HIV Vaccine Trials: Will Intravenous Drug Users Enroll?

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A B S T R A C T

Objectives. The purpose of this study was to assess the willingness of intravenous drug users to participate in a preventive human immunodeficiency virus (HIV) vaccine efficacy trial.

Methods. Of the 347 intravenous drug users in methadone treatment who were approached for participation, 257 completed a battery of self-administered questionnaires assessing risk behaviors, interest in vaccine trials, and other vaccine-related information. Data from 16 known seropositives and 1 inconsistent responder were dropped from analyses (n = 240).

Results. Fifty-two percent of the subjects expressed a willingness to be one of the first individuals to participate in a preventive HIV vaccine efficacy trial. Subjects who had recently shared needles or works and subjects who trusted the government to ensure vaccine safety were both twice as likely to report interest in participation. Twenty-two percent of subjects reported that they would increase needle sharing if vaccinated. Thirty percent did not know what a vaccine was.

Conclusions. These findings suggest that some in-treatment intravenous drug users would volunteer for a preventive HIV vaccine efficacy trial. Education and counseling will be required to ensure that subjects fully understand the trial's purposes, methods, risks and benefits. (*Am J Public Health.* 1994;84:761–766)

Introduction

Despite impressive risk reduction resulting from behavioral and educational interventions launched to halt the spread of human immunodeficiency virus (HIV) infection, sizable portions of both the homosexual/bisexual and intravenous drug using populations continue to engage in, or have relapsed into, behaviors that place them at risk of acquiring the virus.[1–4] Of parallel concern is the apparent absence of meaningful risk change among the large number of individuals who do not view themselves at particular risk (e.g., adolescents, adult heterosexuals).[5–7] In fact, the acquired immunodeficiency syndrome (AIDS) has emerged as a leading cause of death among US adults less than 45 years of age and US children 1 to 5 years old.[8] Thus, there is an urgent need for the development and testing of preventive HIV vaccines.

Currently, a number of experimental HIV vaccines have entered phase I and II clinical trials.[9–11] As this work progresses and preparation for phase III trials begins, epidemiological, ethical, and public health considerations are being cooperatively addressed by national and international groups.[12–16] At the same time, a critical practical question is the willingness of at-risk individuals to participate in the upcoming vaccine trials. To date, little work has been undertaken to delineate the issues associated with recruitment and retention of subjects for HIV vaccine trials.

An initial step in testing the efficacy of candidate HIV vaccines is gaining access to populations at risk of HIV infection. Under a cooperative initiative among the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute on Drug Abuse (NIDA), and the Centers for Disease Control, homosexual/bisexual men, intravenous drug users, and other at-risk individuals are being targeted for participation in these efficacy trials.[12] The active participation of gay men in helping to formulate the HIV research and treatment agenda suggests that this community recognizes the importance of vaccine trials, although their willingness to be participants awaits empirical examination. There is less certainty regarding the willingness of intravenous drug users to participate in vaccine trials, since they are not well organized and tend to be a disenfranchised group.[17] Consequently, it is important to develop some indication of intravenous drug users' willingness to volunteer for such a study. Most important is determination of whether seronegative subjects who are at the greatest risk of infection will be willing to participate. These assessments will have direct bearing on the estimate of sample sizes needed for vaccine trials. For example, if those at greatest risk for seroconversion are unwilling to enroll, sample sizes for vaccine trials will need to be much larger than if such individuals are willing to participate.

With support from the NIAID/NIDA vaccine preparedness initiative, we had the unique opportunity to rapidly collect preliminary data on the willingness of intravenous drug users to participate in efficacy trials for HIV preventive vaccines.

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As part of recruitment procedures for a new cohort of subjects participating in a longitudinal study of risk behaviors and HIV infection among intravenous drug users in Philadelphia,[18] methadone patients were questioned about their willingness to participate in early vaccine trials. Subjects were also briefly questioned regarding their knowledge of vaccines, trust in government, and other issues considered important in gaining a preliminary understanding of the factors associated with trial participation. Methadone patients not only represent the target population of intravenous drug users in treatment but provide access to their out-of-treatment intravenous drug using associates, a group at particularly high risk. Therefore, they constitute a readily available sample from which we can gain some early insight regarding intravenous drug users' willingness to enroll in HIV vaccine trials and an important link to the out-of-treatment community.

This paper presents self-report data from a brief opinion questionnaire about these issues among 240 intravenous drug users. It explores the feasibility of recruiting such individuals for clinical vaccine trials, examines whether seronegative subjects at greatest risk of HIV infection report willingness to participate in HIV vaccine trials, and discusses issues related to their ability to provide informed consent for such trials.

Methods

Procedures

The study sample was composed of methadone maintenance patients from the Girard Methadone Program located in north-central Philadelphia. All eligible methadone patients were approached for screening as part of recruitment procedures for a longitudinal study of HIV infection and associated risk behaviors.[18] Of those screened (n = 347), 257 (74%) agreed to complete our initial assessment.

After providing informed consent, subjects completed a battery of self-administered risk assessment questionnaires in closely supervised groups of 5 to 10. Included in the battery was a one-page vaccine opinion questionnaire developed specifically for this project. Throughout questionnaire completion, research staff members were present to answer questions, assist those with reading difficulty, and screen completed questionnaires for missing data or inconsistent responses. Subjects were paid $5 for their participation.

Subjects

Of the 257 subjects who completed questionnaires, 16 reported being HIV positive and 1 provided inconsistent responses. The data from these 17 subjects were deleted from further analyses, resulting in a final sample of 240 subjects. Subjects ranged in age from 20 to 64 years, with a mean of 39.1 years (SD = 7.0). The sample was ethnically diverse (44% African American, 39% Caucasian, and 17% Latino). Seventy percent of the sample was male. The median monthly income was $246, with most subjects (80%) receiving public assistance as their primary source of income. Fifty-nine percent had a high school diploma or general equivalency diploma. The median length of time in the current methadone program was 1.5 years.

Measures

The Vaccine Opinion Questionnaire was developed for this project on the basis of input from both intravenous drug users and research staff. While the assessment battery was being developed, we asked subjects in our original cohort to comment on vaccine research and what issues might be important for participation from the perspective of potential participants. We also asked our research staff to suggest issues that should be examined. These staff members have extensive contact with intravenous drug users, and they were encouraged to report issues and concerns that existed among the intravenous drug using community in regard to vaccines, treatment, and related issues. On the basis of this information, a brief self-report questionnaire was designed to identify some of the potentially important factors associated with trial participation. The resultant questionnaire was composed of 13 statements with which the subject could either agree or disagree and 3 multiple-choice questions. The questions, which were grouped post hoc, covered HIV-related issues, vaccine histories of both the respondent and his or her children, trust in government, vaccination knowledge, potential behavioral change after participation, and willingness to participate.

Formal reliability and validity testing was not conducted because our opportunity to examine this cohort was time limited. Therefore, we took care to maximize the face validity of the items constituting the questionnaire. For example, we used simple language that would be understood by this population. We also monitored all subjects during and after administration of the questionnaire, answering questions and clarifying inconsistencies. For these reasons, we are confident of the face validity of this instrument. Obviously, the only conclusive method of testing the predictive validity of the instrument would be to correlate answers on the questionnaire with actual participation in a vaccine trial. We will complete this formal study when the opportunity arises.

The Risk Assessment Battery,[19] an instrument composed of 38 closed-ended items that cover frequency and route of administration of various substances, needle sharing and cleaning, and high-risk sexual behavior, including sexual orientation, condom use, and exchange of sex for drugs or money, was used in collecting risk-associated behavioral data. Preliminary validity data show the instrument to have good predictive validity for HIV seroconversion.[19] The Risk Assessment Project Questionnaire yielded demographic and descriptive information about the subjects' current social conditions, drug treatment, history of criminal behavior, and legal history. The entire test battery took approximately 30 minutes for most subjects to complete. A considerable body of literature now exists supporting the validity and reliability of self-report measures within this population.[20,21]

Results

Trust

As can be seen in Table 1, the subjects expressed considerable distrust in the government. Fifty-three percent of the subjects believed that the health department was not doing all that it could to stop the spread of AIDS, and 32% believed that a cure for AIDS was available but being kept from the public. Thirty-six percent endorsed the belief that HIV is a man-made virus created to get rid of "certain groups" of people. Specifically related to trust in vaccine trials, 48% of the subjects did not trust the government to ensure vaccine safety prior to trials. This is particularly troublesome for recruitment, given that safety issues emerged as the most important issue reported by respondents (42%) regarding their participation.

Vaccine Knowledge/Experience

Responses indicated that the subjects were in need of education regarding vaccines. Thirty percent of the sample

were unsure what a vaccine was, and 41% did not know that a vaccine could prevent disease acquisition. This apparent lack of knowledge existed despite high rates of vaccination for other communicable diseases: 84% reported having been vaccinated for measles, mumps, or polio, and 93% of those subjects with children (n = 192) indicated that their children had been vaccinated. A higher proportion of those who admitted not really knowing what a vaccine was than of those who reported such knowledge did not have a high school education or a general equivalency diploma (55% vs 35%; $\chi^2 = 8.3$, $df = 1, P < .005$).

TABLE 1—Subjects' Opinions Regarding Vaccines and Related Issues, by Topic Area (n = 240)

	% Agreeing or Answering Yes
Trust	
The health department is doing all it can to stop the spread of AIDS.	47
There is a cure for AIDS, but the government is keeping it from the public.	32
I trust the government to make sure that vaccines they want to test are safe before they test them on people.	52
HIV is a manmade virus that was created to get rid of certain groups of people.	36
Vaccine knowledge/experience	
A vaccine can protect you from getting a disease.	59
A vaccine does not help someone infected with a disease.	48
Getting vaccinated can be risky.	48
I am not sure what a vaccine is.	30
Have you ever received a vaccine for a disease like measles, mumps, or polio?	84
Were your children vaccinated for things like measles, mumps, or polio?	93
Behavioral impact	
If I was sure I couldn't get AIDS, I'd probably share needles more often.	22
Trial participation willingness	
I would be willing to be one of the first people to try an HIV vaccine.	52
I would be willing to try a vaccine for HIV even if there was a slim chance of getting sick from it.	39
What would be most important for you to try a vaccine for HIV if one were available?	
The vaccine was safe.	42
I would be guaranteed medical care for any problems related to the vaccine.	20
I would have the opportunity to be protected from getting HIV.	35
I would receive money for trying the vaccine.	3

Behavioral Impact

Regarding the potential impact of vaccine trial participation on high-risk behaviors, 22% of the subjects thought that they might share needles more often if they were guaranteed protection from HIV infection. This reported potential for increased risk behaviors was more common among current needle sharers (40%) than among those not sharing (17%) ($\chi^2 = 14.7$, $df = 1$, $P < .001$), but it was not more common among those who reported willingness to participate in the trials. Whether these subjects would attempt to determine their vaccination status was not examined.

Participation Willingness

Despite substantial mistrust and lack of knowledge, a slight majority (52%) of the subjects expressed a willingness to be "one of the first" individuals to participate in an HIV vaccine trial, and 39% reported that they would be trial participants even if there was a slim chance of getting sick as a result of vaccination. When subjects were questioned about the factors that would be most likely to influence their decision to enroll, safety issues emerged as most important, followed by the opportunity to be protected from HIV infection, guaranteed medical care for any vaccine-related problems, and monetary reimbursement for trial participation.

Associated Willingness Factors

To explore factors associated with willingness to participate, subjects were categorized according to their answers on that question. As can be seen in Table 2, those willing to be part of a vaccine trial were demographically similar to those who were unwilling to be part of a trial. However, willing subjects had spent significantly less time in the current methadone program ($t = 1.98, df = 236, P < .05$) and were more likely to report current health problems ($\chi^2 = 5.1, df = 1, P < .05$) than unwilling subjects. Not surprisingly, those willing to be vaccine trial participants were proportionately more likely to believe that the government would ensure vaccine safety prior to testing ($\chi^2 = 5.8$, $df = 1$, $P < .05$), although the groups were proportionately similar on other trust issues. Surprisingly, basic knowledge of vaccines, particularly being unsure of what a vaccine was and knowing that vaccines can be protective, was unrelated to participation willingness.

As stated, an important focus of this study was an exploration of whether subjects engaging in risk behaviors were willing to enroll in vaccine trials. To this end, subjects were grouped according to their risk status on HIV-associated drug behaviors (e.g., shared needles/did not share needles in the prior 6 months) and HIV-associated sexual behaviors (e.g., no or irregular condom use with two or more sexual partners in the prior 6 months). The chi-square statistic was used in conducting a univariate analysis of the proportion of willing participants within these groups.

Significantly more of those who perceived themselves as being at risk of HIV exposure than of those who did not perceive themselves as at risk reported willingness to be one of the first to try a vaccine (59% vs 41%; $\chi^2 = 7.3$, $df = 1$, $P < .01$). Similarly, willingness to try a vaccine was significantly higher among those who recently shared needles than among those who did not share needles (66% vs 48%; $\chi^2 = 6.2$, $df = 1$, $P < .01$). Willingness was also more common among those who engaged in other risky drug using behaviors such as sharing a cooker, cotton, or rinse water in the previous 6 months (62% among those who shared vs

TABLE 2—Factors Associated with Willingness to Participate in HIV Vaccine Trial

	Willing Subjects (n = 125)	Unwilling Subjects (n = 113)
Demographics		
Male, %	66	74
Race, %		
African American	41	48
Caucasian	41	38
Latino	18	12
Mean age, y (SD)	39.5 (6.9)	38.9 (7.2)
High school diploma or GED[a]	60	58
Employed, %	20	14
Treatment-related issues		
Mean no. of months in methadone treatment (SD)	24.3 (33.5)	33.2 (35.3)
Health problems reported,* %	48	34
Trust in government, %		
Believe government tests only those vaccines that are safe*	60	44
Believe health department is doing all it can to stop the spread of AIDS	46	47
Believe there is a cure for AIDS but the government is keeping it from the public	33	33
Knowledge and experience, %		
Believe vaccines are protective	61	58
Not sure what a vaccine is	27	34
Personal vaccination history	89	80

[a]General equivalency diploma.
*$P \leq .05$.

TABLE 3—Logistic Regression Model of Predictors of Willingness to Participate in HIV Vaccine Trials

	Willing Subjects	Odds Ratio	95% Confidence Interval
Demographic variables			
Male (n = 165), %	50	1.5	0.80, 2.8
Minority (n = 144), %	51	1.0	0.56, 1.9
Mean age, y	39.5	1.0	0.98, 1.1
Risk behaviors, %			
Share needles/works (n = 110)	61	2.1	1.2, 3.7*
Have unprotected sex with multiple partners (n = 45)	58	1.2	0.58, 2.5
Trust, %			
Trust government to ensure vaccine safety (n = 121)	60	2.0	1.1, 3.7*
Believe government is doing everything possible to stop the spread of AIDS (n = 110)	52	0.9	0.49, 1.6
Believe HIV is not man-made (n = 151)	53	0.9	0.46, 1.7
Believe government is not keeping cure from the public (n = 158)	53	0.8	0.44, 1.6
Vaccine knowledge, %			
Sure what a vaccine is (n = 166)	55	1.6	0.84, 3.0
Believe vaccines are protective (n = 139)	53	1.0	0.54, 1.7
Believe vaccines are therapeutic (n = 120)	49	0.7	0.39, 1.2

*$P < .05$.

45% among those who did not share; $\chi^2 = 6.5, df = 1, P < .01$).

Willingness was unrelated to our measures of risky sexual behaviors: 58% vs 51% for those engaging in and those not engaging in unprotected intercourse with multiple (two or more in past 6 months) sexual partners ($\chi^2 = 0.6$, not significant* [NS]) and 63% vs 51% for those engaging in and those not engaging in sex for drugs or money in the prior 6 months ($\chi^2 = 1.9, df = 1$, NS).

Logistic regression was used to simultaneously adjust for age, sex, and race as well as the potential predictors of willingness to participate in vaccine efficacy trials: engagement in high-risk behaviors, trust in government, and vaccine knowledge. As can be seen in Table 3, subjects who shared needles or works were twice as likely to report willingness to participate in trials, as were those who reported that they trusted the government to ensure vaccine safety prior to trials. Demographic variables, sexual HIV-risk-associated behaviors, trust issues other than safety, and knowledge of vaccines were not significantly associated with reported willingness to participate in vaccine trials.

Discussion

These data from our initial questionnaire suggest that some in-treatment intravenous drug users would volunteer for HIV vaccine trials. Importantly, those in-treatment users who continued to place themselves at risk for HIV infection were significantly more likely to report that they would be one of the first to try a vaccine than those who engaged in safer behaviors. If these findings are confirmed and high-risk intravenous drug users are truly willing to enroll, the number of subjects necessary for efficacy vaccine trials could be minimized.

However, just under half of the intravenous drug users questioned expressed an unwillingness to enroll in vaccine trials. It was clear that a substantial lack of knowledge about vaccines and distrust in the government were evident among this group, and these factors will have to be addressed if participation rates are to be maximized. The data reported here suggest that mistrust of the government regarding vaccine safety is a key mediating variable in the recruitment of intravenous drug users for HIV vaccine efficacy trials. Efforts to combat this lack of trust and provide safety data should guide subject recruitment and trial imple-

mentation from the outset. In addition to doing everything possible to ensure vaccine safety, it may be helpful to select field workers who are part of the intravenous drug using community, rather than governmental officials, to recruit and engage at-risk users.

While this paper has reported on the responses of in-treatment intravenous drug users, it will also be important for HIV vaccine trials to recruit and retain out-of-treatment users. In our ongoing study of HIV infection, we have successfully used our in-treatment cohort to refer us to out-of-treatment subjects. Our findings indicate that out-of-treatment intravenous drug users engage in substantially higher levels of risk behaviors and have higher seroconversion rates than their in-treatment counterparts.[18] Both of these are important considerations for vaccine trial participation.

This study showed no significant difference in willingness to participate among the racial groups. However, since a high proportion of intravenous drug users are African Americans and Latinos, sensitivity and responsiveness to minority issues will be critical in vaccine trials. As noted by El-Sadr and Capps,[22] minority recruits may be an especially distrustful group, considering the past patterns of insensitivity during clinical trials exemplified by the legacy of the Tuskegee Syphilis Study.

One of the most important issues that will need to be addressed prior to vaccine trials is that of *informed* consent. Although knowledge of vaccines as measured here was unrelated to participation willingness, the reported lack of general knowledge regarding vaccines is alarming. Approximately one third of our subjects admitted to not really knowing what a vaccine was, and more than half did not know that there are preventive and therapeutic vaccines. Of course, it may be that this is representative of the knowledge base of nonusers from the same socioeconomic strata. Despite this apparent lack of basic knowledge, many subjects agreed to consent to trial participation without adequate comprehension of the issues. This scenario will obviously test our ability to ensure that subjects know what vaccines are and fully understand the trial (e.g., placebo-controlled issues) and its uncertainties (e.g., potential risks, efficacy uncertainties) so that they can make truly informed and knowledgeable decisions regarding enrollment. This becomes an even more important issue given the educational level of this group of subjects. Clear and concise information regarding the type of vaccine (e.g., subunit vs live vectors) to be tested in each trial, the research method (e.g., placebo-controlled study), and the consequences of participation (e.g., vaccine-induced seroconversion) will need to be provided in a way that ensures comprehension. The ability to engage subjects in an open, honest dialogue in order to dispel myths, allay fears, and candidly address the type and amount of risk the trial entails will undoubtedly influence enrollment. Included should be a frank discussion of compensation issues, in the event that subjects sustain harm, as well as the potential for discrimination after an immune response resulting from vaccination. In addition, it may be necessary to include a brief factual quiz regarding vaccine participation with a "cutoff score" as part of subject consent procedures. This may be the only definitive method of ensuring truly informed consent in future trials.

As subjects learn more of the specifics of these proposed vaccine trials, willingness will undoubtedly change, although the direction of the change is unknown. In an effort to better understand potential participation issues, we are currently using both interviews and self-report measures to assess reported willingness to participate under conditions that will approximate actual trials (e.g., randomized, placebo-controlled trials). Information delivery methods (e.g., videotapes) and the individuals who disseminate such information (e.g., other intravenous drug users, health officials) will probably vary in efficacy; this area requires study.

An important ethical consideration for recruitment is remuneration for participation. High monetary rewards offered to economically disadvantaged groups can be considered enticing to the point of coercion. Thus, it is particularly important to identify the nonmonetary issues that are most strongly associated with willingness to participate. This will help to identify factors that can attract potential participants based only on scientific and humanitarian issues. Although financial incentives are important for study compliance, they must not become the sole reason for enrollment.

Although few subjects reported the possibility of an increase in risk behaviors, the impact of vaccine trial participation on a subject's practice of risk behaviors requires further attention. Relapse into unsafe behaviors as a result of a "sense of safety" through vaccine trial participation would be problematic not only if the initial vaccines are less than 100% effective, but also in light of other consequences (e.g., hepatitis, sexually transmitted diseases). The ability of intravenous drug users to determine whether or not they received a placebo or vaccine, as well as their interest in doing so, is currently unknown and under investigation. Further exploration of other key vaccine trial issues (e.g., subjects' knowledge of placebo issues, vaccine-induced seroconversion) is an ongoing aim of our current work.

While the data reported here provide some preliminary insight into the willingness of intravenous drug users to participate in HIV vaccine efficacy trials, the only true measure of the validity of these responses will be whether those who say they will participate actually enroll in efficacy trials. We are currently in the process of assessing the degree of stability of a subject's stated participation willingness over the course of the preparedness work. If changes in willingness occur over time, we will ascertain whether any factors correspond to this fluctuation. For example, changes in willingness may be related to changes in risk behaviors. Subjects may be more likely to consider participation in vaccine efficacy trials during periods of high-risk behaviors and less likely to consider participation during safer periods. Whether this phenomenon exists at all and whether it is consistent across categories of risk behaviors will be the subject of future reports.

From these preliminary data, it is clear that the recruitment of intravenous drug users into HIV vaccine efficacy trials will require a sustained cooperative effort on the part of the vaccine and drug research and treatment communities. Together, these communities must determine appropriate incentives and develop and disseminate appropriate educational materials that can provide accurate descriptions of the study and understandable information on potential trial risks. The way in which these issues are addressed will undoubtedly form the cornerstone of recruitment efforts. As vaccine efficacy trials approach, we must quickly address the above issues and our understanding of the factors associated with enrollment if we are to recruit and engage the intravenous drug–using community. □

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