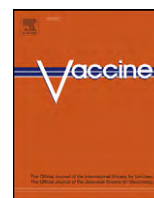




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Are young injection drug users ready and willing to participate in preventive HCV vaccine trials?

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ABSTRACT

Trials to evaluate the efficacy of preventive HCV vaccines will need participation from high risk HCV seronegative injection drug users (IDUs). To guide trial planning, we assessed willingness of young IDU in San Francisco to participate in HCV vaccine efficacy trials and evaluate knowledge of vaccine trial concepts: placebo, randomization and blinding. During 2006 and 2007, a total of 67 participants completed the survey. A substantial proportion (88%) would definitely (44%) or probably (44%) be willing to participate in a randomized trial, but knowledge of vaccine trial concepts was low. Reported willingness to participate in an HCV vaccine trial decreased with increasing trial duration, with 67% of participants surveyed willing to participate in a trial of 1 year duration compared to 43% of participants willing to participate in a trial of 4 years duration. Willingness to enroll in HCV vaccine trials was higher in young IDU than reported by most at-risk populations in HIV vaccine trials. Educational strategies will be needed to ensure understanding of key concepts prior to implementing HCV vaccine trials.

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1. Introduction

Hepatitis C viral infection (HCV) infects an estimated 130 million persons globally, the majority of whom develop chronic infection (HCV RNA positive in 80–100% of cases) and chronic hepatitis (elevated serum ALT in 60–80% of cases) [1]. HCV is responsible for one quarter of worldwide cirrhosis and hepatocellular carcinoma cases, respectively and remains the main indication for liver transplantation in the U.S. [2].

Injection drug use (IDU) is the risk behavior leading to infection in 90% of global HCV infections [3]. HCV infection is epidemic among IDUs, with annual incidence rates highest among young IDUs ranging from 9% to 38% [4–7]. The CDC estimated the number of acute HCV infections in the US has decreased from approximately 230,000 per year in the 1980s to the current level of about 19,000 per year [8]. This decrease is primarily due to screening of the blood supply followed by a reduction in IDU infection due to needle exchange and safer injection practices [9]. Despite these successes, prevalence remains high among IDU in the US. Among

young (<30 years) IDUs in San Francisco, we found 50% prevalence of HCV after 5 years of injecting [10]. In a large sample of young IDUs ($n = 520$), we recently reported a cumulative HCV incidence of 26.7/100 person-years of observation and an estimated reinfection rate of 24.6/100 person-years of observation [11]. Access to HCV treatment is limited for IDUs [12] and as with non-injecting populations, current treatment success is suboptimal. Further decreases in HCV incidence are unlikely to be achieved without large-scale and effective biomedical interventions, notably preventive vaccines [13].

HCV, an RNA virus, has enormous genetic variability, which has challenged vaccine development. The site of greatest variability is within the E2 envelope glycoprotein, a major antibody target [14]. Several candidate vaccines designed to prevent initial HCV infection in uninfected people, reduce viral persistence in infected individuals, or sustain virological response in individuals with chronic infection, are currently in preclinical development or early stage clinical trials. Nonetheless, first generation HCV vaccines are expected to be of only low-to-moderate efficacy. Both efficacy and cross clade protection have emerged as significant factors affecting HIV vaccine trial acceptability [15] and are likely to be important determinants of HCV vaccine trial participation. Additionally, trial duration and cohort retention will be important trial design considerations. Young IDUs are a challenging population to track and retain in clinical trials for many reasons, including distrust

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of the medical establishment, homelessness and mobility. Despite these challenges, young IDUs are the population most at risk for HCV acquisition, the key population for immunogenicity studies and prime candidates for inclusion in future prevention vaccine trials assessing preventive efficacy. In this cross sectional study, we assess willingness to participate in preventive HCV vaccine trials and knowledge of trial concepts among young IDU.

2. Materials and methods

2.1. Participants

Beginning in 2000, young (<30 years) IDUs in San Francisco have been offered participation in multiple prospective studies under variations of the shared title of the “UFO Study” described previously [4]. In brief, young IDU were recruited by peer outreach workers familiar with neighborhoods in San Francisco where young IDU congregate, using study invitation cards and flyers, contacts with youth friendly neighborhood groups and community providers, and word of mouth to participate in HCV screening as the baseline visit for eligibility in a prospective study assessing incident HCV infection. Inclusion criteria for screening were: (1) age under 30 years, (2) self reported use of injection drugs in the past 30 days, (3) ability to provide informed consent and (4) understanding spoken English, and (5) after 2005, self-reported HCV negative or unknown status.

The UFO Study had two waves of data collection, the first wave from 2000 to 2002 and a second wave from 2003 to 2008. During the second wave of data collection, a subgroup of young IDU participating in UFO-3 was asked to participate in this sub-study assessment of vaccine trial willingness, and completed a supplemental interviewer-administered survey on willingness to participate in future HCV vaccine trials and knowledge of key prevention vaccine trial concepts presented as true/false statements ($n=67$). These data were collected at one of the quarterly UFO-3 study visits in 2006 and 2007. Participants in the prospective cohort study completed the supplemental survey on vaccine trial knowledge and willingness if they attended a quarterly study visit during 2006 and 2007.

2.2. Study design and measures

Eligible consenting participants were interviewed, counseled, and tested for antibodies to HCV (anti-HCV) and HCV RNA. Each was remunerated \$10 at screening, and \$20 at results visits. Participants who were HCV negative and did not plan to travel in the next 3 months were offered enrollment into the prospective cohort (UFO-3 Study). Follow-up included monthly “check-ins” and quarterly study visits which included structured interviews to assess exposures, HCV status (including anti-HCV and HCV RNA testing), and risk reduction counseling and referrals.

The vaccine trial willingness survey instrument was adapted and constructed from previously published assessments of vaccine trial willingness [16–19]. Participants were asked to rate willingness to participate in an HCV vaccine trial that began that week on a four point scale (definitely, probably, probably not and definitely not willing). The survey evaluated baseline knowledge of prevention vaccine trial concepts including need for baseline HCV seronegativity, randomization, placebo control, blinding, adverse events, experience with vaccines, motivation for participation in, support for, or against an HCV vaccine trial, trusted sources of trial information and expectancies for positive and negative outcomes related to an HCV vaccine trial among young IDU. Questions on willingness and knowledge were asked without reference to a specific vaccine candidate or product. At survey completion, participants

were provided correct answers on knowledge questions through a brief educational session on HCV and vaccine trial design concepts. The protocol and informed consent were approved by the institutional review board (IRB) of the University of California, San Francisco.

2.3. Statistical analyses

Sociodemographic information and drug use behavior at the baseline interview were compared between vaccine survey participants and HCV-negative cohort participants in the second wave of data collection who did not complete the vaccine willingness survey. Participants who did not complete the survey were those who did not have quarterly study visits during the time period of the vaccine willingness sub-study. Differences were assessed using the Chi-square test of association for categorical variables and the Kruskal–Wallis median test for continuous variables. Frequency distributions were tabulated for each questionnaire item and bivariate associations between questionnaire items and age group were analyzed using the Chi-square test of association. In order to examine differences in vaccine trial willingness and knowledge by age, all subjects were classified into two age-stratified subgroups for data analysis: <23 and ≥ 23 years.

3. Results

Overall, demographics and IDU related behaviors for the study population of vaccine trial survey participants ($n=67$) and HCV antibody negative UFO participants who were not offered the supplemental survey ($n=202$) are summarized in Table 1. Vaccine trial survey participants reported injecting drugs for longer (median 5.1 years) compared to other HCV antibody (anti-HCV) negative UFO-3 participants (median 4.1 years) and using more frequent daily injections (median 3 compared to 2), however these differences did not reach statistical significance. Gender and age at baseline interview did not vary significantly between groups. Heroin was the drug most frequently injected by both groups, reported by two thirds of participants. Incarceration in the last 3 months was reported by one quarter of vaccine trial survey participants and one third of HCV-negative cohort participants who did not complete willingness survey.

Table 2 summarizes knowledge of vaccine trial concepts and willingness to enroll in HCV vaccine trial by age among the sixty-seven young IDU surveyed. Approximately, one quarter of survey participants had previously received immunizations (most commonly hepatitis B virus (HBV) and hepatitis A virus (HAV) vaccine) through the UFO Study. IDU ≥ 23 years were more than ten times as likely to have previously received a vaccine as younger IDU ($p \leq 0.01$). Over 90% of survey participants knew that a vaccine served to prevent disease. Aside from an understanding that an HCV clinical trial would enroll only anti-HCV negative persons, vaccine trial knowledge did not vary significantly by age. Injectors ≥ 23 years of age were twice as likely as younger injectors to know that an HCV vaccine trial would be limited to anti-HCV negative participants. Less than half (45%) of all survey participants correctly reported that vaccine assignment would be random in an HCV vaccine clinical trial. Approximately half of all trial participants correctly recognized blinding of trial participants as an important design feature. The majority (67%) of survey participants correctly reported that unblinding of vaccine status would occur at trial conclusion. Over three quarters of IDU surveyed, correctly answered that adverse events related to study vaccine would be treated by study staff.

Overall, 88% (58/66) of participants who completed a supplemental survey indicated that they would definitely or probably

Table 1

Baseline sociodemographic characteristics and risk behaviors among young IDU in HCV vaccine trial willingness survey ($n=67$) and participants in HCV-negative cohort study ($n=202$), San Francisco, 2003–2008.

	Vaccine trial survey participants % (95% CI) or median (IQR)	HCV negative UFO cohort participants % (95% CI) or median (IQR)	<i>p</i> -value
Age	23.7 (21.1–27.2)	22.8 (20.6–25.5)	n.s. [*]
Male	65.7	68.8	n.s.
Non-white race/ethnicity	20.0	30.2	n.s.
Less than high school education	36.9	45.6	n.s.
Homeless last 3 mo.	67.2	67.0	n.s.
Years injecting	5.1 (2.9–9.2)	4.1 (1.7–7.6)	n.s.
No. of daily injections	3.0 (1.8–4.0)	2.0 (1.0–3.0)	n.s.
Drug used most days last month – heroin	69.4	59.1	n.s.
Borrowed used needle last 3 mo.	34.9	36.2	n.s.
Incarcerated last 3 mo.	23.4	30.8	n.s.

^{*} Non-significant, $p \geq 0.05$.

be willing to participate in a HCV vaccine trial that began that week (Table 2). Levels of willingness to enroll in an HCV vaccine trial varied significantly by age ($p \leq 0.01$). Reported willingness to participate in an HCV vaccine trial decreased with increasing trial duration, with 67% of participants surveyed willing to participate in a trial of 1 year duration compared to 43% of participants willing to participate in a trial of 4 years duration. For IDU \geq age 23, willingness to enroll in an HCV vaccine trial showed a decreasing trend with hypothetical trial duration (Fig. 1).

The UFO Study was the most frequently reported trusted source of information on trial safety measures and adverse events, reported by over 85% of participants. Other sources of trusted information on candidate vaccine safety and adverse events reported by greater than one half of participants were: San Francisco

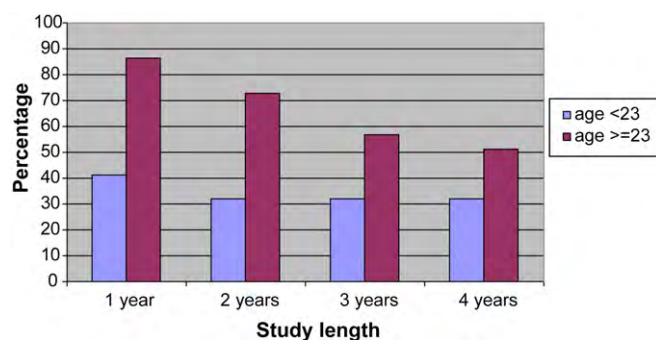


Fig. 1. Willingness to enroll in an HCV vaccine trial by trial length and age group.

Table 2

Knowledge of clinical trial concepts and willingness to enroll in an HCV vaccine trial among young, HCV antibody negative IDUs by age in San Francisco, 2006–2007 ($n=67$).

	Total <i>n</i> (%)	Age <23 <i>n</i> (%)	Age \geq 23 <i>n</i> (%)
Overall	67 (100)	25 (37.3)	42 (62.7)
Ever received a vaccine from UFO ($n=66$)	19 (28.8)	1 (4.2)	18 (42.9)**
Vaccine knowledge			
What do you think a vaccine is for?			
To prevent	47 (70.2)	21 (84.0)	26 (61.9)
To treat disease	3 (4.5)	1 (4.0)	2 (4.8)
To prevent and treat disease	16 (23.9)	3 (12.0)	13 (31.0)
The study would only enroll people not infected with HCV [True]	33 (57.4)	7 (28.0)	26 (61.9) [*]
Participants would be randomly assigned to get actual vaccine or placebo [True]	30 (44.8)	13 (52.0)	17 (40.5)
No one knows who received actual vaccine or placebo until trial end [True]	39 (58.2)	12 (48.0)	27 (64.3)
Only researchers know who received actual vaccine or placebo before trial end [True] ($n=66$)	30 (45.5)	11 (45.8)	19 (45.2)
Participants told whether received actual vaccine or placebo at trial end [True]	45 (67.2)	18 (72.0)	27 (64.3)
Participants would be treated for vaccine related health problems [True]	53 (79.0)	19 (76.0)	34 (81.0)
Willingness to enroll			
Willingness to enroll by study length ($n=66$)			
1 year	44 (66.7)	10 (40.0)	34 (82.9)**
2 years	36 (54.6)	7 (28.0)	29 (70.7)**
3 years	30 (45.5)	7 (28.0)	23 (56.1) [*]
4 years	28 (42.4)	7 (28.0)	21 (51.2)
Willingness to enroll if study started this week ($n=66$)			
Definitely willing	29 (43.9)	7 (28.0)	22 (53.7)
Probably willing	29 (43.9)	13 (52.0)	16 (39.0)
Probably unwilling	5 (7.6)	3 (12.0)	2 (4.9)
Definitely unwilling	3 (4.6)	2 (8.0)	1 (2.4)
Trust to explain safety and side effects ($n=66$)			
UFO Study	58 (87.9)	20 (80.0)	38 (92.7)
San Francisco DPH	37 (56.1)	15 (60.0)	22 (53.7)
UCSF Committee on Human Research	35 (53.1)	10 (40.0)	25 (61.0)
San Francisco General Hospital ^a	31 (50.8)	15 (62.5)	16 (43.2)
Doctor	39 (59.1)	17 (68.0)	22 (53.7)
Government	17 (25.8)	6 (24.0)	11 (26.8)
Pharmaceutical company	9 (13.6)	5 (20.0)	4 (9.8)
Media/Newspapers	6 (9.1)	2 (8.0)	4 (9.8)

^a $n=61$.

^{*} $p \leq 0.05$.

** $p \leq 0.01$.

Department of Public Health, University Human Subjects Research committee, County Hospital and their physician.

Survey participants rated the following reasons as “very true” or “somewhat true” in decision making about vaccine trial participation: potential benefits for future IDU (75%), monetary benefits (55%), potential benefits to themselves (53%), and reduced chance of HCV infection due to trial participation (43%).

4. Discussion

In the context of the current reappraisal of the empirical approach to vaccine development [20] and the increasing recognition of the importance of two way dialogue with affected communities in vaccine trials, this study is the first to document young IDU vaccine trial knowledge and willingness to enroll in preventive hepatitis vaccine trials. We report higher levels of willingness to participate in an HCV vaccine trial (defined as definitely or probably willing to participate) than those reported by high risk adults in a hypothetical HIV vaccine trial (76–81% vs. 88%) [16,17] and higher levels than those reported by male IDU (77%) [18] or female IDU (60%) in hypothetical HIV vaccine trials. Similar willingness to participate levels (82%) were reported in a Spanish study among female sex workers, injection and non-injection drug users and men who have sex with men which evaluated HIV vaccine trial readiness [21]. Others have reported willingness to participate in HIV vaccine efficacy studies was related to high risk sexual or injection behavior in the last 6 months [17,22]. These data taken in conjunction with the risk profile of the cohort at baseline suggest that identification of willing high risk IDU participants for future HCV trials is feasible. This is consistent with prior interventions showing IDUs are amenable to participation in a variety of prospective research settings [23–25].

Our study suggests significant resources will be needed for recruitment of IDUs for HCV vaccine trials. HCV incidence is very high among young IDU and there is a rapid saturation of the population with disease (with almost 50% becoming positive after 5 years of injecting) [4,26,27]. Given the challenge of finding seronegative IDU and the decreased willingness of younger IDU to participate in trials, collaboration will be needed between existing research study cohorts as well as reaching out to new IDU social networks and communities to enroll sufficient numbers of HCV seronegative IDUs. The sample size needed for an adequately powered trial of a vaccine that confers a 60% reduction in incidence of chronic infection among vaccinated participants compared to unvaccinated controls will be a total of 320 participants (160 per group). These estimates assume an 18-month follow-up period, a 10% loss to follow-up and a 14% annual incidence of chronic infection.

Young IDUs in our cohort were less willing to enroll in an HCV vaccine trial than older IDUs. A recent study among high risk adults including IDUs reported a similar association between HIV vaccine trial willingness and older age [21], while others have not found such an association [22]. Multivariate analysis, limited by our modest sample size, evaluated willingness to participate in an HCV vaccine trial for trials of 1–3 years in duration. For HCV vaccine trials of 1–2 years in duration, age greater than 23 years is an independent predictor of willingness to participate, along with planning to stay in the San Francisco area and a higher knowledge score. For an HCV vaccine trial of 3 years duration, the age effect was not significant, with trust in physicians, media or government, no plans to leave San Francisco, longer time enrolled in the UFO Study, and a higher knowledge score predicting trial willingness.

Our findings also show that work needs to be done to educate young IDU vaccine candidates on key trial concepts, especially randomization and blinding as well as the need for baseline seronegative status. While a basic knowledge of a vaccine's role

in preventing disease acquisition was higher in our study than an earlier study in Philadelphia IDU [22], knowledge of placebo in a theoretical HIV prevention vaccine trial appeared higher among 4892 adults at high risk for HIV infection than suggested by participants in our study [19]. These authors reported prototype consent procedures which included intensive educational efforts at baseline, followed by targeted semiannual ‘booster’ educational sessions were associated with statistically significant and sustained increases in participant knowledge of key concepts. The impact of these prototype consent procedures was similar for IDUs compared to other risk groups [19].

Our study provides encouraging results on the use of existing public health research infrastructure to recruit IDU for hepatitis vaccine trials. One third of survey willingness participants had previously received a vaccine through the UFO Study. We report high levels of knowledge on trial coverage of vaccine related adverse events. Trusted sources of vaccine trial information reported by participants were UFO Study staff, physicians and local public health authorities. Advertising vaccine trial opportunities for IDU should occur in collaboration with public health partners in settings where valued services such as syringe and needle exchange, drop-in counseling, treatment and legal services are offered.

Particular strengths of this study were the assessment of willingness with common instruments for IDU in hepatitis vaccine trials, a population for which there are no data with regard to preparedness for future hepatitis vaccine trials. Limitations of this study include its modest sample size and lack of longitudinal data on willingness to participate and vaccine trial concept knowledge. With the cross sectional data we present here, we cannot determine if willingness to participate changes over time or if changes in vaccine trial knowledge affect changes in willingness. Others have reported willingness to participate in HIV vaccine trials was significantly lower at six, 12 and 18 month follow-up visits compared to baseline in study populations including IDUs [18]. In this study, we report a large proportion of young IDU are willing to participate in future HCV vaccine efficacy trials. Participant counseling and community education need to address seronegativity at baseline in participants, and other key vaccine trial concepts.

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