

Social Harms in Injecting Drug Users Participating in the First Phase III HIV Vaccine Trial in Thailand

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Objective: To study related social harms due to identification with a group of participants in an HIV-1 vaccine trial who are potentially high risk for HIV/AIDS.

Material and Method: Two thousand five hundred forty six injecting drug users (IDU) were enrolled in a 36-month vaccine trial. Volunteers received education and risk reduction counseling at every six-month study visit. Social harms were not actively solicited, but volunteers were encouraged to report any during the process of counseling at every six-month visit. If a social harm was reported, a questionnaire was administered and the harm was tracked. If necessary, clinic staff assisted in resolving the social harm.

Results: Thirty-nine social harms were reported by 37 participants; 33 (84.6%) were disturbances in personal relationships, three (7.7%) in employment, one (2.6%) was medically related, one (2.6%) was related to admission in the military and one (2.6%) was related with misbelieve about the vaccine. The most common reason for disturbances in personal relationships was suspicion of HIV infection ($n = 20$). The impact of these harms on quality of life was characterized as minimal by 31 (79.5%) participants, as moderate by seven (17.9%), and as major by one (2.6%). All social harms were documented to be resolved by the end of the study.

Conclusion: A few participants reported study-related social harms during the course of the trial. Most harm had minimal impact and all could be resolved by the end of the present study.

Keywords: HIV vaccine, Phase III trial, Social harm, Injecting drug users, Thailand

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Not long after the human immunodeficiency virus (HIV) was discovered as the causative agent of the acquired immunodeficiency syndrome (AIDS) in 1983, vaccine strategies were proposed to prevent

primary infection⁽¹⁻⁴⁾. An HIV vaccine must be effective against multiple strains of HIV in order to prevent the majority of HIV infections, most of which occur outside the Western hemisphere⁽⁴⁾. Compared to anti-retroviral treatment of HIV-infection, an HIV vaccine is thought to be a safer and cheaper method to control HIV epidemics.

Over 60 vaccines have been evaluated worldwide since 1987. Two AIDS VAX vaccines, VaxGen B/

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B2 and B/E, were the first to have entered Phase III trials. A population with high HIV incidence, regardless of country of residence, is a likely candidate for HIV vaccine evaluation. Negative social impact experiences have been reported in multiple trials, including trials enrolling persons at low risk for HIV infection in the U.S. and developing countries. Hence, these events are not limited to individuals at high-risk for HIV infection in developing countries^(5,6). High-risk populations in developing countries are likely candidates for the evaluation of HIV vaccines, because of their high HIV incidence. However, these populations are often considered vulnerable and susceptible to potential negative behavioral, psychosocial and community effects associated with HIV vaccine trials⁽⁵⁻⁷⁾.

According to UNAIDS guidelines for consideration in HIV preventive vaccine research, documentation of a vaccine trial should include risk reduction intervention, e.g., intensive education and counseling⁽⁵⁻⁷⁾. The provision of counseling to reduce risk should be monitored to ensure its quality and to avoid the potential conflict of interest between the risk-reduction goals and the vaccine trial specific interest of evaluating HIV incidence⁽⁷⁾. Thus, monitoring of risk of participants is mandatory for HIV vaccine testing especially in non-Western and developing countries. There also is the risk of experiencing social harm associated with trial participation. Vaccine trial participants may be associated with HIV risk, stigmatized illegal behaviors and disclosed of being at risk for HIV infection and they may also be falsely identified as HIV-infected, not only socially, but also technically due to vaccine induced HIV seropositivity. These events may lead to disturbances in personal relationships, loss of employment or employment opportunities, denial of health and life insurance and travel restrictions.

The most commonly reported negative social impact was friends, family, or a partner thinking the volunteer was HIV positive and therefore, judging or avoiding the participant⁽⁶⁾. In order to reduce such social harms, these events must be monitored and reported⁽⁵⁻⁷⁾. The authors report frequency and resolution of social harms reported by participants in Thailand's AIDS VAX B/E (VaxGen, Inc., Brisbane, CA, USA) vaccine trial, the first phase III HIV vaccine efficacy trial conducted in a non-Western country.

Material and Method

The present study was a randomized, double-blind, placebo-controlled trial to test the efficacy of AIDS VAX B/E in preventing HIV-1 infection in inject-

ing drug users (IDU). Between March 1999 and August 2000, 2,546 IDU were enrolled in the trial. One volunteer was excluded from further participation in the trial because of HIV infection at the day of enrollment. Detailed methods and characteristics of the trial have been reported elsewhere^(8,9).

Trial procedures

At the start, participants were randomly assigned to receive either AIDS VAX B/E vaccine or placebo (in a 1:1 ratio) at months 0, 1 and 6, with booster doses at months 12, 18, 24 and 30. Participants were followed for 16 scheduled visits over a 36-month study period. As part of the screening process, education was conducted via video, booklets, group discussions, individual counseling and a test of understanding of trial procedures. After that, participants were asked to read and sign an informed consent form.

Social harm was defined as a trial related event with a significant adverse psychological or social outcome. Determination of harm is by self-report from the subject and is based on the subject's perception of harm and its impact on their lives over time.

Reports of social harms were not actively solicited, but volunteers were encouraged to report if they felt harmed as a result of participating in the trial. If a social harm was reported, a questionnaire was completed (see list of questions below). Questions addressed the type of social harm, whether, when, and how it was resolved, whether the volunteer was HIV tested as part of the social harm (Table 1), and what the perceived impact of the social harm was on the participant's quality of life. If necessary and desired, clinic staff assisted in resolving the social harm, including tracking and following-up of the harm until it was resolved.

Listing of social harms questions⁽¹⁰⁾

Social harms report

1. Describe the social harms event
2. What type of social harm is reported on this form?
3. Do you think this situation is resolved? If not, what would help to resolve it?
4. Was HIV antibody testing an issue in this situation? If yes, was HIV antibody testing required?
5. Did your participation in the present study become known to others? If yes, how did your participation become known to a person outside the study?
6. In response to this situation, did you use the study ID card, tell the study staff about his

problem, and ask the study staff to call or write a letter, other?

7. Please give answers to what impact this situation has had on your quality of life as follows: minimal, moderate or major.

8. Is there anything else that you would like to tell about this situation?

9. What has been done to respond to this situation?

Social harms follow-up

1. Date of the follow up
2. Event number from original Social Harms report
3. Resolution Status: resolved or unresolved
4. What has been done since the last report to respond to this situation?

Statistical analysis

Statistical analysis was descriptive statistics. A χ^2 test was used to assess associations between age, sex, education, risk behavior, study-arm assignment and reported social harm.

Results

Demographic and risk behavior profile

The 2,545 participants had a median age of 26 years (range: 20-59 years), 93.4% (2,376) were male, and 1,711 (67%) had at least completed 9th grade education. During the 6 months prior to baseline, 2,388 (94%) reported having injected drugs, of whom 789 (33%) reported having shared needles, and 2,092 (82%) reported receiving methadone treatment. Heroin injection was reported by 2,351 (99%) participants, methamphetamine by 376 (16%), and midazolam by 243 (10%). Daily injection was reported by 936 (39%) participants.

Social harms

After 36 months of trial duration, 37 participants (1.5%) reported 39 social harm (two participants each reported two events); 24 were from the vaccine and 13 were from the placebo group ($\chi^2 = 3.3, p = 0.07$). Among these 37 participants, one in the vaccine group and two in the placebo group became HIV infected during the trial. 18 participants (48.7%) reported that people in their environment thought they were HIV infected (12 vaccine recipients (67%) and six placebo recipients (33%), 5 (13.5%) reported that others thought the vaccine was made from HIV, and 14 reported that their relatives or friends expressed concern or disagreed with their participation in the trial (Fig. 1).

Table 1. Summary of social harms event

	Total (n = 2545)
Number of participants reporting social harm*	37 (1.5%)
Number of social harms events reported	39
Number of social harms events resolved**	39 (100%)
Social harms type**	
Personal relationship	33 (84.6%)
Health insurance	-
Life insurance	-
Travel	-
Employment	3 (7.7%)
Medical/Dental	1 (2.6%)
Education	-
Other	1 (2.6%)
Housing	-
Military	1 (2.6%)
Impact of the social harms event**	
Minimal	31 (79.5%)
Moderate	7 (17.9%)
Major	1 (2.6%)

* Each subject reporting social harm events is counted once, percentages are based on the total number of subjects in the study

** Percentages are based on the number of events reported

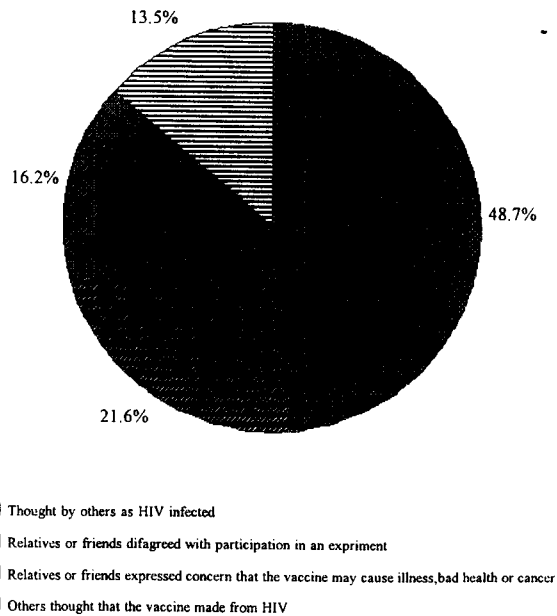


Fig. 1 Description of social harms and percentages of participants reporting

Table 2. Type of social impact by type of social harm

	Type of social harm				Total
	1*	2*	3*	4*	
Type of social impact					
Personal Relationship	16	4	8	5*	33
Employment	2	1			3
Medical services	1				1
Military conscription	1				1
Misbelieve about the vaccine	1				1
Impact on quality of life					
Minimal	13	5	8	5	31
Moderate	6		1		7
Major	1				1
Harm resolved in within six months					
Yes	11	4	6	4	25
No	9	1	2	2	14

1* = Thought by others as being HIV infected

2* = Others thought that the vaccine was made from HIV

3* = Relatives or friends disagreed with participation in an experiment

4* = Relatives or friends expressed concern that the vaccine might cause illness, bad health or cancer

The majority of the social harms (33/39 or 84.6%) were related to disturbances in personal relationships, three were related to employment, one each was related to misbelieve about the vaccine that the vaccine might cause harms such as health problems, receipt of medical services and conscription in the military (Table 1, 2). As part of the last two social harms, the participant underwent an HIV test. Volunteers indicated that most of the social harms they reported had minimal impact on the quality of life (31/39 or 79.5%), seven (17.9%) had a moderate effect and one (2.6%) had a major effect (Table 1). Reported harms of a moderate or major effect were almost all (7/8 or 87.5%) related to other people's thinking that the volunteer was HIV infected because of participation in the trial. In four cases, this was a family member or friend, in two cases, this was an employer and in one case, this was related to conscription in the military.

More than half (25, or 64.1%) of social harms were resolved within six months of their first report and all were resolved before the end of the trial. There were no statistical differences in the number of social harms according to demographic and behavioral characteristics at baseline (age, sex, education, drug injection history, sharing of needles and methadone treatment in the previous six months, data not shown) nor to being in the vaccine or the placebo group.

Discussion

The present study shows that little social harm was reported in the first HIV vaccine trial among IDU in a non-Western country. Reports of social harm were not associated with demographic characteristics, risk behavior profile or study arm assignment. Study from Jenkins et al showed that concern about family influence produced the largest negative odds ratio to willingness, although concerns about social and physical harm, as well as practical considerations also had significant negative associations with willingness^(10,11).

The other study showed that the large number of people who reported a mix of motives suggests that the decision to enter trials can involve multiple considerations. The need to reconcile prosocial motives with practical concerns would seem to be a reasonable response to making a decision about a time-consuming trial, where some degree of risk may be perceived⁽¹²⁾. The authors did not actively solicit reports of social harms, but participants were encouraged to report so if they felt harmed as a result of participating in the trial.

Of the small number of social harms reported, most were related to disturbances in personal relationships and all were resolved by the end of the trial. The number of social harms reported in the present

trial was lower than that reported in a comparable vaccine trial among men who have sex with men (MSM) and women at risk for sexual transmission in North America and Europe^(10,13). Since surveillance of social harms assessed on a six-month schedule in both trials, the lower number reported in the Thai trial may be explained by differences in population characteristics and cultural norms about what is perceived as a social harm.

MSM in the industrialized world are usually well educated, have a well-organized community, and have a history of activism regarding social and legal issues, which they perceive as unjust. It may be that IDU in Thailand were already experiencing a number of social harms related to their drug use, such as discrimination and stigmatization, and therefore, may not have perceived additional social harm as trial-related. In addition, the Thai belief-system contemplates that life is, to a certain extent, pre-determined and the result of one's own destiny or "karma". It is possible that the lower number of reported social harms in Thailand was due to a higher threshold of what is perceived as a social harm.

Disturbances of personal relationships were the most common form of study-related social harm. These were usually related to concerns about HIV infection and participation in a medical experiment. Social harms related to employment and insurance status were infrequently reported. In the North-American-European trial, the inability to obtain or to lose employment or health and life insurance as a result of trial participation was identified as a potential significant study-related social harm⁽¹³⁾. In Thailand, there was less potential for such harm, since most study participants were self-employed day laborers, such as messengers and motorcycle taxi-drivers, and the existence of universal public health insurance. In addition, life-insurance and other types of insurance based on life years are uncommon in Thailand; only around 10% of the population has some kind of life insurance policy⁽¹⁴⁾.

In conclusion, a small number of social harms were reported in this first trial of a HIV vaccine among IDU in a non-Western country. However, these data should be interpreted with caution, since social harms were not actively solicited during the course of the trial. A more active surveillance system for social harms in future vaccine trials is, therefore recommended (e.g., more frequent visits and time are necessary to assess social harms and follow up). Whether similar or higher numbers will be reported, and how they differ between

other groups at risk for HIV infection and between countries with different cultural belief-systems remains to be seen.

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References

1. Gallo RC, Sarin PS, Gelmann EP, Robert-Guroff M, Richardson E, Kalyanaraman VS, et al. Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). *Science* 1983; 220: 865-7.
2. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 1983; 220: 868-71.
3. Francis DP, Petricciani JC. The prospects for and pathways toward a vaccine for AIDS. *N Engl J Med* 1985; 313: 1586-90.
4. Esparza J, Osmanov S, Kallings LO, Wigzell H. Planning for HIV vaccine trials: the World Health Organization perspective. *AIDS* 1991; 5(Suppl 2): S159-63.
5. Guenter D, Esparza J, Macklin R. Ethical considerations in international HIV vaccine trials: summary of a consultative process conducted by the Joint United Nations Programme on HIV/AIDS (UNAIDS). *J Med Ethics* 2000; 26: 37-43.
6. Fuchs J, Durham M, McLellan-Lemal E, Vittinghoff

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- E, Buchbinder S. Younger HIV vaccine trial participants report negative social impacts. Abstract The XV International AIDS Conference, Bangkok, Thailand; July 11-16, 2004. (Abstract no. ThPeC7444)
7. Bloom BR. The highest attainable standard: ethical issues in AIDS vaccines. *Science* 1998; 279: 186-8.
 8. Vanichseni S, Tappero JW, Pitisuttithum P, Kitayaporn D, Mastro TD, Vimutisunthorn E, et al. Recruitment, screening and characteristics of injection drug users participating in the AIDS VAX B/E HIV vaccine trial, Bangkok, Thailand. *AIDS* 2004; 18: 311-6.
 9. van Griensvan F, Keawkungwal J, Tappero JW, Sangkum U, Pitisuttithum P, Vanichseni S, et al. Lack of increased HIV risk behavior among injection drug users participating in the AIDS VAX B/E HIV vaccine trial in Bangkok, Thailand. *AIDS* 2004; 18: 295-301.
 10. Jermano J, Popovic V, Vincelette J, Hogg RS, Logue K. Social harm monitoring in the first HIV vaccine efficacy trial: program design and preliminary data. Abstract presented at the IXth Annual Canadian Conference on HIV/AIDS Research, Montreal, Canada; April 25-28, 2000.
 11. Jenkins RA, Torugsa K, Markowitz LE, Mason CJ, Jamroentana V, Brown AE, et al. Willingness to participate in HIV-1 vaccine trials among young Thai men. *Sex Transm Infect* 2000; 76: 386-92.
 12. Slack C, Lindegger G, Vardas E, Richter L, Strode A, Wassenaar D. Ethical issues in HIV vaccine trials in South Africa. *S Afr J Sci* 2000; 96: 291-5.
 13. Surasiengsunk S, Prakobphol V, Kiranandana S, van Griensven GJ. The HIV/AIDS epidemic and its impact on life insurance in Thailand. Bangkok: Chulalongkorn University Printing Office; 2001.
 14. Thapinta D, Jenkins RA, Morgan PA, Chiu J, Boenim W, Bussaratid V, et al. Recruiting volunteers for a multisite phase I/II HIV preventive vaccine trial in Thailand. *J Acquir Immune Defic Syndr* 2002; 30: 503-13.

**ผลกระทบทางสังคมในผู้ติดเชื้อเสพติดฉีดเข้าเส้นที่เป็นอาสาสมัครโครงการวิจัยระยะที่ 3 ทดสอบ
หาประสิทธิภาพของวัคซีนเอดส์แวกซ์ บี/อี เพื่อป้องกันการติดเชื้อเอช ไอ วี ในประเทศไทย**

**พรรณิ ปิติสุทธิธรรม, ขจิต ชูปัญญา, วลัย บุขราทิจ, สุกตฤ วาณิชเสนี, Frits van Griensven, เบ็ญจลักษณ์ ผลรัตน์,
Michael Martin, เอี่ยม วิมุติสุนทร, อุดมศักดิ์ สังข์คุ้ม, ทวีป กิตยาภรณ์, Jordan W Tappero, William Heyward,
Donald Francis**

วัตถุประสงค์: เนื่องจากอาสาสมัครในโครงการทดสอบวัคซีนป้องกันการติดเชื้อ เอช ไอ วี - 1 โครงการนี้เป็นผู้ติด
สารเสพติดชนิดฉีดเข้าเส้นซึ่งเป็นกลุ่มที่สังคมตราหน้าว่ามีความเสี่ยงสูงต่อการติดเชื้อ เอช ไอ วี / เอดส์ ดังนั้น
การเข้าร่วมโครงการศึกษานี้ อาจก่อให้เกิดผลกระทบ ทางด้านสังคมต่ออาสาสมัครได้

วัตถุประสงค์และวิธีการ: มีอาสาสมัครเข้าร่วมโครงการรวมทั้งหมด 2,546 คน อาสาสมัครทุกคน ได้รับความรู้เกี่ยวกับเอชไอวี,
โครงการวิจัยอย่างละเอียด และได้รับคำปรึกษาเพื่อ ลดพฤติกรรมเสี่ยงทุก ๆ 6 เดือนตามตารางนัดของโครงการ
จนครบ 36 เดือน การรายงานผลกระทบทางสังคมใช้วิธีให้อาสาสมัครรายงาน พบว่ามีเหตุการณ์ที่มีผลกระทบ
ทางด้านสังคมต่ออาสาสมัคร อาสาสมัครได้ตอบแบบสอบถามและจะได้รับการติดตามผลกระทบนั้นจนสิ้นสุด โดย
เจ้าหน้าที่ประจำคลินิกจะช่วยแก้ปัญหาผลกระทบ ทางด้านสังคมนั้นร่วมกับอาสาสมัคร

ผลการศึกษา: อาสาสมัคร 37 ราย รายงานว่ามีผลกระทบทางด้านสังคม 39 ครั้ง, 33 ราย (84.6%) ได้รับผลกระทบ
ด้านสัมพันธ์ภาพส่วนตัว, 3 ราย (7.7%) ได้รับผลกระทบด้าน การจ้างงาน, 1 ราย (2.6%) ได้รับผลกระทบด้านการ
รักษาพยาบาล, 1 ราย (2.6%) ได้รับผลกระทบด้านการเข้ารับราชการทหาร และ 1 ราย (2.6%) ได้รับผลกระทบด้าน
ความเชื่อที่ผิดเกี่ยวกับวัคซีน เหตุผลส่วนใหญ่ที่รบกวนด้านสัมพันธ์ภาพส่วนตัวคือ ถูกสงสัยว่าติดเชื้อ เอช ไอ วี
(จำนวน 20 ราย) ผลกระทบทางด้านสังคมเหล่านี้มีผลกระทบสูงต่อ คุณภาพชีวิตในระดับต่ำ 31 ราย (79.5%),
มีผลกระทบระดับปานกลาง 7 ราย (17.9%), และมีผลกระทบในระดับสูง 1 ราย (2.6%) ผลกระทบทุกเหตุการณ์ถูก
บันทึกไว้โดยละเอียด และทั้งหมดได้รับการแก้ไขก่อนจะจบการศึกษา

สรุป: มีอาสาสมัครจำนวนเล็กน้อยที่รายงานว่ามีผลกระทบทางด้านสังคมที่มีความสัมพันธ์กับการศึกษาในระหว่าง
อยู่ร่วมโครงการ ผลกระทบส่วนใหญ่อยู่ในระดับต่ำ และผลกระทบทั้งหมด สามารถแก้ไขได้ก่อนจบการศึกษา