

Enhanced retention strategies and willingness to participate among hard-to-reach female sex workers in Barcelona for HIV prevention and vaccine trials

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The potential for implementation of HIV vaccine trials in hard-to-reach female sex workers in an inner city area of Barcelona, Spain was assessed via a study of HIV risk, willingness to participate and the success of retention strategies. In 130 women, serological HIV status, behavioral risk exposures and willingness to participate in future HIV vaccine trials were recorded every six months using a confidential questionnaire. An enhanced retention (ER) strategy was compared with a control retention (CR) strategy comprising the recording of data on appointment cards. HIV seroincidence and retention rates were estimated. Retention rates after 6 and 12 mo of follow-up in the ER group were 76% and 69% respectively compared with 16% and 13% in the CR group. Among the ER group 97% were willing to participate in HIV vaccine trials at baseline and, after 12 mo of follow-up. Willingness was significantly associated with higher HIV risk exposure, and higher education level. Successfully retaining these cohorts over time in settings with a high HIV seroincidence rate is an ongoing challenge that will need to be addressed to ensure participation in future trials. Furthermore, as we have demonstrated, the fact that retaining hard-to-reach populations is difficult should not exclude this target population for HIV vaccine and prevention trials.

Introduction

According to the UNAIDS World AIDS Day Report for 2011, at the end of 2010 an estimated 34 million people were living with HIV worldwide and 2.7 million individuals became newly infected with the virus in 2010. In that year the number of people dying of AIDS-related causes totalled 1.8 million, and it is estimated that more than 16 million children have been orphaned by AIDS.¹ In Spain, 1,162 new diagnoses of HIV infection were recorded in 2010. The percentage of HIV infected women due to unprotected heterosexual relations rises to almost 60%. From 2001 to 2010, in Catalonia, an autonomous community of Spain (north-eastern of Spain and over 7 million inhabitants with Barcelona as its largest city), 7,136 cases of HIV infection were recorded, of which 78.5% were men and 21.5% were women.² Women's participation in HIV vaccine trials and prevention interventions is particularly important for those with limited prevention options. Condom use, a mainstay of prevention, requires male cooperation and beside that women at highest risk for HIV infection often are impacted by multiple competing health and

life challenges including poverty, unstable housing, substance abuse, illegal activities and violence.³

Although enormous progress has been made in curbing the epidemic, the successes in treatment and care have not been matched by progress in prevention. New evidence of rising HIV infection rates is emerging, particularly in marginalized communities. New strategies to prevent the spread of HIV are urgently needed, such as vaccines, topical microbicides and providing antiretrovirals to people who are not infected with HIV but who are at high risk of acquiring the infection, called pre-exposure prophylaxis (PrEP). The development of an HIV preventive vaccine is critical for women with limited access to health care and prevention interventions. Phase 1 and 2 clinical studies with preventive vaccine candidates are ongoing.^{4,5} Both women and men will be needed to participate in future Phase 2 and 3 HIV vaccine efficacy trials. Biomedical HIV prevention methods, as well as behavioral prevention, will be most effective if one takes into account structural and social factors, that increase risk and vulnerability, including gender inequality, HIV stigma and discrimination, and the social marginalization of the populations most at risk of HIV exposure.

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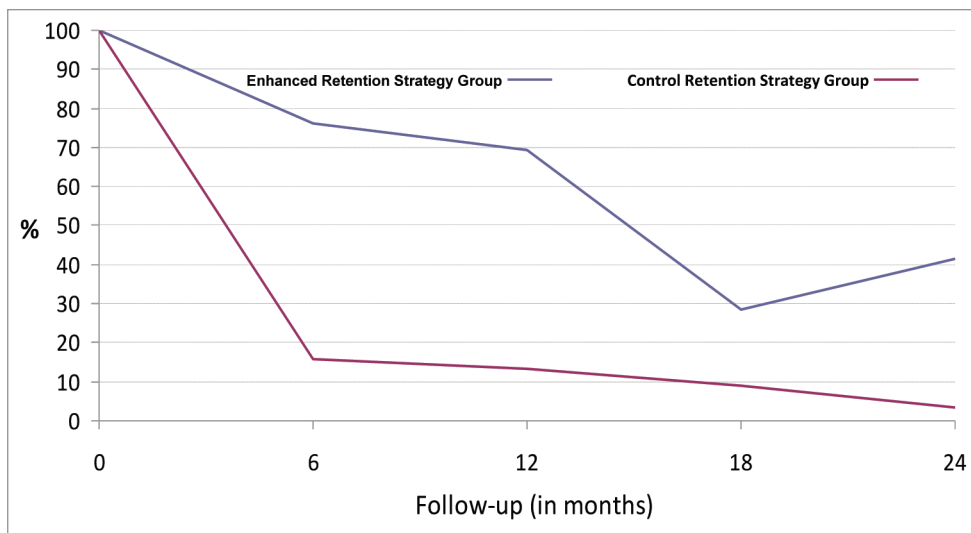


Figure 1. Retention rate by study visit and study arm.

Studies assessing prevention interventions, including prophylactic vaccines, require recruitment, long-term follow-up and high retention rates of high risk volunteers who are willing to consider future participation in vaccine trials.^{6,7} Previous studies have considered willingness to participate (WTP), knowledge, barriers and motivators of enrollment in HIV vaccine trials.⁸⁻¹² One study with high-risk groups conducted in Philadelphia indicated a declining WTP after participants learned of the hazards of HIV vaccine trials.¹³ However, other studies have shown that the more participants know about the trials, the more willing they are to volunteer.^{14,15} Long-term follow-up and high retention rates are often particularly difficult to achieve when subjects are homeless or live in temporary housing, with no formal address or telephone and few resources to travel to health centers. In recent years strategies for retaining participants in health care research have been identified focused on participant retention in randomized controlled trial studies of health problems such as diabetes, heart disease and cancer.¹⁶⁻¹⁹ Surprisingly few reports have been published on retention strategies for HIV vaccine preparedness studies among the hard-to-reach population.^{20,21}

In 2005 we embarked on a pilot study to identify both women and men in three high risk target populations: commercial sex workers (CSW), injection and non-injection drug users (IDUs and NIDUs, respectively) and men who have sex with men (MSM).²² In 2008 we launched the Project “Cuenta Contigo,” a vaccine preparedness study targeting women at risk for HIV transmission through sexual contact with men. This is a collaborative study between the Hospital Clínic Barcelona, and Àmbit-Prevenció, a non-governmental organization (NGO) with extensive experience in providing psychological, social and health support services for CSW. This study was designed to focus on recruitment of volunteers, retention of the cohort and HIV seroincidence. In this paper, we describe the strategies used to recruit and retain women and compare retention outcomes between two groups in which different strategies

were applied: enhanced retention (ER) and control retention (CR). We also present the socio-demographic characteristics of the women at baseline, risk behaviors over time, HIV testing histories and correlates of willingness to participate in future vaccine trials among the enhanced retention (ER) group. We also discuss implications for enrolling women in HIV vaccine efficacy trials. The results of the study should help to design targeted HIV prevention strategies among at risk populations in Spain and provide critical insights for the execution of successful future international HIV vaccine efficacy studies.

Results

Figure 1 shows retention rates over time in ER and CR groups. At enrollment, 130 women/transgenders in the ER group and 121 in the CR group from the Àmbit-Prevenció center were participating in the “Cuenta Contigo” project. At 6 mo, 76% of participants in the ER arm and 16% in the CR group remained in follow-up; these figures were 69% and 13% at 12 mo and 28% and 9% at 18 mo. The retention rate increased to 41% at month 24 in the ER group. Trends in retention differed significantly ($p < 0.0001$) between the two groups. We examined loss to follow-up by demographic and risk behavior characteristics in the ER group and found no differences between participants who completed the 6 and 12 mo follow-up visits and those who did not. No variables were associated with retention in the ER group (data not shown).

In **Table 1** we describe baseline demographic, risk behavior, serologic testing, vaccination and willingness to participate in CR ($n = 121$) and ER arms ($n = 130$). In both groups, participants were primarily female (over 70%) and most of them immigrants. More than half were born in Latin American, around 30% from Africa and only 7% from Spain. Almost 80% were aged between 18–30 y and heterosexually identified. In the CR group, over half had completed secondary studies and 8% had completed university studies compared with less than half of completing secondary or university studies in the ER group. In the CR group, 46% were non-injection drug-users, compared with 31% in the ER group ($p = 0.01$). There were also significant differences ($p = 0.03$) regarding the participants who had had sex with a known HIV positive partner in the last 6 mo (4% in the CR group vs. 1.5% in the ER group). In contrast, more participants in the ER study arm had had sex with an IDU partner in the last month (3% vs. 0.8%, $p < 0.01$). Regarding serologic testing, more than half of the ER group had been previously tested for HIV, HCV and syphilis compared with fewer than one-third in the CR group ($p < 0.01$). In addition, participants from the ER study arm were

Table 1. Baseline demographic, risk behavior, serologic testing, vaccination and willingness to participate in Control and Retaining Group

	Control group		Retaining group		p-value
	n	%	n	%	
Demographics					
Overall	121	100	130	100	
Gender					
Female	88	72.7	97	74.6	0.73
Transgender	33	27.3	33	25.4	
Age					
18–30	78	64.5	71	54.6	0.26
> 31–45	35	28.9	50	38.5	
> 45	8	6.6	9	6.9	
Origin					
Spain	7	5.8	14	10.8	0.08*
Other European Country	7	5.8	19	14.6	
Latin America	70	58.3	62	47.7	
Africa	33	27.5	33	25.4	
Asia /Oceania	3	2.5	2	1.5	
Education					
No studies	9	7.4	14	10.8	0.04
Primary	33	27.3	55	42.3	
Secondary	69	57.0	54	41.5	
University	10	8.3	7	5.4	
Sexual Behavior (ever)					
Heterosexual	89	74.2	98	75.4	0.18*
Homosexual	28	23.3	23	17.7	
Bisexual	3	2.5	9	6.9	
Risk behaviors					
Injection drug use (ever)	0	0	0	0	–
Non-injection drug use (ever)	56	46.3	40	30.8	0.01
Performs sex work in last 6months	121	100	130	100	–
Performs sex work in last month	121	100	130	100	–
Sex with a known HIV positive partner in last 6 mo	5	4.1	2	1.5	0.03*
Sex with a known HIV positive partner in last month	2	1.7	1	0.8	0.09*
Sex with an IDU partner in last 6 mo	3	2.5	9	6.9	< 0.01*
Sex with an IDU partner in last month	1	0.8	4	3.1	< 0.01*
Sex with a partner using other drugs in last 6 mo	68	56.2	77	59.2	0.49
Sex with a partner using other drugs in last month	45	37.2	41	31.5	0.14
Sex with a partner having multiple sexual partners in last 6 mo	107	88.4	114	87.7	0.57
Sex with a partner having multiple sexual partners in last month	74	61.2	63	48.5	0.13
UA/V sex with casual/steady partner in last 6 mo	66	54.6	60	46.2	0.18
UA/V sex with clients in last 6 mo	5	4.1	6	4.6	0.85
Self reported STI symptoms in last 6 mo	5	4.7	6	4.7	0.99
Serologic testing					
HIV ever tested: yes/no	34	28.1	85		
HIV in past 6 mo tested: yes/no	4	3.3	25	65.4	< 0.01
Tested HIV positive	4	3.3	0	19.2	< 0.01
HCV ever tested: yes/no	12	9.9	73	0	< 0.01

*Fisher's exact p-value.

Table 1. Baseline demographic, risk behavior, serologic testing, vaccination and willingness to participate in Control and Retaining Group (continued)

	Control group		Retaining group		p-value
	n	%	n	%	
Serologic testing (continued)					
HCV in past 6 mo tested: yes/no	2	1.7	21	56.2	< 0.01
Tested HCV positive	1	0.8	4	16.2	< 0.01*
Syphilis ever tested: yes/no	13	10.7	73	3.5	0.20*
Syphilis in past 6 mo tested: yes/no	3	2.5	21	56.2	< 0.01*
Tested Syphilis positive	16	13.9	19	16.2	< 0.01*
HBV (Anti-HBc) positive	39	32.8	35	18.8	0.36
HBV (HBs Ag) positive	5	4.3	2	30.4	0.70
Vaccination				1.7	0.45*
HBV vaccination ever vaccinated: yes/no	35	34.0	34		
Willingness to participate				35.1	0.87
Probably + definitely YES	108	89.3	126		
Probably + definitely NOT	13	10.7	4	96.9	0.02

*Fisher's exact p-value.

more willing to participate in future vaccine trials at baseline (97%), compared with the CR group (89%) ($p = 0.02$).

Table 2 summarizes the significant bivariate and multivariate predictors of WTP in future vaccine trials for the ER group. Among the 130 participants interviewed regarding HIV vaccine trial willingness, a large majority (97%) reported that they would probably (60%) or definitely participate (37%) at baseline. We observed that willingness to participate was significantly associated with time in the study (12 mo vs. baseline, $p < 0.01$) and level of education (primary and secondary school, $p < 0.05$). Regarding HIV risk behaviors, WTP was associated with performing sex with a known HIV positive partner in the last month ($p < 0.01$). Importantly, the ER group presented an increase in proportion definitely willing to participate from 37.0% at baseline, 39.4% at 6-mo study visit, to 55.0% at the 12-mo study visit ($p < 0.01$) (data not shown).

Table 3 shows the bivariate predictors of WTP in future HIV vaccine trials among the CR and ER groups at baseline. We observed statistically significant differences between groups, with a greater WTP among transgender ($p = 0.02$) participants ($p < 0.01$) in the CR group than in the ER group. In addition we observed higher WTP in the CR arm than in the ER arm among those who had had sex with a partner using other drugs in the last 6 mo ($p = 0.05$) and those who had had sex with a partner having multiple sexual partners in the last month ($p = 0.04$).

Overall, the estimated HIV-1 seroincidence rate was 0.9/100PYO (95% CI: 0.2–3.6). Two new HIV-1 infections were found at the 12 mo study visit in the ER study arm, yielding an estimated seroincidence rate of 1.1/100 PYO (95% CI: 0.3–4.3).

Discussion

To our knowledge, this longitudinal study is the first to evaluate and monitor sexual behavioral risk, retention rates and WTP in HIV vaccine trials among female commercial sex-workers in

Spain. We achieved higher levels of retention rates compared with our previous results in the same target population.²² Moreover, the retention rates in our study were comparable to those in other previous studies with a similar target population.²⁰ The rate of WTP in an HIV vaccine trial found in this study was higher than those reported in other high risk groups in hypothetical HIV vaccine trials: female commercial sex workers and men attending sexually transmitted disease clinics (63%),²³ male IDUs (77%),²⁴ female IDUs (60%), IDUs and non-IDUs (83%),²⁵ and also sex-workers and motorcycle taxi drivers (66.5%).²⁶

Analyzing both study arms of these high risk sex-workers from the inner city of Barcelona, we detected significant differences in retention rates between CR and ER groups. At the 6 and 12 mo follow-up visits the influence of implementing retention strategies and financial incentives in the ER group was clear, with high levels of retention rates compared with the CR group. Furthermore, at 18 mo of follow-up, when neither retaining strategies were applied nor financial compensation provided, the retention rate decreased to its lowest level in ER participants. Significantly, at the 24 mo follow-up, when only retaining strategies and no financial incentives were used, the retention rate increased but remained below 50%. Thus, we demonstrate the importance and influence of offering financial compensation and implementing enhanced retention strategies in retaining hard-to-reach populations. Other studies in experienced trial sites (USA, Caribbean, Southern Africa and in Latin America) have already shown how financial compensations and retention measures help with retention of marginalized populations.^{27–30}

Although each group reported substantial levels of risk, the overall proportion of participants with behavioral risk was higher among CR participants. A potential explanation could be the decreased contact with education and prevention programs provided in the *Ambit-Prevençió* center compared with the ER arm. We observed significantly higher rates of HIV, HCV and syphilis serological testing among the ER participants than in the CR

group at baseline, probably reflecting the importance of NGOs like Àmbit-Prevençió in reinforcing prevention and education programs for early HIV and other STD testing and diagnosis.

Willingness to participate was associated with several independent predictors in the ER population. In multivariate analyses, it was significantly associated with time in the study (receiving vaccine trial education) and level of education. A higher level of education promotes access to information and aids understanding of the modes of transmission, prevention and WTP in vaccine trials. It may also increase an individual's perception of risk, and may promote behavioral change and the adoption of safer sex practices. Previous studies have found a direct relationship between an individual's level of education and knowledge of vaccines and vaccine studies.³¹⁻³⁴ On the other hand, the high proportion of WTP observed in both groups (CR and ER) in individuals at greater risk for HIV may indicate their desire for protection due to a high perception of the risk combined with a lack of knowledge regarding modes of transmission and prevention. Our findings were similar to those reported in previous studies involving other populations with a high risk of HIV infection.³⁵⁻³⁹ It is important that these groups receive education on clinical trial procedures including randomization and blinding, as well as messaging about unknown protection against HIV infection with trial participation. Although it was a vaccine preparedness study (VPS), WTP was hypothetical, as no specific information about the trial or candidate vaccine was given. Participants may be less willing to participate once they are presented with details of an actual vaccine trial. Other study described the relationship between hypothetical and actual willingness to enroll in a preventive vaccine trial.⁴⁰

This study has some limitations. First, the non-randomized design and potential explanation for our results is that only those participants with high health seeking behavior may have been captured in the study, which may not reflect the true population thereby limiting the external validity of the study. The non-randomized nature of the assigning intervention may have introduced some confounding effect. For example all those who had attended the health facility more than once were assigned to ER and all first timers were assigned to CR group. The higher retention rates found in the ER group could then be due to confound. The fact that those participants had better information and knowledge about the facility programs offered by the institution and better rapport with the social workers may account for our results. Despite this limitation, our study provides substantial evidence of high WTP in future HIV vaccine trials and introduces a successful model for achieving high retention among this hard-to-reach CSW population. Second, we might have underestimated the prevalence of these behaviors in some groups using interviewer-administered questionnaires due to socially desirable reporting. In future studies we might consider using audio computer-assisted self-interviewing (ACASI) which has been shown to capture risk reporting more accurately^{41,42} and can be used in low literacy populations. However, programming ACASI questionnaires even in one language is time-consuming and may present barriers to enrolling people who are fluent in other languages instead of the majority language. Third, the retention rates observed in the ER group are insufficient for a vaccine trial;

Table 2. Bivariate and multivariate predictors of willingness to participate in future vaccine trials among retaining group

Demographics	RR (95% CI)	ARR (95% CI)
Study visit		
Baseline	1.0	1.0
6 mo	1.0 (0.9–1.1)	1.1 (1.0–1.2)
12 mo	1.2 (1.1–1.4)**	1.2 (1.1–1.4)**
Gender		
Female	1.0	
Transgender	0.9 (0.8–1.1)	
Age		
18–31	1.0	
> 31–45	1.0 (0.8–1.1)	
> 45	1.1 (0.8–1.3)	
Origin		
Spain	1.0	
Other European Country	1.0 (0.8–1.3)	
Latin America	1.2 (0.9–1.4)	
Africa	1.0 (0.8–1.3)	
Asia	1.1 (0.6–1.9)	
Education		
No studies	1.0	1.0
Primary	1.2 (0.98–1.4)	1.2 (1.01–1.5)*
Secondary	1.2 (1.01–1.4)*	1.2 (1.02–1.5)*
University	1.1 (0.8–1.5)	1.2 (0.9–1.7)
Sexual Behavior (ever)		
Heterosexual	1.0	1.0
Homosexual	0.8 (0.7–0.98)*	0.8 (0.7–1.00)
Bisexual	1.0 (0.7–1.3)	1.0 (0.8–1.3)
Risk Behaviors		
Injection drug use (ever)	–	
Non-injection drug use (ever)	1.0 (0.9–1.1)	
Performs sex work in last 6months	–	
Performs sex work in last month	–	
Sex with a known HIV positive partner in last 6 mo		
No	1.0	
Yes	1.0 (0.5–2.0)	
Unknown	0.8 (0.7–0.9)**	
Sex with a known HIV positive partner in last month		
No	1.0	1.0
Yes	1.5 (1.3–1.7)**	1.4 (1.2–1.6)**
Unknown	0.8 (0.7–0.9)**	0.7 (0.6–0.8)**
Sex with an IDU partner in last 6 mo		
No	1.0	
Yes	1.1 (0.8–1.4)	
Unknown	1.2 (1.0–1.3)	
Sex with an IDU partner in last month		
No	1.0	1.0
Yes	1.1 (0.8–1.4)	1.4 (0.9–2.3)
Unknown	1.2 (1.0–1.3)*	1.3 (1.1–1.4)**

*p < 0.05; **p < 0.01.

Table 2. Bivariate and multivariate predictors of willingness to participate in future vaccine trials among retaining group (continued)

Sex with a partner using other drugs last 6 mo	
No	1.0
Yes	0.8 (0.7–1.0)*
Unknown	0.9 (0.7–1.0)
Sex with a partner using other drugs in last month	
No	1.0
Yes	1.0 (0.9–1.2)
Unknown	1.0 (0.9–1.2)
Sex with a partner having multiple sexual partners in last 6 mo	
No	1.0
Yes	1.0 (0.7–1.5)
Unknown	1.0 (0.7–1.5)
Sex with a partner having multiple sexual partners in last month	
No	1.0
Yes	1.1 (1.0–1.2)
Unknown	1.1 (0.9–1.3)
UA/V sex with steady or casual partner in last 6 mo	1.0 (0.9 - 1.1)
UA/V sex with clients in last 6 mo	1.0 (0.8–1.4)
Self reported STI symptoms in last 6 mo	1.1 (0.8–1.6)

* $p < 0.05$; ** $p < 0.01$.

despite our efforts, one-third of the original sample was lost to follow-up after a year. Unfortunately, many who enrolled were reluctant to give us the name and address of two contacts, which left us with less-than-adequate locator information when participants moved. Importantly, the retention rates in our study at 12 mo of follow-up (69%) were similar to those in other previous studies with a same target population (67%).²⁰ In fact, our site can be similar to other currently successful biomedical HIV prevention trial sites, which may have had to learn to improve their retention strategies over time.^{29,30,35} Finally, in this cohort only two seroconversions were detected. It may be that our sample was not large enough to measure seroincidence over the period of 24 mo. It is also possible that any seroconversions that occurred were among women who were lost to follow-up. Nevertheless, the non-detection of high seroincidence rates during the study period does not minimize the HIV risk status of this cohort.

Our results indicate that recruitment, retention and WTP are feasible in vaccine preparedness studies among hard-to-reach populations. To ensure broad participation in clinical trials and cohort studies including women at high risk for HIV infection, modifications of the retention strategies, such as building in more study visits to maintain sufficient participant contact and fully identification may also be required. Furthermore, financial compensations and outreach activities might increase the engagement to participate in future vaccine trials. On the other hand, the ability to produce reliable identification may be a reasonable requirement in Barcelona, but in many areas this could be a barrier for recruiting marginalized subjects. Our findings highlight the continued need for targeting prevention programs, harm

reduction interventions and counseling as well as vaccine development and vaccine trial education. Successfully retaining these cohorts over time in settings with a high HIV seroincidence rate is an ongoing challenge that will need to be addressed to ensure participation in future trials. Furthermore, as we have demonstrated, the fact that retaining hard-to-reach populations is difficult should not exclude this target population for HIV vaccine and prevention trials.

Materials and Methods

Ethics statement. The study protocol and materials were reviewed and approved by the Ethical and Clinical Research Committee of the Hospital Clínic Barcelona.

Participants. From February to December 2008, women and transgender commercial sex workers (CSW) who attended the Àmbit-Prevençió center were invited to enroll. Àmbit-Prevençió is an NGO based in the Ciutat Vella district of Barcelona and has offered social, psychological and health assistance to CSW since 1995. The Ciutat Vella district is located in the inner city, with a population of approximately 90,000 and high rates of social marginalization and poverty. The study was coordinated by the AIDS Research Unit at the Hospital Clínic Barcelona, a referral health center for HIV/AIDS care and treatment. Women/transgenders meeting the following criteria were included: (1) 18–40 y old; (2) residence in Spain; (3) ability to provide informed consent in the participant's preferred language; (4) HIV serostatus negative or unknown and (5) classification in one of the following risk behavior groups: (A) being at a high risk of HIV through unprotected vaginal or anal intercourse; (B) having a recent or current sex partner infected with HIV, multiple sexual partners, or one or more IDU sexual partners in the previous year; (C) having exchanged sex for money; or (D) having had a sexually transmitted infection in the last year. The exclusion criteria were: (1) documented positive HIV test; (2) inability to provide consent, reliable identification or contact information; (3) unwillingness to participate in the study; (4) current pregnancy or intention to become pregnant and (5) injection drug use in the past year, in order to limit the study population to those at risk of HIV through sexual contact. Subjects were approached by trained staff (social workers) in waiting rooms, consultation rooms and HIV care workshops at recruitment site and through outreach activities in the community.

Study design and measures. Participants were assigned sequentially to either the enhanced retention group (ER) or control retention group (CR) in a non-randomized fashion. Participants who had had previous visits (i.e.: attended during the last year) in the Àmbit-Prevençió center were assigned to the ER group, because we had contact information available and we are interested to recruit them in the study. Those attending the center for baseline visit between February and December 2008 were considered as the CR group. Each group was asked to return for study visits every 6 mo over a 24 mo period. Participants in the ER group received an enhanced retention intervention (strategies described below), and participants in the CR group were the control group.

Table 3. Bivariate predictors of willingness to participate in future vaccine trials among control and retaining group at baseline

Demographics	Control group OR (95% CI)	Retaining group OR (95% CI)	p-value†
Gender			
Female	1.0	1.0	
Transgender	4.1 (1.6–10.4)**	1.0 (0.4–2.2)	0.02
Age			
18–31	1.0	1.0	
> 31–45	1.1 (0.4–2.9)	0.7 (0.3–1.5)	0.53
> 45	2.5 (0.5–11.7)	3.3 (0.8–14.1)	0.81
Origin			
Spain	1.0	1.0	
Other European Country	0.4 (0.03–6.1)	0.6 (0.1–2.9)	0.78
Latin America	1.1 (0.2–6.0)	1.4 (0.4–4.6)	0.81
Africa	0.1 (0.01–1.0)	0.8 (0.2–2.9)	0.12
Asia	–	1.8 (0.1–35.4)	–
Education			
No studies	–	0.2 (0.03–1.8)	–
Primary	0.3 (0.1–1.3)	1.0 (0.2–1.7)	0.27
Secondary	0.5 (0.1–1.8)	0.8 (0.2–3.9)	0.61
University	1.0	1.0	
Sexual Behavior (ever)			
Heterosexual	1.0	1.0	
Homosexual	4.8 (1.8–12.6)**	0.7 (0.3–1.9)	< 0.01
Bisexual	–	1.3 (0.3–5.2)	–
Risk Behaviors			
Injection drug use (ever)	–	–	–
Non-injection drug use (ever)	1.3 (0.7–4.0)	1.2 (0.6–2.6)	0.61
Performs sex work in last 6 months	–	–	–
Performs sex work in last month	–	–	–
Sex with a known HIV positive partner in last 6 mo			
No	1.0	1.0	
Yes	–	0.9 (0.1–16.4)	–
Unknown	3.6 (0.5–29.5)	0.4 (0.2–1.0)	0.07
Sex with a known HIV positive partner in last month			
No	1.0–	1.0	–
Yes	4.6 (0.6–36.3)	–	0.05
Unknown	–	0.5 (0.2–1.1)	–
Sex with an IDU partner in last 6 mo			
No	1.0	1.0	
Yes	2.5 (0.2–32.2)	1.4 (0.3–5.6)	0.69
Unknown	1.4 (0.5–3.9)	1.0 (0.5–2.1)	1.43
Sex with an IDU partner in last month			
No	1.0	1.0	
Yes	–	5.5 (0.5–55.0)	–
Unknown	1.5 (0.5–4.1)	1.0 (0.5–2.2)	0.56
Sex with a partner using other drugs last 6 mo			
No	1.0	1.0	
Yes	4.6 (0.6–37.9)	0.4 (0.1–1.2)	0.05
Unknown	1.2 (0.1–11.8)	0.2 (0.1–0.8)*	0.22
Sex with a partner using other drugs in last month			
No	1.0	1.0	
Yes	1.1 (0.4–2.9)	1.2 (0.5–2.7)	0.85
Unknown	0.3 (0.1–1.1)	0.5 (0.2–1.3)	0.55

*p < 0.05; **p < 0.01; †p-value for difference in willingness by study arm.

Table 3. Bivariate predictors of willingness to participate in future vaccine trials among control and retaining group at baseline (continued)

Demographics	Control group OR (95% CI)	Retaining group OR (95% CI)	p-value†
Sex with a partner having multiple sexual partners in last 6 mo			
No	1.0	1.0	
Yes	1.6 (0.2–14.3)	0.9 (0.2–5.9)	0.70
Unknown	1.0 (0.1–20.0)	0.3 (0.03–3.5)	0.57
Sex with a partner having multiple sexual partners in last month			
No	1.0	1.0	
Yes	0.6 (0.2–1.4)	2.0 (0.9–4.2)	0.04
Unknown	0.4 (0.04–4.1)	0.5 (0.1–2.6)	0.92
UA/V sex with steady or casual partner in last 6 mo	0.7 (0.3–1.7)	0.9 (0.4–1.8)	0.76
UA/V sex with clients in last 6 mo	–	1.8 (0.3–9.1)	–
Self reported STI symptoms in last 6 mo	2.7 (0.4–17.5)	0.9 (0.2–4.9)	0.38

*p < 0.05; **p < 0.01; †p-value for difference in willingness by study arm.

After obtaining signed informed consent and confirming eligibility, volunteers underwent pre-test counseling by a trained HIV counselor. Counseling was client-centered and included information on HIV and other sexually transmitted infections (STI), with advice on reducing sexual exposure risk, and HIV testing information including an explanation of testing procedures and a guide to interpreting the results. Following pre-test counseling, a venous blood sample was obtained for HIV-1, hepatitis and syphilis testing. Socio-demographic characteristics, behavioral risk factors and willingness to participate were recorded using an interviewer-administered questionnaire in the participant's primary language (Spanish, English, Romanian, German or French) by trained interviewers fluent in the respective language. Post-test HIV risk reduction counseling was performed in coordination with the disclosure of HIV, hepatitis and STI testing results, interpretation and associated referrals for comprehensive health care and treatment. WTP was measured at baseline and at each follow-up visit on a 4-point scale, ranging from: (1) Definitely not willing; (2) Probably not willing; (3) Probably willing; to (4) Definitely willing, in response to the question, "How willing would you be to join a study of a hypothetical vaccine trial to prevent HIV infection?" Predictors of WTP were determined only in the ER group at 6 and 12 mo (shown in Table 2) because too few of the CR participants were followed to permit analysis. Measurements at 18 and 24 mo could not be performed because we did not have enough follow-up visits to perform the analysis. Factors associated with willingness to participate at baseline in both ER and CR groups are described in Table 3.

HBV vaccine (three dose series) was offered to all susceptible participants. Information and materials for prevention of sexually and parenterally transmitted infections were supplied at all sites. Condoms were also provided and a workshop was held every three months to review HIV, STIs and sex education topics. HIV positive participants were scheduled and referred to the Hospital Clínic Barcelona for confirmatory testing, HIV care, treatment and follow-up.

Retention strategies and follow-up visits. HIV-1 seronegative women and transgenders at risk of HIV infection were invited to come back every 6 mo over a 24 mo period to repeat HIV-1 counseling, antibody testing and clinical visits. Contact tracing

information was collected for each participant in the first visit and every three months. At enrollment, participants from the ER and CR groups gave their name, mail and e-mail addresses, phone number (if available) and when possible, two additional phone contacts. At the end of each interview (baseline or first follow-up), they received project appointment cards displaying the day and time scheduled for the follow-up interview. The appointment cards also included the address and phone number of the Àmbit-Prevençió center office in case participants needed to contact the research staff. Several retention strategies were implemented in the ER group: (1) Contact visits were held every 3 mo to update contact information; (2) A reminder phone call was made to the participant, or her phone contacts when she did not have a phone, the day before the visit; (3) In the event that a participant was located in the field, the outreach worker attempted to bring the participant back to the office for her appointment; (4) Sending e-mails and short message service (sms) to thank responders for their participation and to remind them of their upcoming scheduled follow-up interview appointments. In a few cases, when the women were unable to visit the study site, visits were conducted at Hospital Clínic; (5) The participants in the ER group were compensated with 15€ at the 6-mo-study visit, and 30 € at the 12-mo study visit for the time invested and travel expenses. All these retention strategies were implemented till the 12-mo follow-up visit in the ER group; between the 12 and 18 mo follow-ups, no financial compensation was provided and only an appointment card was given to remind them of their visits. Between the 18 mo and 24 mo follow-up visits, no financial compensation was provided but the retention strategies described above were implemented in order to assess the effect of the financial incentives on retention rates.

Laboratory methods. Sera were tested for HIV-1 antibody by enzyme-linked immunosorbent assay (ELISA, Sanofi Diagnostic Pasteur). Positive or indeterminate samples were confirmed by Western Blot (New LAB- Blot 1, Sanofi Diagnostic Pasteur). Syphilis screening tests were performed with a rapid test (Determine) and confirmed by *Treponema pallidum* hemagglutination assay (TPHA). Hepatitis B virus surface antigen (HBsAg) and core antibodies (anti-HBc) as well as antibodies to hepatitis C virus (anti-HCV) were tested by ELISA. After blood

collection, all individuals were scheduled to return one week later to receive their serology results and post-test counseling.

Data analysis. At the baseline visit we calculated frequency and percentage of demographic characteristics, serologic testing and vaccination history, test results, drug and sexual risk behavior and willingness to participate in future HIV vaccine trials. Differences between the CR and ER groups were assessed using the Pearson Chi-square test and Fisher exact test for cell sizes of 5 or less. Visit retention rates were estimated as the number of participants who completed the visit within the required time window divided by the number of participants who were not HIV-infected before the visit. Study visits occurring between 120–299 d from baseline were counted as 6-mo visits, visits occurring 300–479 d from baseline were counted as 12-mo visits, visits occurring 480–659 d from baseline were counted as 18-mo visits, and visits during 660–719 d from baseline were counted as 24-mo visits. Differences in retention by demographic, drug and sexual risk behavior and willingness to participate in the ER group were assessed using the Pearson Chi-square test and Fisher exact test for cell sizes of 5 or less. Retention rates in both groups over time were assessed by the Cochran-Armitage test for trend.

A dichotomous outcome variable was created from the 4-category WTP responses comparing “Definitely willing” vs. “Probably willing,” “Probably not willing,” and “Definitely not willing.” Odds ratios and 95% confidence intervals for baseline willingness between CR and ER groups were calculated for demographic and risk characteristics using logistic regression models. Differences in baseline willingness between study groups were assessed by adding an interaction term for study group by characteristic in each model and considered significant if the p-value

was < 0.05. The proportion of subjects “willing to participate” in the ER group was calculated at the 6 and 12 mo visits and bivariate and multivariate predictors of WTP were determined using a repeated-measures regression model. Bivariate risk ratios of WTP were calculated for each demographic and risk characteristic. Risk ratios with a p-value of < 0.05 were entered into a multivariate model and retained if the adjusted risk ratio had a p-value of < 0.05. Analyses were performed using STATA 11.0 (STATA).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Author contributions

Conceived and designed the study: J.J. and F.E. Performed the study: J.J., F.E., E.M. and M.M. Analyzed the data: J.J., F.E., J.E., E.M. and J.M.G. Contributed materials/analysis tools: J.E., K.P. and E.S. Wrote the paper: J.J. and F.E.

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