly change due to the fact that the percentages of those who had such risks at baseline were quite low (1–4%). That is why only having a casual partner with a high percentage at baseline (11.5%) is the only risk that showed a significant reduction.

The change in risk behavior appeared to be similar for each occupation risk group. Almost all occupation risk groups had significantly less sexual risk behaviors. Similarly, for women

with different marital status, most reported significantly decreased sexual risk behaviors. Women with no formal education did not significantly change their risk behaviors except for fewer casual partners compared with women who had primary and secondary education. Women who were low risk and medium risk appeared not to significantly change their risk behavior except for decreasing the odds of having regular and casual partners; however, the low-risk group had increasing incarceration. The high-risk group reported decreasing odds in all risk behaviors except being IDUs.

Participation qualities among women participants

More women aged ≥ 26 (82%) followed by those aged 21–25 (76%) had vaccine completion compared with those aged ≤ 20 (72%). Being a housewife and married showed higher odds of vaccine completion. Vaccine completion was highest among housewives (82%), among students and other occupations (76–77%), among sex workers (72%), and among different marital status: married (79%), single (74%), and ever married (72%). Baseline risk behaviors appeared not to be associated with vaccine completion but showed an increasing trend—low risk (78%) and moderate and high risk (76%).

With retention at month 42, housewives (97%) had the highest retention followed by students and sex workers (92–93%) and others (94%). Being married (96%) had the highest retention followed by others (93%). Baseline risk behaviors

TABLE 4. BASELINE RISK BEHAVIORS OF WOMEN PARTICIPANTS, THAILAND, 2003–2009

Participant characteristics	Being IDU		Having >1 sexual partners		Having casual partner		Sex with sex worker		Having STD		Being incarcerated	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Age groups												
≤20	1,486	36 (2.42)	1,178	44 (3.74)	1,497	172 (11.49)	1,496	23 (1.54)	1,520	65 (4.28)	1,566	12 (0.77)
21–25	2,546	40 (1.57)	2,215	81 (3.66)	2,537	261 (10.29)	2,532	47 (1.86)	2,609	132 (5.06)	2,674	16 (0.60)
≥26	1,810	43 (2.38)	1,606	58 (3.61)	1,769	212 (11.98)	1,767	37 (2.09)	1,824	55 (3.02)	1,869	14 (0.75)
Occupation risk groups												
Housewife	711	20 (2.81)	725	2 (0.28)	711	58 (8.16)	700	9 (1.29)	734	23 (3.13)	746	4 (0.54)
Student	367	5 (1.36)	189	4 (2.12)	365	37 (10.14)	365	0 (0.00)	359	9 (2.51)	376	1 (0.27)
SW and entertainment	295	6 (2.03)	260	83 (31.92)	298	129 (43.29)	288	47 (16.32)	292	31 (10.62)	305	1 (0.33)
Others	4,460	88 (1.97)	3,825	94 (2.46)	4,429	421 (9.51)	4,442	52 (1.15)	4,568	189 (4.14)	4,682	36 (0.77)
Marital status												
Single	1,189	19 (1.60)	493	36 (7.30)	1,169	122 (10.44)	1,192	10 (0.84)	1,197	46 (3.84)	1,232	4 (0.32)
Married	3,858	85 (2.20)	4,009	60 (1.50)	3,828	296 (7.73)	3,818	46 (1.20)	3,958	158 (3.99)	4,052	28 (0.69)
Ever married	795	15 (1.89)	497	87 (17.51)	806	227 (28.16)	785	51 (6.50)	798	48 (6.02)	825	10 (1.21)
Education												
No formal education	105	5 (4.76)	104	5 (4.81)	103	27 (26.21)	104	3 (2.88)	109	4 (3.67)	114	1 (2.63)
Primary education	1,904	63 (3.31)	1,777	71 (4.00)	1,884	266 (14.21)	1,867	58 (3.11)	1,954	84 (4.30)	2,017	21 (1.04)
Secondary education	3,274	51 (1.37)	3,062	107 (3.49)	3,709	346 (9.33)	3,716	46 (1.24)	3,784	162 (4.28)	3,870	18 (0.47)
Bachelor	109	0 (0.00)	0	0 (0.00)	107	6 (5.61)	108	0 (0.00)	106	2 (1.89)	108	0 (0.00)
Baseline risk groups												
Low risk	3,053	23 (0.75)	2,483	0 (0.00)	3,127	0 (0.00)	3,127	0 (0.00)	3,127	0 (0.00)	3,127	0 (0.00)
Medium risk	1,475	20 (1.36)	1,272	0 (0.00)	1,357	147 (10.83)	1,401	12 (0.86)	1,513	0 (0.00)	1,625	25 (1.54)
High risk	1,314	76 (5.78)	1,244	183 (14.71)	1,319	498 (37.76)	1,267	95 (7.50)	1,313	252 (19.19)	1,357	17 (1.25)

IDU, intravenous drug user; STD, sexually transmitted disease; SW, sex worker.

did not seem to be associated with retention. Using a failure curve (Fig. 1), no significant trend was found among different baseline risk categories even though low-risk groups had lower discontinuation toward the last follow-up visit. Discontinuation appeared to increase during the vaccination period (first 6 months) and the period close to the scheduled final visit.

Participation outcomes among women

There was no statistically significant association between infection and demographic characteristics except ever-married women (1.64%) were more infected than single women (0.55%). Baseline risk categories were not significantly associated with infection even though increasing trends of risk levels were observed in both infection rates (Table 6) and time-to-infection (Fig. 1). A total of 12,345 adverse events occurred in 4,472 of 6,334 (70.60%) women. Those aged 21–25 (72%) and ≥26 (71%) had significantly higher odds of AEs compared to women aged ≤20 (68%) (Table 6). Three hundred and thirty-six of 6,334 women (5.30%) had 370 PIEs, of which 28 (8.33%) had two PIEs. High-risk women had more PIEs compared to low-risk women. There was an increasing trend on risk levels in both proportions of PIEs (Table 6) and time-to-first PIE (Fig. 1). In 336 initial PIEs, 210 events (62.50%) occurred during the vaccination period.

Pregnancy during the study period

The pregnancy rate was quite high in Thailand among the study age groups. A total of 1,922 of 6,334 women (30.34%) became pregnant during the study period, of whom 255 (4.03%) and 13 (0.21%) had second and third pregnancies, respectively. The highest rate of pregnancy was in women aged ≤20 (41%), followed by the 21–25 (31%) and ≥26 (21%) aged groups. Pregnancy within the first 6 months of the study was noted in 362 of 1,922 women (18.83%), of whom 22.32% were aged ≤20 followed by 21–25 (17.76%) and ≥26 (15.48%). There was no difference in pregnancy rates between vaccinated and placebo recipients.

Discussion

The percentage of women participating in clinical trials varies by year, phase, and product type.⁶ In this trial, almost 40% women were enrolled and retained. This was large enough to be considered a good representative of HIV risk groups in Thailand, where men are at higher risk than women. Factors associated with women's participation vary by community settings and so future HIV prevention and/or treatment programs targeting women should address their needs within individual communities.^{15–18}

This trial utilized gender-sensitive and risk-based communication media and conducted community outreach

TABLE 5. BASELINE CHARACTERISTICS AND RISK BEHAVIORS AMONG WOMEN PARTICIPANTS, THAILAND, 2003–2009

<i>Participant characteristics</i>	<i>Being IDU OR 95% CI</i>	<i>Having >1 sexual partners OR 95% CI</i>	<i>Having casual partner OR 95% CI</i>	<i>Sex with sex worker OR 95% CI</i>	<i>Having STD OR 95% CI</i>	<i>Being incarcerated OR 95% CI</i>
Age groups						
≤20	1.02 (0.97–1.07)	0.99 (0.92–1.06)	0.89 (0.85–0.93)	0.89 (0.77–1.04)	0.96 (0.91–1.02)	1.09 (0.96–1.24)
21–25	1.04 (0.99–1.08)	0.93 (0.88–0.98)	0.85 (0.83–0.88)	0.88 (0.82–0.94)	0.97 (0.93–1.01)	1.18 (1.09–1.28)
≥26	1.03 (0.99–1.08)	0.90 (0.84–0.97)	0.88 (0.85–0.92)	0.93 (0.86–1.00)	0.99 (0.94–1.04)	1.12 (1.02–1.24)
Occupation risk groups						
Housewife	1.05 (0.99–1.12)	1.19 (1.03–1.38)	0.96 (0.90–1.02)	0.99 (0.86–1.14)	0.98 (0.90–1.06)	1.17 (1.01–1.36)
Student	0.96 (0.85–1.08)	0.71 (0.51–0.99)	0.76 (0.66–0.86)	0.51 (0.11–2.29)	0.98 (0.83–1.15)	0.51 (0.18–1.48)
SW and entertainment	1.04 (0.93–1.16)	0.83 (0.77–0.90)	0.84 (0.80–0.89)	0.80 (0.71–0.89)	0.89 (0.81–0.99)	1.11 (0.91–1.36)
Others	1.03 (1.00–1.06)	0.95 (0.91–0.99)	0.87 (0.85–0.89)	0.92 (0.87–0.98)	0.98 (0.95–1.01)	1.15 (1.08–1.23)
Marital status						
Single	1.04 (0.97–1.11)	0.90 (0.83–0.98)	0.88 (0.84–0.93)	0.91 (0.79–1.05)	0.99 (0.92–1.06)	1.03 (0.86–1.23)
Married	1.03 (1.00–1.06)	1.01 (0.96–1.06)	0.90 (0.87–0.93)	0.93 (0.86–0.99)	0.98 (0.95–1.01)	1.18 (1.10–1.26)
Ever married	1.02 (0.95–1.09)	0.81 (0.75–0.87)	0.80 (0.77–0.84)	0.86 (0.79–0.93)	0.94 (0.88–1.01)	1.08 (0.96–1.22)
Education						
No formal education	1.01 (0.88–1.16)	0.99 (0.79–1.24)	0.76 (0.66–0.87)	0.82 (0.61–1.10)	1.03 (0.83–1.28)	1.39 (0.79–2.44)
Primary education	1.04 (1.00–1.09)	0.92 (0.87–0.97)	0.87 (0.85–0.90)	0.92 (0.86–0.98)	0.99 (0.95–1.05)	1.09 (1.01–1.17)
Secondary	1.02 (0.98–1.06)	0.94 (0.90–0.99)	0.88 (0.85–0.90)	0.88 (0.81–0.95)	0.96 (0.92–0.99)	1.21 (1.11–1.33)
Bachelor	1.34 (0.94–1.89)	1.20 (0.78–1.86)	0.89 (0.73–1.08)	0.51 (0.12–2.28)	1.10 (0.90–1.34)	1.28 (0.69–2.37)
Baseline risk groups						
Low risk	1.03 (0.99–1.07)	1.00 (0.91–1.09)	0.91 (0.87–0.96)	0.97 (0.83–1.13)	1.02 (0.97–1.07)	1.28 (1.16–1.40)
Medium risk	1.01 (0.96–1.06)	0.97 (0.90–1.05)	0.87 (0.83–0.91)	1.01 (0.88–1.15)	1.04 (0.98–1.10)	1.11 (0.99–1.25)
High risk	1.06 (1.01–1.11)	0.90 (0.86–0.94)	0.85 (0.82–0.87)	0.86 (0.82–0.91)	0.91 (0.88–0.95)	1.03 (0.93–1.13)

programs targeting women, therefore encouraging their participation. Results of this trial suggest that men and women were comparable in most aspects. Similar to other clinical trials, most of our study participants were young with a high school level of education and lived in urban and semiurban areas. This study showed results similar to other trials involving heterosexual transmission with men having more than one partner, more casual and high-risk sex partners, and less use of condom for protection.^{19–21}

Compared to their respective subgroups, a higher proportions of sex workers and ever married women had more than one sex partner, with casual and high-risk partners, and a history of STDs. Housewives and students had about 10% casual sex and a 3% history of STDs despite being perceived as a low-risk group. Most women who were IDUs (4%) with a history of incarceration had neither formal education nor primary education. Risk behaviors in most subgroups significantly decreased within 36 months of follow-up. These may be due to intensive counseling by research teams and preventive measures on each follow-up visit. Similar results were obtained in other studies using the same product (AIDSVAX) alone, one of the two vaccines in the RV 144 prime-boost protocol.^{22,23}

Vaccine completion in men and women were about 85%, and both groups were in compliance with the protocol immunization schedule for about 75% of the time. More women (88%) were retained compared with men (85%). In addition, 17% women had missed visits compared to men (21%). Subgroup analysis showed married women aged 21 and above and being a housewife had more retention on last follow-up visit and with complete vaccination compared to other

groups. Recruitment and retention of women are more complex and expensive than men due to differences in socioeconomic status and expectations and requirements for participation.¹⁶ Women may be reluctant to address their sexual behaviors, restrain from being pregnant, and burdened with family care.^{24–26} Several strategies for study compliance and retention include consented home visits, weekend and off-hour clinic visits, consented confidential visits when incarcerated, and community advocacy. Other studies used telephone reminders for missed visits, giving certificates of completion on final visits, and a high level of acknowledgment for participating in the study.^{27–31}

Results of the main study showed that 132 subjects were diagnosed with HIV infection (56 in the vaccine group and 76 in the placebo group), therefore providing preliminary evidence that an HIV vaccine regimen has the potential to prevent infection in the modified ITT analysis.¹⁴ Similar findings were obtained in our study when male-to-female infection rates and vaccine efficacy were compared.

Also, in the main study most local and systemic reactions to the vaccine were mild to moderate; at least one adverse event was reported in 69.4% of subjects in the two study groups, with similar severity in both groups.¹⁴ It was found that women had at least one AE more than men. Most of the AEs of men were related to injuries sustained from motorcycle accidents (35% events in men compared to 15% in women) because participants were young and motorcycles were the main mode of transportation. The second most frequent AEs (33% men and 37% women) were upper respiratory infections. The subgroup analyses of women participants revealed that those aged above 21 had more AEs than younger women.

FIG. 1. Time to participation events during study period.

However, with regard to the safety of preventive vaccines,³² this vaccine regimen was still considered to be safe because there were very few vaccine-related AEs with no difference in AEs between placebo and vaccine recipients.

The HIV vaccine trial poses an unusual challenge for both investigators and volunteers as study participants may experience discrimination and social stigma.^{16,27,32,33} In several studies, discrimination ranged from <5% to 30%.^{34–40} Only about 4% of participants reported PIEs in this study, a finding that was similar to another trial in Thailand.⁴⁰ This could be due to differences in the background and culture of the study community as well as different procedures in assessing PIEs among participants. While men and women were concerned that participation could potentially damage their personal relationships, the concern was greater for women, who were more likely to be economically dependent.²⁸ In this study, women experienced more PIEs than men, and women who were in the high-risk group had more PIEs than those in low-risk groups. Similar to other studies, the most frequent PIE reported in this study was personal relationship problems, especially for women.^{35,37} In addition, female student participants experienced stigma during the first 6 months after enrollment. This could be due to lack of knowledge and misunderstanding about HIV/AIDS at the early phase of the trial, as PIEs were much less frequent after that period. In this study, PIEs were rated as not serious with minimal impact on

their daily lives, a finding that was similar to other vaccine efficacy trials conducted in Thailand.^{37,40} Positive PIEs reported in this study include positive recognition and personal relationships.^{24,38,40}

Pregnancy is one of the reasons why some women do not want to participate in a study. Guidelines from UNAIDS recommend that women who are pregnant, potentially pregnant, and breast-feeding should be eligible for enrollment in HIV preventive vaccine trials, both as a matter of equity and because women are at high risk of HIV infection in many communities.⁴¹ However, most investigators were reluctant to enroll pregnant and breast-feeding women because of concerns about health risks from the candidate vaccine. Still, pregnancy rates during HIV prevention trials were high.^{19,42} As women participants in this study were young, almost one-third became pregnant during the trial. Women aged ≤20 had higher pregnancy rates compared with other groups. Over 25% of pregnant women were either single, students, or ever married. These were groups with less risk for pregnancy. Further investigation regarding this issue should be considered as a study on hormonal contraceptives showed that although women in vaccine trials frequently used prevention methods, misconceptions and their incorrect use might have led to inconsistent use resulting in undesired pregnancies.¹⁹

Women's participation in HIV vaccine trials represents an important challenge due to women's susceptibility to

TABLE 6. PARTICIPATION QUALITIES AND OUTCOMES BY BASELINE CHARACTERISTICS AND RISK BEHAVIORS OF WOMEN PARTICIPANTS, THAILAND, 2003–2009

Participant characteristics	Complete vaccinations (per-protocol)						Retention at 42 months			HIV infection			Experienced at least 1 PIE			Experienced at least 1 AE			Pregnancy		
	Baseline		N		n (%)		OR (95% CI)		N (%)		OR (95% CI)		n (%)		OR (95% CI)		n (%)		OR (95% CI)		
Age groups	≤20	1,613	1,153 (71.58)	1	1,370 (84.93)	1			11 (0.68)	1	78 (4.84)	1	1,096 (67.95)	1	654 (40.55)	1					
	21–25	2,771	2,118 (76.43)	1.29 (1.13–1.49)	2,443 (88.16)	1.32 (1.10–1.58)			28 (1.01)	1.49 (0.74–2.99)	144 (5.20)	1.08 (0.82–1.43)	1,987 (71.71)	1.20 (1.04–1.37)	867 (31.29)	0.67 (0.59–0.76)					
	≥26	1,950	1,596 (81.85)	1.80 (1.54–2.11)	1,771 (90.82)	1.75 (1.43–2.15)			14 (0.72)	1.05 (0.48–2.33)	114 (5.85)	1.22 (0.91–1.64)	1,389 (71.23)	1.17 (1.01–1.35)	401 (20.56)	0.38 (0.33–0.44)					
Occupation risk groups	Housewife	779	641 (82.28)	1.44 (1.18–1.75)	718 (92.17)	1.57 (1.19–2.06)			8 (1.03)	1.32 (0.61–2.83)	40 (5.13)	0.99 (0.71–1.40)	545 (69.96)	0.95 (0.81–1.12)	219 (28.11)	0.89 (0.75–1.05)					
	Student	383	295 (77.02)	1.04 (0.81–1.34)	319 (83.29)	0.66 (0.50–0.88)			2 (0.52)	0.67 (0.16–2.77)	23 (6.01)	1.18 (0.76–1.83)	268 (69.97)	0.95 (0.76–1.20)	104 (27.15)	0.85 (0.67–1.07)					
	SW and entertainment	318	229 (72.01)	0.80 (0.62–1.03)	263 (82.70)	0.64 (0.47–0.86)			5 (1.57)	2.02 (0.79–5.18)	23 (7.23)	1.44 (0.92–2.24)	215 (67.61)	0.85 (0.67–1.09)	114 (35.85)	1.27 (1.00–1.61)					
Others	4,854	3,702 (76.27)	1	4,284 (88.26)	1			38 (0.78)	1	250 (5.15)	1	3,444 (70.95)	1	1,485 (30.59)	1						
Marital status	Single	1,272	937 (73.66)	1	1,078 (84.75)	1			7 (0.55)	1	70 (5.50)	1	876 (68.87)	1	336 (26.42)	1					
	Married	4,206	3,314 (78.79)	1.33 (1.15–1.54)	3,781 (89.90)	1.60 (1.33–1.92)			32 (0.76)	1.39 (0.61–3.15)	217 (5.16)	0.94 (0.71–1.23)	2,994 (71.18)	1.11 (0.97–1.28)	1,309 (31.12)	1.26 (1.09–1.45)					
	Ever married	856	616 (71.96)	0.91 (0.75–1.11)	725 (84.70)	0.99 (0.78–1.27)			14 (1.64)	3.00 (1.21–7.48)	49 (5.72)	1.04 (0.72–1.52)	602 (70.33)	1.07 (0.89–1.29)	277 (32.36)	1.33 (1.10–1.61)					
Education	No formal education	121	99 (81.82)	1	113 (93.39)	1			2 (1.65)	1	5 (4.13)	1	92 (76.03)	1	30 (24.79)	1					
	Primary education	2,106	1,651 (78.40)	0.80 (0.50–1.29)	1,889 (89.70)	0.62 (0.30–1.28)			20 (0.95)	0.57 (0.13–2.47)	126 (5.98)	1.48 (0.59–3.68)	1,469 (69.75)	0.73 (0.47–1.11)	627 (29.77)	1.29 (0.84–1.96)					
	Secondary education	3,996	3,023 (75.65)	0.69 (0.43–1.10)	3,487 (87.26)	0.49 (0.24–0.99)			31 (0.78)	0.47 (0.11–1.97)	197 (4.93)	1.20 (0.49–2.98)	2,820 (70.57)	0.76 (0.50–1.15)	1,240 (31.03)	1.36 (0.90–2.07)					
Bachelor	111	94 (84.68)	1.22 (0.61–2.46)	95 (85.59)	0.42 (0.17–1.03)			0 (0.00)	—	8 (7.21)	1.80 (0.57–5.68)	91 (81.98)	1.43 (0.76–2.71)	25 (22.52)	0.88 (0.48–1.62)						
Baseline risk groups	Low risk	3,127	2,427 (77.61)	1	2,777 (88.81)	1			21 (0.67)	1	142 (4.54)	1	2,204 (70.48)	1	944 (30.19)	1					
	Medium risk	1,789	1,367 (76.41)	0.93 (0.81–1.07)	1,577 (88.15)	0.94 (0.78–1.12)			15 (0.84)	1.25 (0.64–2.43)	99 (5.53)	1.23 (0.95–1.60)	1,237 (69.14)	0.94 (0.83–1.06)	545 (30.46)	1.01 (0.89–1.15)					
	High risk	1,418	1,073 (75.67)	0.90 (0.77–1.04)	1,230 (86.74)	0.82 (0.68–0.99)			17 (1.20)	1.79 (0.94–3.41)	95 (6.70)	1.51 (1.15–1.97)	1,031 (72.71)	1.12 (0.97–1.28)	433 (30.54)	1.02 (0.89–1.17)					

PIE, participatory impact event; AE, adverse event.

infection and sociocultural and legal inequality. Other barriers in recruiting and retaining women in trials include age, occupation, education, and marital status. To achieve women's participation in this trial, several strategies were developed and fully implemented by the research teams. They considered the rights and needs of these women while encouraging community involvement and representation.

In conclusion, female volunteers showed the same qualities and outcomes of participation as males in the HIV vaccine trial. The analyses of gender issues and women's participation in this study revealed behavioral, social, and cultural indicators that could be used for future trials. Data collected from the target population may be of great help in developing effective educational materials, resolving ethical issues, and finding useful sociocultural indicators for a successful HIV vaccine trial design.

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References

- Mosenifar Z: Population issues in clinical trials. *Proc Am Thorac Soc* 2007;4:185–188.
- Berlin JA and Ellenberg SS: Inclusion of women in clinical trials. *BMC Med* 2009;7:56.
- Screening, recruiting and predicting retention of participants in a multisite HIV prevention trial. NIMH Multisite HIV Prevention Trial. *AIDS* 1997;11:S13–19.
- National Research Council: *Women's Health Research: Progress, Pitfalls, and Promise*. The National Academies Press, Washington, DC, 2010.
- Evelyn B, Toigo T, Banks D, *et al.*: Women's participation in clinical trials and gender related labeling: A review of new molecular entities approved 1995–1999. U.S. Food and Drug Administration, Office of Special Health Issues, Office of International and Constituent Relations, Office of the Commissioner, Washington, DC, 2001.
- Yang Y, Carlin AS, Faustino PJ, *et al.*: Participation of women in clinical trials for new drugs approved by the Food and Drug Administration in 2000–2002. *J Womens Health* 2009;18:303–310.
- Pinnow EE, Sharma P, Parekh A, *et al.*: Increasing participation of women in early phase clinical trials approved by FDA. *Womens Health Issues* 2009;19:89–93.
- Poon R, Khanijow K, Umarjee S, *et al.*: Participation of women and sex analyses in late phase clinical trials of New Molecular Entity (NME) Drugs and Biologics approved by the FDA in 2007–2009. FDA Office of Women's Health R&D Presentation, Primary Interest Area (TRACK 9): Regulatory Affairs and Science, Quality, and GXP Compliance, 2011.
- Newman PA, Duan N, Roberts KJ, *et al.*: HIV vaccine trial participation among ethnic minority communities: Barriers, motivators, and implications for recruitment. *J Acquir Immune Defic Syndr* 2006;41:210–217.
- Wassenaar DR, Barsdorf NW, and Richter LM: Gender and HIV vaccine trials: Ethics and social science issue. *Harvard Health Policy Issue* 2005;6:124–129.
- Buchbinder SP, Mehrotra DV, Duerr A, *et al.*: Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): A double blind, randomised, placebo-controlled, test-of-concept trial. *Lancet* 2008;372:1881–1893.
- Koblin BA, Heagerty P, Sheon A, *et al.*: Readiness of high-risk populations in the HIV Network for Prevention Trials to participate in HIV vaccine efficacy trials in the United States. *AIDS* 1998;12(7):785–793.
- UNAIDS: Report on the global AIDS epidemic 2008. UNAIDS, Geneva, 2008.
- Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, *et al.*: Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009;361(23):2209–2220.
- Joint United Nations Programme on HIV/AIDS (UNAIDS): Good participatory practice: Guidelines for biomedical HIV prevention trials 2011. UNAIDS/JC1853E, 2nd ed., June 2011.
- Mystakidou K, Panagiotou I, Katsaragakis S, *et al.*: Ethical and practical challenges in implementing informed consent in HIV/AIDS clinical trials in developing or resource-limited countries. *SAHARA J* 2009;6:46–57.
- Lake JE, Friedman RK, Cunha CB, *et al.*: Participation of women in HIV clinical trials: The IPEC-FIOCRUZ experience. *HIV/AIDS Res Palliative Care* 2011;3:61–68.
- Freedberg KA, Sullivan L, Georgakis A, *et al.*: Improving participation in HIV clinical trials: Impact of a brief intervention. *HIV Clin Trials* 2001;2:205–212.
- Kibuuka H, Guwatudde D, Kimutai R, *et al.*: Contraceptive use in women enrolled into preventive HIV vaccine trials: Experience from a Phase I/II trial in East Africa. *PLoS One* 2009;4:e5164.
- Karim QA, Kharsany ABM, Frohlich JA, *et al.*: Recruitment of high-risk women for HIV prevention trials: Baseline HIV prevalence and sexual behavior in the CAPRISA 004 tenofovir gel trial. *Trials* 2011;12:67.
- Nadine EC, Jaimie PM, and Sandra AS: Advances in the prevention of heterosexual transmission of HIV/AIDS among women in the United States. *Infect Dis Rep* 2011;3:8.
- Migasena S, Choopanya K, Vanichasen S, *et al.*: Conducting an HIV vaccine efficacy trial in Thailand: Lessons learned and experience gained. Presented at the First IAS Conference on HIV Pathogenesis and Treatment, Buenos Aires, Argentina, 2001.
- Bartholow BN, Buchbinder S, Celum C, *et al.*: HIV sexual risk behavior over 36 months of follow-up in the world's first HIV vaccine efficacy trial. *J Acquir Immune Defic Syndr* 2005;39:90–101.
- Mills E, Nixon S, Singh S, *et al.*: Enrolling women into HIV preventive vaccine trials: An ethical imperative but a logistical challenge. *PLoS Med* 2006;3:e94.
- Currier J, Bridge DA, Hagins D, *et al.*: Sex-based outcomes of darunavir–ritonavir therapy: A single-group trial. *Ann Intern Med* 2010;153(6):349–357.
- Hessol NA, Schneider M, Greenblatt RM, *et al.*: Retention of women enrolled in a prospective study of human immunodeficiency virus infection: Impact of race, unstable housing, and use of human immunodeficiency virus therapy. *Am J Epidemiol* 2001;154:563–573.
- Ramjee G, Coumi N, Dladla-Qwabe N, *et al.*: Experiences in conducting multiple community-based HIV prevention trials among women in KwaZulu-Natal, South Africa. *AIDS Res Ther* 2010;7:10.
- International AIDS Vaccine Initiative (IAVI): Understanding the role of social science research in clinical trials. (www.iavireport.org/vax-primers/clinical-trials/Pages/VAX-primer-social-science). Accessed August 2009.
- Dhalla S, Woods R, Strathdee SA, Patrick DM, and Hogg RS: HIV vaccine preparedness studies in the organization for

- economic cooperation and development (OECD) countries. *AIDS Care* 2007;19:1118–1127.
30. Middelkoop K, Myer L, Mark D, *et al.*: Adolescent and adult participation in an HIV vaccine trial preparedness cohort in South Africa. *J Adoles Health* 2008;43:8–14.
 31. Kibuuka H, Guwatudde D, Kimutai R, *et al.*: Contraceptive use in women enrolled into preventive HIV vaccine trials: Experience from Phase I/II trial in East Africa. *PLoS One* 2009;4: e5164.
 32. U.S. Congress, Office of Technology Assessment: *Adverse Reactions to HIV Vaccines: Medical, Ethical, and Legal Issues*. U.S. Government Printing Office, Washington, DC, September 1995.
 33. Ho J: The quest for an HIV vaccine. Logistical and ethical considerations in HIV vaccine clinical trial. (www.vaccineethics.org/issue_briefs/HIV_clinical_trials.php). Accessed July 2010.
 34. Sheon AR, Wagner L, Mc Elrath MJ, *et al.*: Preventing discrimination against volunteers in prophylactic HIV vaccine trials: Lessons from a Phase II trial. *J Acquir Immune Defic Syndr* 1998;19:519–526.
 35. Allen M, Israel H, Rybczyk K, *et al.*: Trial-related discrimination in HIV vaccine clinical trials. *AIDS Res Hum Retroviruses* 2001;17:667–674.
 36. Fuchs J, Durham M, McLellan-Lemal E, *et al.*: Negative social impacts among volunteers in an HIV vaccine efficacy trial. *J Acquir Immune Defic Syndr* 2007;46:362–368.
 37. Pitisuttithum P, Choopanya K, Bussaratid V, *et al.*: Social harms in injecting drug users participating in the first Phase III HIV vaccine trial in Thailand. *J Med Assoc Thai* 2007;90:2442–2448.
 38. Allen M and Lau CY: Social impact of preventive HIV vaccine clinical trial participation: A model of prevention, assessment and intervention. *Soc Sci Med* 2008;66:945–951.
 39. Allen MA, Gray G, Churchyard G, *et al.*: Social impact events in Phambili, the first Phase 2B HIV vaccine trial in South Africa. (www.retrovirology.com/content/6/S3/P190). Accessed July 2010.
 40. Jenkins RA, Thapinta D, Morgan PA, *et al.*: Behavioural and social issues among volunteers in the preventive HIV vaccine trial in Thailand. *J Acquir Immune Defic Syndr* 2005;40:592–599.
 41. Joint United Nations Programme on HIV/AIDS: Ethical considerations in HIV preventive vaccine research. UNAIDS guidance document, April 2004.
 42. International AIDS Vaccine Initiative's (IAVI): VAX Primers: AIDS vaccine clinical trials. Understanding the recruitment and retention of women in clinical trials. (www.iavireport.org/vax-primers/clinical-trials/Pages/VAX-primer-recruitment-retention.html). Accessed March 2008.

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