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Factors Associated with Willingness to Participate in HIV Vaccine Trials Among HIV-Negative Injection Drug Users and Young Gay and Bisexual Men

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We identified factors associated with willingness to participate in HIV vaccine trials among HIV-negative injection drug users (IDU) and young men having sex with men (MSM) enrolled in prospective cohort studies in Vancouver. Of 435 IDU and 330 MSM, 83% and 63% were willing to participate in HIV vaccine trials, respectively. In both samples, greater willingness was associated with high perceived HIV threat, and with initiating injection or first having sex with men at younger ages. Among IDU, frequent needle exchange programs attenders were more willing to participate than infrequent attenders ($p = .004$). Among MSM, those with a higher depression score were more willing to participate ($p < .001$). In logistic regression models, independent predictors of willingness to participate included frequent needle exchange attendance among IDU, and high depression score and high perceived HIV threat among MSM. This suggests that needle exchange programs are ideal venues for recruiting high-risk IDU into HIV vaccine trials. Since MSM reporting more depressive symptoms were more willing to participate, HIV vaccine trials should provide appropriate counseling to safeguard participants' psychological and physical health.

KEY WORDS: HIV vaccine trials; injecting drug users; homosexual men; risk behavior; needle exchange programs.

INTRODUCTION

Since 90% of global HIV infections occur in developing countries where antiretroviral therapies are not readily available, development and field testing of preventative HIV vaccines remains an urgent public health priority (Burton and Moore, 1998). The first Phase III efficacy trial of a candidate HIV vaccine was launched in 1998 (Anonymous, 1998). In both developed and developing countries, several Phase II HIV vaccine trials are ongoing and are expected to pave the way for other large efficacy trials (Clements-Mann *et al.,* 1998; Graham *et al.,* 1998; Heyward *et al.,* 1994).

Apart from concerns regarding preventative vaccine safety, immunogenicity, and ethical standards, a number of criteria have been proposed in choosing appropriate study populations for evaluating HIV vaccine efficacy (Rida *et al.,* 1997). First, to ensure that a feasible sample size can be studied, HIV incidence must be sufficiently high among populations under study (e.g., ≥2% per 100 person-years). Second, excellent follow-up rates must be rigorously maintained to avoid bias, for example, due to attrition

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of high-risk subjects who are at greater risk of HIV seroconversion. Third, a high proportion of HIV-seronegative subjects at high risk of seroconversion must be willing to participate, since very large numbers will be required to evaluate vaccine efficacy and effectiveness.

In Vancouver, two ongoing prospective studies of HIV incidence and risk behaviors among injection drug users (IDU) and young men having sex with men (MSM) could provide a population base for future vaccine trials. Among a cohort of IDU, HIV incidence has averaged 8.3 per 100 person-years since 1996 (Schechter *et al.,* 1999). In the MSM cohort, HIV incidence is currently 1.72 per 100 person-years (Strathdee *et al.,* 2000). In both cohorts, annual follow-up rates are approximately 80% per year, and there is disturbing evidence of ongoing high-risk behaviors among HIV-negative participants (Strathdee *et al.,* 1997, 1998a).

We assessed the extent to which these HIV-negative cohort participants would be willing to participate in future HIV vaccine trials. For both cohorts, we also identified independent predictors of willingness to participate in such trials. Such information is valuable for preparing target populations for future trials, optimizing recruitment of high-risk individuals, and identifying issues that need to be taken into account in study design.

METHODS

Vancouver Injection Drug User Study

Beginning in May 1996, persons who had injected illicit drugs at least once in the previous month and resided in the Greater Vancouver region were recruited into the Vancouver Injection Drug User Study through self-referral and street outreach. The study design has been previously described (Strathdee *et al.,* 1997, 1998b). Briefly, at baseline and semiannually thereafter, subjects provided blood samples for HIV and hepatitis C antibody testing and completed an interviewer-administered questionnaire. Subjects were reimbursed $20 CDN for each study visit.

Vanguard Project

Beginning in May 1995, young MSM were recruited into an ongoing prospective study of HIV incidence and risk behaviors that was described previously (Strathdee *et al.,* 1998a). In brief, men were eligible to participate if they were aged 18–30 years, lived in the Greater Vancouver region, had not previously tested HIV-seropositive, and self-identified as gay/bisexual or had sex with other men. Potential participants were recruited through community outreach at gay community events, community health clinics or local physicians, and through the gay and mainstream media. Eligible participants were referred to local HIV testing clinics, the study's research nurse, or their physicians' offices, where they completed a confidential self-administered questionnaire and provided a blood sample for HIV testing. Standard survey and testing techniques are used at each location to limit potential biases that might arise from differences between sites. Follow-up visits were conducted annually thereafter.

HIV Testing

In both studies, participants were provided with pre- and posttest HIV counseling by trained personnel, performed at every visit. Blood specimens that were HIV-reactive upon ELISA were confirmed by Western blot according to standard procedures at the provincial laboratory of the British Columbia Centre for Disease Control. Participants were encouraged to return to their physician, clinic, or the study's research nurse to receive their HIV test results. In both studies, referrals were provided for universal medical care, HIV/AIDS care, available drug and alcohol treatment, and counseling, where appropriate.

Study Instruments

Instruments were intentionally designed to be similar in both studies to facilitate analytic comparisons. Follow-up questionnaires pertained to the period since the last study visit. Information was collected on sociodemographics, sexual behaviors with men and women, substance use, and psychosocial variables, as described previously (Strathdee *et al.,* 1997, 1998a). Specifically, data were collected on total numbers of male and female sexual partners in the previous year and lifetime, age at which respondents first engaged in sexual activity, and frequencies of specific sexual practices. Sexual behaviors were recorded for regular partners, defined as partners with whom respondents had sex on a regular basis, at least

once a month on average, and casual male partners, defined as partners with whom they had sex with less than once a month on average, including 'one-nighters'.

Respondents were also asked to indicate their frequency of use of various recreational drugs (e.g., cocaine, heroin, nitrites) and route of administration. Subjects who reported injecting drugs were asked if, during the follow-up period, they had used a needle someone else had already used, and their frequency of attendance at needle exchange programs (NEP).

Both instruments included an abbreviated seven-item version of the Center for Epidemiological Study Depression Scale (CES-D) that has been validated (Mirowsky and Ross, 1992). The MSM cohort also included a 26-item social support scale (Ensel and Woelfel, 1986). In 1997, an item was added to both study instruments that asked participants if they would be willing to participate in a future HIV vaccine trial. This question was preceded by a definition of a vaccine that had been pretested for comprehension.

Statistical Analysis

The proportion of respondents who were willing to participate in HIV vaccine studies was calculated separately for both cohorts, according to the range of possible responses to the question, ''If an HIV vaccine were tested in Canada on people who don't have HIV, would you be interested in participating in a study to see if it works?'' (yes/no for the IDU cohort; definitely, probably, don't know, probably not, and no for the MSM cohort). Since possible responses were not identical for both cohorts, caution should be exercised when making comparisons between studies. For the MSM cohort, subjects responding ''definitely'' or ''probably'' were considered to be willing to participate. The definition of vaccine that was provided in both questionnaires was, ''A vaccine is a shot which protects you from getting infected with a specific disease, such as measles or hepatitis. There is currently no vaccine for HIV, but one may be made available in the future.''

The following variables were coded according to procedures defined *a priori.* Attendance at NEP was coded as ever attending any NEP, or frequent versus less frequent attendance (i.e., more than once per week versus less frequently). The latter categorization was chosen following inspection of the distribution of self-reported attendance. As in previous analyses (Strathdee *et al.,* 1997, 1998a), unstable housing was defined as living primarily in a hotel, boarding room, hostel, transition house, jail, or on the street during the follow-up period.

CES-D and IES scores were independently scored (e.g., never = 1, always = 5) and summed; scores above the median value were considered to represent elevated depression scores and low social support, respectively. Perceived threat of HIV infection was determined by an item that asked respondents' opinion about their likelihood of becoming infected with HIV. Persons who responded ''much more likely'' or ''somewhat'' were considered to have a high perceived HIV threat.

Contingency table analysis was used to compare willing versus unwilling subjects for both cohorts, according to the variables described above. Logistic regression models were also developed for each cohort, whereby variables that attained a significance level of 5% in univariate models were offered separately into multivariate models. In multivariate models, all possible two-way interactions were examined.

RESULTS

By the end of the 1997 a total of 1,156 IDU had been enrolled in the VIDUS study. Of these, 435 participants tested HIV-negative and completed a follow-up questionnaire in 1997. In comparison to those HIV-negative participants who did not complete a follow-up questionnaire, responders were significantly more likely to be older and White. There were no significant differences between responders and nonresponders in terms of gender and education. Similarly, by the end of 1997 a total of 636 MSM had been enrolled in the Vanguard study. Of these, 330 participants tested HIV-negative and completed a follow-up questionnaire in 1997. In comparison to those HIV-negative participants who did not complete a follow-up questionnaire, responders were significantly more likely to be older, White, have a higher income, and have a high school diploma. Sociodemographic characteristics for the study samples (Tables I and II) did not differ from previously published reports (Strathdee *et al.,* 1997, 1998a). Among the IDU cohort, the majority of subjects were male (66%). Compared to the IDU cohort, subjects in the MSM study were younger and were more likely to be White. Both studies were ethnically diverse, with 5% of the MSM cohort being Native and 8% of the IDU being Native (i.e., Aboriginal, First Nations,

Inuit, or Metis). As expected, compared to the MSM cohort, a larger proportion of IDU had less than a high school education, or had unstable housing.

Among the IDU cohort, a high proportion of respondents (83%) reported that they would be willing to participate in a future vaccine trial. Willing subjects were marginally more likely to have first injected drugs at a younger age (median: 18 vs. 19 years; $p = .07$), but did not differ from unwilling subjects with respect to sociodemographic characteristics (Table I). Interestingly, frequent NEP attenders were significantly more willing to participate compared to infrequent attenders ($p = .004$). IDU with a high-perceived threat of HIV infection were also more willing to participate.

Among the MSM cohort, 34% of respondents said they would ''definitely'' participate in a future HIV vaccine trial, and 29% said they would ''probably'' participate. One fourth (25%) said they were unsure, 10% said probably not, and 2% said they would not participate. As in the IDU cohort, willing and unwilling subjects did not differ with respect to

Table I. Factors Associated with Willingness to Participate in an HIV Vaccine Trial Among 435 HIV-Negative Injection Drug Users

Variable	Not willing ($n = 74$) n (%)	Willing ($n = 361$) n (%)	Total ($n = 435$) n (%)	χ^2 p value
Sociodemographics				
Median age (years)	39	38.5	39	0.79††
(IQR)	(31–42)	(31.5–43)	(31–43)	
Gender				
Male	55 (75)	236 (66)	291 (67)	0.10
Female	18 (25)	124 (34)	142 (33)	
Ethnicity				
White	50 (68)	234 (65)	284 (65)	0.19
Native[b]	15 (20)	101 (28)	116 (27)	
Other	9 (12)	26 (7)	35	
Education ≥ high school	24 (32)	94 (26)	118 (27)	0.27
Unstable housing[c]	59 (80)	295 (82)	354 (81)	0.69
Risk behaviors[d]				
Median age first injected (years)	19	18	18	0.07††
(IQR)	(16–28)	(15–25)	(15–25)	
Median number of years of injection career	15	17	17	0.35††
(IQR)	(5–26)	(7.5–26)	(7–26)	
Borrowed needles	20 (27)	101 (28)	121 (28)	0.85
Injected cocaine most frequently	38 (51)	208 (58)	246 (57)	0.32
Sex trade involvement	8 (11)	65 (18)	73 (17)	0.13
Incarceration	22 (30)	130 (36)	152 (35)	0.27
Homosexual/bisexual activity	2 (3)	23 (6)	25 (6)	0.28#
Regular sex partner	29 (39)	152 (42)	181 (42)	0.64
Previous STD	41 (55)	175 (48)	216 (50)	0.28
Borrowed needles from HIV+ person	2 (3)	18 (5)	20 (5)	0.50#
Sex with an HIV+ partner	6 (8)	15 (4)	21 (5)	0.15#
Harm reduction measures				
Attended NEP (ever/never)	63 (85)	332 (92)	395 (91)	0.06
Attended NEP >1/week	30 (41)	213 (59)	243 (56)	0.004
Consistent bleach use	7 (44)	38 (50)	45 (49)	0.65
Drug/alcohol treatment	35 (48)	137 (39)	172 (40)	0.15
Discussed HIV with others	50 (68)	225 (63)	275 (63)	0.35
Psychosocial variables				
High perceived HIV threat	9 (13)	83 (23)	92 (21)	0.04
Median CES-D score (IQR)	25 (20–29)	25 (19–29)	25 (19–29)	0.62††
Suicide ideation	21 (28)	95 (26)	126 (27)	0.74

[a]IQR, Interquartile range.
[b]Aboriginal, First Nations, Inuit, or Metis.
[c]Living primarily in a hotel, boarding room, hostel, transition house, or on the street.
[d]Unless otherwise stated, behaviors refer to time since last interview (median: 7 months).
#Based on Fisher's exact test; ††Wilcoxon rank-sum test.

Table II. Factors Associated with Willingness to Participate in an HIV Vaccine Trial Among 330 HIV-Negative Young Gay/Bisexual Men

Variable[a]	No (n = 121) n (%)	Yes (n = 209) n (%)	Total (n = 330) n (%)	χ^2 p value
Sociodemographics				
Median age (years)	27.5	27	27	0.89[††]
(IQR)	(25–50)	(24.5–30)	(25–30)	
Ethnicity				
White	92 (76)	164 (78)	256 (78)	0.85
Native[b]	6 (5)	10 (5)	16 (5)	
Asian/South Asian	14 (12)	18 (9)	32 (10)	
Other	9 (7)	17 (8)	26 (8)	
Education ≥ high school	53 (45)	88 (43)	141 (43)	0.75
Unstable housing[c]	3 (3)	5 (3)	8 (3)	0.97
Employed	112 (97)	193 (95)	305 (92)	0.43
Risk behaviors[d]				
Median age at first sex with another male	19	18	18	0.06[††]
(IQR)	(16–21)	(15–20)	(16–21)	
Unprotected anal sex with casual male partner	21 (17)	50 (24)	71 (22)	0.16
Regular male sex partner	89 (74)	167 (81)	256 (78)	0.09
Anal sex with HIV+ partner	15 (13)	42 (21)	57 (18)	0.08
Previous STD (ever)	48 (40)	71 (34)	119 (36)	0.30
Sex trade involvement	5 (4)	15 (7)	20 (6)	0.27
Poppers use	27 (22)	62 (30)	89 (27)	0.15
Cocaine use	26 (22)	53 (25)	79 (24)	0.44
Ecstasy use	25 (21)	51 (25)	76 (23)	0.43
Psychosocial variables				
Median CES-D depression score	12	13	12	<0.001[††]
(IQR)	(9–14)	(10.5–15)	(10–15)	
High perceived HIV threat	5 (4)	23 (11)	28 (8)	0.03
Median IES social support score	46	49	48	0.04[††]
(IQR)	(40–53)	(42–60)	(41–58)	
Discussed HIV with anyone	109 (92)	192 (94)	301 (91)	0.49
Suicide ideation	59 (52)	103 (54)	162 (49)	0.75
Know >5 HIV-positive people	41 (34)	87 (42)	128 (39)	0.15

[a]IQR, Interquartile range.
[b]Aboriginal, First Nations, Inuit, or Metis.
[c]Living primarily in a hotel, boarding room, hostel, transition house, or on the street.
[d]Unless otherwise stated, behaviors refer to time since last interview (median: 13 months).
[††]Wilcoxon rank-sum test.

sociodemographic variables (Table II). However, willing subjects were marginally more likely to have a regular male sexual partner (p = .09), and tended to have first had sex with another male at a younger age (median: 18 vs. 19 years; p = .06). Willing subjects were marginally more likely to report having had anal sex with a man they knew at the time was HIV-infected (p = .08), and had a higher perceived threat of HIV infection (p = .03). Notably, willing subjects had significantly higher depression scores ($p < .001$) and lower social support (p = .04).

In multivariate logistic regression models, frequent NEP attendance was the strongest predictor of willingness to participate among IDU (Table III), with frequent attenders being more than twice as likely to participate. After adjusting for this variable, high perceived HIV threat was only marginally significant. However, among MSM, those demonstrating a high perceived HIV threat were nearly three times more willing to participate (Table IV). Further,

Table III. Multivariate Logistic Regression Model: Independent Predictors of Willingness to Participate in an HIV Vaccine Trial Among 435 HIV-Seronegative IDU

Variable	AdjOR	95% CI
Frequent NEP attendance[a]	2.16	1.28–3.64
High perceived HIV threat	1.91	0.90–4.03

Note: AdjOR, Adjusted odds ratio; CI, confidence interval.
[a]Attendance at needle exchange programs more than once per week.

Table IV. Multivariate Logistic Regression Model: Independent Predictors of Willingness to Participate in an HIV Vaccine Trial Among 330 HIV-Seronegative MSM

Variable	AdjOR	95% CI
High perceived HIV threat	2.92	1.10–7.97
High depression score[a]	1.74	1.09–2.80

Note: AdjOR, Adjusted odds ratio; CI, confidence interval.
[a]CES-D score above the median value.

MSM with higher CES-D depression scores were nearly twice as willing to participate. In multivariate models, odd ratios were essentially unchanged after adjusting for other sociodemographic and behavioral factors. No significant interactions were observed.

DISCUSSION

Characterizing the proportion of high-risk populations that are willing to participate in HIV vaccine trials is important for assessing the feasibility of large-scale efficacy trials (Koblin *et al.,* 1998; Rida *et al.,* 1997). If factors associated with willingness to participate in a vaccine efficacy trial are not taken into account, a number of problems could arise. For example, if HIV incidence is high among the target population, but subjects at high risk of seroconversion are less willing to participate, the ability to detect a significant decrease in HIV incidence will be seriously compromised.

It is therefore encouraging that in our study of HIV-seronegative IDU and young MSM, the majority of subjects were willing to participate. There was no evidence to suggest that persons engaging in high-risk behaviors were more likely to refuse. Other studies have suggested that high-risk individuals tend to be more willing to participate in HIV vaccine studies (Bartholow *et al.,* 1997; Gross *et al.,* 1996; Koblin *et al.,* 1998; Vlahov *et al.,* 1994). Although our study found no association between level of risk and willingness, there is no reason to believe that high-risk individuals in Vanguard or VIDUS are less likely to be willing to participate in a vaccine trial.

Beyond self-reported risk behaviors, we found that a high perceived threat of HIV infection was a strong independent predictor of willingness to participate among MSM, and to a lesser extent among IDU. Perceived susceptibility to HIV infection was associated with willingness to participate in HIV vaccine trials among college students (Liau *et al.,* 1998), but findings among MSM have been inconsistent (Bartholow *et al.,* 1997; Gross *et al.,* 1996; Koblin *et al.,* 1997).

Fewer studies have assessed perceived risk of HIV infection among IDU and its relationship to interest in HIV vaccine trials. Some have found IDU to have a complex belief system (Des Jarlais *et al.,* 1997, Meyers *et al.,* 1994), and to have considerable mistrust in the government and other authorities (Meyers *et al.,* 1994). In a recent study, IDU cited invulnerability to HIV infection as a reason for continued high-risk behavior (Des Jarlais *et al.,* 1997). While our findings suggest that educational programs that increase awareness of HIV susceptibility may increase interest in HIV vaccine trials, appropriate counseling and education should be offered throughout to ensure that participation does not reinforce unwarranted assumptions regarding natural or induced immunity.

Of interest, we observed that young MSM who had higher depression scores and lower social support were significantly more willing to participate in HIV vaccine trials. High depression scores were predictive of willingness to participate independent of high perceived HIV threat. Although it is possible that depressive symptoms were a marker of risk-taking behavior, this is unlikely to account for our findings. Few of the risk behaviors we examined were significantly associated with increased willingness, and none of these variables altered the adjusted odds ratios. One explanation for our findings could be that emotional need or a sense of belonging is a major motivating factor affecting willingness to participate for some young MSM. Motivations for participation in an HIV vaccine trial may differ for younger versus older MSM (Gross *et al.,* 1996). Among older MSM, reasons associated with willingness to participate have included a sense of optimism about HIV vaccine development (Gross *et al.,* 1996) or altruism (Koblin *et al.,* 1997), but these findings have not been confirmed among younger MSM (Gross *et al.,* 1996).

Regardless of the explanation, these findings underscore the need for appropriate counseling in HIV vaccine trials, and raise some ethical concerns. The vulnerability of persons experiencing depression or low social support is of particular concern, given that some HIV vaccine trial participants have increased their level of unprotected sex, despite being counseled that the vaccine may not protect from infection (Chesney *et al.,* 1997). Since low social support is independently associated with sexual risk-taking among MSM (Catania *et al.,* 1991; Strathdee *et al.,* 1998a), additional measures may be needed to safe-

guard against increased risk-taking in HIV vaccine trials if this group is overrepresented. Counseling of couples might be one way to influence attitudes and sexual behaviors among vaccine trial participants (Celentano *et al.,* 1995). At present, psychological status and other medical issues are a central part of the eligibility criteria for vaccine trials. The present study highlights the importance of this process and future studies should attempt to evaluate what threshold of distress should trigger exclusion.

Among IDU, we observed frequent NEP attendance to be the strongest predictor of willingness to participate in an HIV vaccine trial. This finding has not been previously reported, and suggests that IDU who regularly attend NEP may be more concerned about their health than other IDU. Interaction with NEP staff may also foster trust or confidence in other public health activities. Since previous studies have found that both high-risk behavior and HIV incidence have remained high among frequent NEP users in British Columbia (Strathdee *et al.,* 1997), NEPs may be an ideal venue for offering other HIV interventions (Strathdee *et al.,* 1998c), including vaccines.

There exists some debate about the eligibility and feasibility of including IDU in vaccine trials. For reasons such as poor follow-up, it has been suggested that IDU should be excluded from preventative vaccine trials. Like others, however, (Harrison *et al.,* 1995; Meyers *et al.,* 1994; Vlahov *et al.,* 1994), we observed a very high level of interest in HIV vaccine trials among IDU, among whom HIV incidence and follow-up rates are high (Schechter *et al.,* 1999, Strathdee *et al.,* 1997; Vlahov *et al.,* 1994). These findings suggest that there is no reason to exclude IDU from HIV vaccine trials.

In our study, the proportion of IDU who were willing to participate was somewhat higher than in other studies (Koblin *et al.,* 1998; Meyers *et al.,* 1994), whereas the proportion of willing MSM was somewhat lower (Buchbinder *et al.,* 1996; Gross *et al.,* 1996). These differences could be due to study design, selection factors, or the fact that the survey of young MSM was self-administered while the survey of IDU was interviewer-administered. Therefore caution should be exercised when making comparisons between studies. For example, in our studies, IDU were remunerated, but MSM were not. Monetary incentives have been shown to increase acceptability of HIV vaccine studies in both populations (Koblin *et al.,* 1998; Vlahov *et al.,* 1994). Since willingness to participate in HIV vaccine trials can dampen over time (Bartholow *et al.,* 1997), we may have underestimated participants' interest. Subjects included in the present analysis had been enrolled for at least 1 year, but their demographic characteristics did not differ from earlier published reports (Strathdee *et al.,* 1997, 1998a). In addition, it is important to note that participants were given little information beyond the definition of a vaccine. It is arguable that providing additional information, such as potential side effects, could have had a dampening effect on the willingness of potential participants. It is therefore also possible that our methods have overestimated participants' willingness to participate.

Our analysis identified a number of factors that are relevant in the design of Phase III efficacy trials of HIV vaccines. While the depression scale used in our study was not a diagnostic measure of clinical depression, we found that a higher depression score independently predicted willingness to participate among young MSM. This indicates that HIV vaccine trials need to take into account measures that safeguard both the psychological and physical health of potential participants. Among IDU, we found that frequent NEP attenders were more than twice as willing to participate. Since NEP often attract IDU at high risk of HIV infection (Strathdee *et al.,* 1998c), recruitment of IDU through NEP may maximize feasibility of HIV vaccine trials.

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