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The HVTN503/Phambili HIV vaccine trial: a comparison of younger and older participants

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Abstract

By comparing younger to older participants enrolled in a HIV vaccine efficacy trial, we aimed to gain insights into the inclusion of adolescents in future trials. This was a sub-analysis of a

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Conflicts of Interest Declaration
Authors JEV, NAH, GJC, KM, MN, SPB, JGK, GEG and LGB have no conflicts to declare.
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multisite HIV vaccine randomized clinical trial in South Africa, conducted January-September, 2007. Motivations for trial enrollment, social harms, adverse events, and loss to follow-up were compared between younger (18-20 years old) and older participants (21-35 years old). Both younger (n=238) and older participants (n=563) were equally likely to report enrolling for altruistic reasons. Younger females were less likely than older participants to join for trial reimbursement (p=0.005), while younger males were more likely to enroll because the vaccine may provide protection from HIV-acquisition (p<0.001). There were no significant differences in the number of social harms reported. Compared to males over 20 years-old, 18-20-year-old females were less likely to experience adverse events (OR=0.1, CI 0.01-0.80) and no more likely to be lost to follow up (OR=0.7, CI 0.39-1.25), while 18-20-year-old males were no more likely to experience adverse events (OR=1.3, CI 0.58-2.83) or loss to follow-up (OR=0.8, CI 0.51-1.41). Our data support the inclusion of younger participants who are at risk for HIV in future HIV vaccine efficacy trials.

Keywords

HIV; vaccine trials; clinical trials; youth; South Africa

INTRODUCTION

HIV vaccines that prevent infection offer the greatest promise for ending the HIV epidemic,[1] yet to maximize effectiveness, young adolescents need to be vaccinated before they start to engage in the behaviors that place them at risk for HIV-acquisition. Vaccination at 18 years of age is too late for many young adults. In a large survey of nearly 12,000 young people (15-24 years) in South Africa, nearly half (48%) of the 15-19 year old survey respondents reported a history of vaginal or anal intercourse, with 17.5% of males and 7.8% of females reporting sexual debut before age 15.[2] As of 2010, 14% of 15-19 year old females visiting antenatal clinics in South Africa were HIV-infected.[3]

Vaccine safety profiles, immunogenicity, and efficacy may be different for children and adolescents younger than 18 years old than for those 18 and older.[4] As many countries require safety and immunogenicity data in children and adolescents prior to licensure of vaccines for this population, the failure to enroll participants younger than 18 in future HIV vaccine efficacy trials will ultimately delay vaccine introduction for this at-risk population.[5, 6] This delay may result in many potentially avoidable life-threatening infections. Reasons given for excluding adolescents from HIV vaccine trials include research regulations for the protection of vulnerable subjects, concerns regarding informed consent,[6-8] and the risk for social harms, adverse events, and loss to follow-up.[8] Notably, there are no data available from participants younger than 18 in HIV vaccine efficacy trials to directly assess motivations for trial enrollment, social harms, adverse events, and loss to follow-up.

Among the participants enrolled in HVTN 503/Phambili, a HIV vaccine efficacy trial in South Africa, more than one-third of the participants were younger than 21 years old.[9] These data provide a unique opportunity to explore whether 18-20 year olds differ from older participants in an HIV vaccine efficacy study regarding 1) motivations for enrollment, 2) social harms, 3) vaccine-related adverse events, and 4) loss to follow-up. We hypothesized that younger study participants would report similar motivations for enrolling in a HIV vaccine efficacy trial and would not be more likely to have adverse reactions, social harms, or be lost to follow-up when compared to older participants. While this study did not enroll participants under age 18, we aimed to provide insights into the potential safety and feasibility of including minors at risk for HIV infection in future HIV vaccine trials.

METHODS

Study Sample

Participants enrolled in HVTN 503/Phambili Study, a phase 2b test-of-concept vaccine trial of the MRKAd5 HIV-1 gag/pol/nef subtype B vaccine in South Africa, were included in the following analyses. This multisite South African study has been described in detail previously.[9] In brief, 801 predominantly heterosexual participants between the ages of 18-35 were enrolled and randomized to either vaccine (400 participants) or placebo (401 participants) from January 24th, 2007 to September 19th, 2007 at five South African sites (Soweto, Cape Town, Klerksdorp-Orkney-Stilfontein-Hartbeesfontein (KOSH), Durban, and Pretoria). Given the high HIV prevalence and incidence in South Africa, the only inclusion criterion was any reported sexual activity in the six months prior to study enrollment. Written informed consent was obtained from all study participants in either English or their local language. The trial was registered in clinicaltrials.gov (NCT00413725) and in South Africa (DOH-27-027). The study was approved by all relevant ethical review committees and institutional biosafety committees as previously described.[9] The trial was stopped prior to the 3000 participant target enrollment when interim analysis of the Step trial concluded that the vaccine was not going to demonstrate efficacy in reducing HIV-acquisition or early HIV viral.[10]

Measures

Our primary dependent variables were motivations for study enrollment, social harms, adverse events, and loss to follow-up. Patients were asked to rate several different potential motivations for trial enrollment on a 5-point Likert scale during their initial study visit (1=disagree strongly, 2=disagree, 3=neutral, 4=agree, 5=strongly agree), and mean values were calculated. Social harms and adverse events were assessed at all follow-up clinic visits after the baseline visit. Initially, follow-up study visits were scheduled every six months, but a protocol revision was obtained after the study was unblinded, and follow-up visits were changed to every 3-months. Participants were followed for 3.5 years after enrollment if they remained HIV-uninfected, or 18 months after diagnosis of HIV. Social harms included any negative experiences with family, friends, significant others, and sex partners, as well as problems with employment, education, travel, medical care, health insurance, life insurance, housing, or military service that may have resulted from participation in the trial. Participants were asked whether social harms resulted in a minimal, moderate, or major disturbance on quality of life. Participants were also asked to report any beneficial impacts from study participation. All adverse events that were deemed definitely, probably, or possibly related to the vaccine were included regardless of severity score. Participants were considered lost-to-follow-up if they exited the study prior to study closure because they refused further participation, relocated, could not be contacted, or died. Participants were also classified as lost to follow-up if the investigator determined the participant could no longer participate for safety reasons.

Demographic explanatory variables considered for analyses included age at study enrollment, gender, race/ethnicity, and study site. The young age group, 18-20 year olds, was chosen as the next age stratum above the age of minority in South Africa that represented a reasonable number of participants for statistical analyses. Consequently, to simultaneously assess the effect of both age and gender, four categorical variables were created: 18-20 year old females, 18-20 year old males, 21-35 year old females, and 21-35 year old males (the referent). Adenovirus 5 (Ad5) neutralizing antibody titers were included in our models because of their potential as a confounder of adverse events; serum Ad5 titers were obtained at the baseline study visit and made into a dichotomous variable (≤200 or >200).

Participants' perception of having received the vaccine or the placebo prior to unblinding was assessed post-hoc through an interviewer-administered questionnaire and was coded as a nominal categorical variable. Self-reported HIV risk behaviors in the last six months prior to study enrollment were also included in these analyses. Any unprotected vaginal intercourse, use of alcohol or drugs during sexual intercourse, casual or anonymous sexual partners, exchange sex, and self-reported history of sexually transmitted infections were made into dichotomous variables. Also using data from the six months prior to study enrollment, we calculated the mean number of days participants consumed more than five drinks/day and the mean number of sexual partners.

Statistical Methods

In gender-stratified contingency table analysis, comparisons between younger (18-20 years-old) and older participants (21-35 years-old) were assessed using Chi-square, Fisher's exact, and 2-sided t-tests. Differences in motivation for trial enrollment, stratified by age and gender, were measured using a generalized linear model for assessing the Likert scale mean scores. Data were reported as the adjusted least square means and the type III sums of square *P*-value. Post hoc Tukey-Kramer adjustments for multiple comparisons of means were performed to determine if particular pairs of values were significantly different from each other when the variables were categorized into three or more groups. Due to a small number or reported social harms, descriptive statistics and bivariate analyses were used to summarize the results. Multivariable logistic regression models evaluated the risk of adverse events and loss to follow-up using backward stepwise elimination until all predictors had a p-value of less than 0.10. Each candidate model was run separately to avoid excessive case-wise deletion of observations that had missing values on other unselected candidate predictors. When the final models were selected (one model for adverse events and one model for attrition), we retained those variables that were significant at the $P<0.05$ level and all other risk factors were added one at a time to determine the adjusted risk, 95% confidence interval, and p-values for that particular variable. To further explore the associations with age, we repeated the multivariable logistic regression models and separated out the 21-24 year olds from those 25 and older.

P values of <0.05 were used to determine statistical significance. No adjustments were made for multiple comparisons. Statistical analyses were performed using SAS® software version 9.3. [11]

RESULTS

Baseline demographic characteristics and main study outcomes are described in Table 1. Of the 801 participants enrolled in HVTN 503/Phambili, 238 participants (30%) were between 18-20-years-old at the time of enrollment. Most of the younger participants were male (n=139, 58%). Baseline adenovirus 5 antibody titers were similar between younger and older participants.

In bivariate analyses of risk behaviors in the six months prior to study enrollment, younger females reported a higher mean number of sexual partners than older female participants (1.3 vs. 1.1, p=0.001). Younger male participants were less likely than older participants to report any unprotected vaginal sex (45.7% vs. 63.5%, p<0.001) or to report a history of a sexually transmitted infection (2.9% vs. 7.6%, p=0.03) in the six months prior to study enrollment (Table 1). Five incident HIV infections were observed among 18-20 year old trial participants prior to turning 21 years old (1.8 per 100 person-years, 95% CI 0.6-4.2), and 57 incident infections were observed among participants 21 years old and older (4.7 per 100 person-years, 95% CI 3.5-6.0).

No differences were seen between younger and older participants in stratified bivariate analyses with regard to reported social harms. Of the nine social harms reported among the 18-20-year-olds in the study, only three resulted in either moderate or major disturbances in quality of life. Similarly, loss-to-follow-up did not differ between younger and older participants in bivariate analyses when stratified by age and gender. However, 18-20 year old female participants were less likely to report adverse events that were definitely, probably, or possibly related to the vaccine as compared to older female participants (1.0% vs. 8.5%, p=0.004), a difference not observed for younger and older males (7.9% vs. 7.3%, p=0.82) (Table 1).

Younger and older participants were equally likely to have enrolled in the vaccine trial for altruistic motivations such as the desire to help the community or to help find an effective vaccine (Table 2). Older participants were more likely than younger participants to have joined the trial because they know someone personally affected by HIV (p=0.02). Younger male participants were more likely than older male participants to agree that they joined the study because the vaccine may provide protection against HIV-acquisition (p<0.001), while younger female participants were less likely than older female participants to agree that they joined the vaccine trial for trial reimbursement (p=0.005).

In a multivariate model of adverse events, 18-20-year-old females were less likely to experience adverse events compared to 21-35 year old males (OR 0.1, 95% CI 0.01-0.80, p=0.03, Table 3). When age was categorized into 3 groups (18-20, 21-24, and 25-35 year olds), 18-20-year-old females were less likely to experience adverse events compared with 25-35 year old males (OR 0.11, 95% CI 0.01-0.88, p=0.04). Participants who reported joining the trial because of free counseling were also less likely to report adverse events (OR 0.7, 95% CI 0.43-0.99, p=0.05, Table 3).

No differences were seen between 18-20 year old participants and participants 21-35 years-old in a multivariate model of loss-to-follow-up (Table 3). Similar results were obtained when age was categorized into 3 groups: 18-20, 21-24, and 25-35 year olds (data not shown). In this model, participants who reported joining the trial for the free counseling provided were significantly less likely to be lost to follow-up (OR 0.7, 95% CI 0.52-0.97, p=0.03), while those who reported joining the trial because of the free HIV testing were significantly more likely to be lost to follow-up (OR 1.7, 95% CI 1.20-2.32, p=0.002).

DISCUSSION

In our analyses of participants enrolled in a large HIV vaccine trial in South Africa, 18-20 year-old females were less likely than 21-35 year-old males to report adverse events and no more likely to report social harms or to be lost to follow-up than older trial participants, while 18-20 year old males were no more likely to experience adverse events, social harms, or loss-to-follow-up when compared to 21-35 year-old males. Notably, the youngest females in this trial reported a greater number of sexual partners than older females, and more than 50% reported unprotected vaginal sex. Although close monitoring and safeguards will be needed to protect minors should they enroll in HIV vaccine trials, our data from 18-20 year old trial participants are reassuring. Given the high prevalence and incidence of HIV among individuals under 18 years old in many areas of the world, the timely inclusion of participants younger than 18 years old in HIV vaccine research is critical to prevent delays in vaccine licensure for this vulnerable population.

Despite concerns that younger participants may be motivated to join a vaccine trial for different reasons, 18-20 year old participants in HVTN 503/Phambili reported similar altruistic motivations for study enrollment as older participants. This is consistent with prior

research that has identified altruism as a primary reason for HIV vaccine trial participation.[1213] Furthermore, 18-20 year old females were actually less likely than older females and male participants to report trial reimbursement as a primary motivator, and 18-20 year old males were no more likely to report financial motivations for joining the trial as compared with older male and female participants. Prior studies of adolescents have similarly concluded that monetary incentives may be less important than altruism in recruiting and retaining adolescents in longitudinal research.[14, 15] This may serve to reassure those developing research regulations for the protection of vulnerable subjects that monetary incentives may not be an undue incentive to younger individuals' participation in clinical trials.

While 18-20 year olds were no more likely than 21-35 year olds to report they believed that they had been randomized to receive the vaccine as compared to the placebo, 18-20 year old males were more likely than older males and younger females to report joining the vaccine trial because they believed the vaccine may confer personal protection from HIV-acquisition. This suggests that younger males may not have fully understood the risks and benefits of trial enrollment during the informed consent process. This is consistent with prior research in South Africa that found both self-reported understanding and forced responses to check-list questions to be insufficient tools to accurately assess comprehension of challenging study concepts such as placebo and preventive misconception during the informed consent process.[16] Interactive strategies to ensure understanding should be part of all vaccine trials, especially those enrolling youth.

Our data also raise the concern that young men who believe that the study vaccine is protective may increase their risk behavior. In focus groups with 15-17 year-olds in the United States, participants expressed concern that some peers would stop using condoms if enrolled in a HIV vaccine trial.[17] Similarly, young South Africans (18-26 year old) participating in focus groups also worried that peers enrolled in vaccine trials may have increased risk for HIV acquisition because of behavioral disinhibition.[18] Only one study of 48 gay and bisexual men enrolled in two small HIV vaccine trials in the United States in the early 1990s suggested that risk behavior might increase among participants who hoped the vaccine provided protection from HIV acquisition.[19] In contrast, analyses from several large HIV vaccine efficacy trials, including HVTN 503, did not demonstrate an overall increase in HIV risk behaviors among trial participants.[20, 21] Despite these reassuring data, a certain subset of study participants may still increase their risk. In the VAX004 trial of the bivalent rgp120 vaccine conducted primarily in North America, increased rates of sexually transmitted infections were seen among participants seeking HIV testing outside of the study,[22] and men who have sex with men who were younger or believed they received the vaccine were more likely to report unprotected anal sex.[20] Ultimately, the informed consent process will need to emphasize the experimental nature of vaccine efficacy trials, especially if even younger male participants are enrolled.

Notably, previous vaccine efficacy trials for the prevention of sexually transmitted infections (STIs) other than HIV have successfully enrolled participants younger than 18 years old.[23, 24] While significant differences between HIV and Human Papilloma Virus (HPV) preclude a direct comparison, immunogenicity and safety studies for a HPV vaccine have included both males and females as young as 9 years old.[25] As a result of these studies, an HPV vaccine is now approved for both males and females between 9 and 26 years old.[26] In these HPV studies, retention was impressive; with strategies to minimize loss to follow-up such as parental education and involvement, reminder cards, and reimbursements for travel expenses if participants relocated during the trial, more than 90% of young adolescents enrolled in these trials completed all study follow-up.[25] Furthermore, despite

concerns regarding behavioral disinhibition, this has not been observed in follow-up studies after HPV vaccination.[27]

Several methodological limitations should be acknowledged when interpreting our study results. First, our trial only included 18-35 year olds who consented to participate in an HIV vaccine efficacy trial, and therefore our data may not be representative of 18-35 year olds more generally. Furthermore, although participants were recruited from geographically diverse sites throughout South Africa, differences likely exist between 18-35 year olds in different areas of the world. Extensive community outreach and preliminary research prior to initiating HVTN 503/Phamibli may have also minimized social harms, adverse events, and loss to follow-up, and this may further limit the generalizability of our findings to future vaccine efficacy trials. Second, in these analyses, it is possible that age and gender may have been confounded by other non-measured factors such as financial independence, family support, and living situation. Third, all behavioral data included in the models were obtained through self-report, and it is possible that younger study participants may differentially report their risk behaviors. Although efforts were made to elicit all types of social harms and adverse events, it is possible that there was also differential reporting of these outcomes between younger and older participants or between male and female participants because of varying susceptibility to social desirability bias. Despite these concerns, the greater number of sexual partners reported among younger as compared to older women suggests that younger women were comfortable disclosing personal information during the study. In addition, although loss-to-follow up did not vary by age in our analyses, it may have resulted in an underreporting of social harms and adverse events.

Our data do not address many of the potential challenges with enrolling adolescents into HIV vaccine efficacy trials. To successfully enroll adolescents younger than 18 years old into future studies, efforts will be needed to mitigate the potential impact of peer pressure on enrollment,[28] to confirm that participants fully comprehend the risks and benefits of participation, to obtain informed consent from parents while also protecting the privacy of adolescent participants, and to address concerns regarding possible behavioral disinhibition.[29] Moreover, future trial design will need to address that the age of independent consent varies by country, and sometimes even between different regions of the same country.[30] As no HIV vaccine trials to date have enrolled minors, we have used data from 18-20 year old trial participants to make inferences about the possible experiences of younger adolescents should they be included in future vaccine trials. Despite our findings, it is possible that participants younger than 18 may be more susceptible to adverse outcomes during trial participation. However, the only way to assess this question directly will be to include minors in future efficacy trials. Fortunately, results from adolescent HIV vaccine preparedness trials have also been encouraging. A cohort of HIV-uninfected, 14-17 year old adolescents from Cape Town, South Africa was successfully recruited into a longitudinal HIV vaccine trial preparedness study with retention rates of more than 80%.[31]

Individuals younger than 18 in South Africa have demonstrated a willingness to participate in future HIV vaccine research.[15, 32] In fact, 73% of males and 77% of females in a survey of 16-18 year olds in Soweto, South Africa reported that they still would be willing to participate in future HIV vaccine trials even after learning about this prematurely halted HVTN 503/Phambili study.[33] Our data provide indirect support for the possible inclusion of younger participants in future HIV vaccine trials. The safe and timely inclusion of participants less than 18 years old in future HIV vaccine trials should be a global research priority.

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Table 1

Participant characteristics stratified by age and sex among the 801 participants enrolled in HVTN 503/Phambili, 2007.

	Females 18-20 (n=99) %	Females 21-35 (n=261) %	p-value	Males 18-20 (n=139) %	Males 21-35 (n=302) %	p-value	Overall p-value 18-20 vs. 21-35
Race			0.42			0.22	0.28
Black	99.0	98.8		100.0	98.7		
Other	1.0	1.2		0	1.3		
Study site			0.31			<0.001	<0.001
Soweto	40.6	40.2		47.5	31.5		
Cape Town	25.7	29.0		4.3	20.5		
KOSH	26.7	19.3		37.4	29.8		
CAPRISA	5.9	7.0		4.3	7.6		
Medunsa	1.0	4.6		6.5	10.6		
Adenovirus 5 titer			0.15			0.64	0.56
<200	37.6	46.0		46.8	44.4		
>200	63.4	54.0		53.2	55.6		
Risk behaviors in previous 6 months:							
Number of sexual partners (MEAN)	1.3	1.1	0.001	2.5	2.2	0.21	0.05
Unprotected vaginal sex (YES VS. NO)	50.5	57.1	0.25	45.7	63.5	<0.001	<0.001
Drinking or drugs with sex (YES VS. NO)	13.9	10.0	0.30	35.3	41.4	0.22	0.58
Casual or anonymous partner (YES VS. NO)	13.9	10.0	0.30	48.2	47.0	0.82	0.48
Exchanged sex for money or gifts (YES VS. NO)	1.0	1.2	0.42	7.2	4.6	0.27	0.33
Sexually transmitted infection (self report) (YES VS. NO)	3.0	6.2	0.11	2.9	7.6	0.03	0.02
Heavy drinking (>5 drinks/day) (MEAN NUMBER OF DAYS)	1.4	1.4	0.99	6.5	7.0	0.71	0.71
Believe vaccine is:			0.86			0.87	0.97
Very effective	5.9	5.0		7.2	7.0		
Somewhat effective	19.8	17.8		19.4	22.9		
Not effective	2.0	1.5		2.2	2.0		
I don't know	72.3	75.7		71.2	68.2		

	Females 18-20 (n=99) %	Females 21-35 (n=261) %	p-value	Males 18-20 (n=139) %	Males 21-35 (n=302) %	p-value	Overall p-value 18-20 vs. 21-35
Prior to unblinding, I think I received:			0.97			0.07	0.28
Vaccine	31.5	32.9		51.6	42.2		
Placebo	19.1	19.0		20.5	17.5		
I don't know	49.4	48.2		27.9	40.2		
Participation in trial had beneficial impact on life	69.0	67.7	0.92	83.8	72.7	0.04	0.14
Social harm from study involvement:			0.50			0.22	0.20
Minimal disturbance	5.0	8.4		0.7	3.1		
Moderate/Major disturbance	2.0	1.2		0.7	2.0		
Loss to follow-up during study	21.2	19.8	0.76	22.6	28.3	0.21	0.43
Adverse event:							
Related to study product	1.0	8.5	0.004	7.9	7.3	0.82	0.14

Table 2

Generalized linear model of participant motivations for joining HVTN 503/Phambili among the 801 participants enrolled in HVTN 503/Phambili, 2007.

	Mean Likert Score*	p-value
To find a vaccine that works		
Female 18-20	4.52	
Male 18-20	4.37	0.35
Female 21-35	4.43	
Male 21-35	4.44	
To help community		
Female 18-20	4.41	
Male 18-20	4.27	0.22
Female 21-35	4.24	
Male 21-35	4.33	
Free HIV tests		
Female 18-20	4.37	
Male 18-20	4.24	0.15
Female 21-35	4.37	
Male 21-35	4.26	
To be informed about HIV research		
Female 18-20	4.34	
Male 18-20	4.23	0.48
Female 21-35	4.22	
Male 21-35	4.26	
Free counseling		
Female 18-20	4.22	
Male 18-20	4.16	0.95
Female 21-35	4.17	
Male 21-35	4.18	
Know someone with HIV		
Female 18-20	3.44	
Male 18-20	3.16	0.02
Female 21-35	3.58	
Male 21-35	3.34	
Vaccine may protect me from HIV		
Female 18-20	2.79	
Male 18-20	3.46	<0.001
Female 21-35	3.16	
Male 21-35	3.06	

	Mean Likert Score*	p-value
To get paid		
Female 18-20	1.87	
Male 18-20	2.22	0.005
Female 21-35	2.29	
Male 21-35	2.21	

*(1=disagree strongly, 2=disagree, 3=neutral, 4=agree, 5=strongly agree).

Table 3

Adjusted logistic regression analyses for adverse events and loss-to-follow-up among the 801 participants enrolled in HVTN 503/Phambili, 2007.[a]

INDEPENDENT VARIABLE	*ADVERSE EVENTS*		*LOSS-TO-FOLLOW-UP*	
	OR (95% CI)	***p-value***	**OR (95% CI)**	***p-value***
Age and gender				
18-20 year-old females	**0.1 (0.01-0.80)**	**0.03**	0.7 (0.39-1.25)	0.23
18-20 year-old males	1.3 (0.58-2.83)	0.54	0.8 (0.51-1.41)	0.52
21-35 year-old females	1.0 (0.52-1.85)	0.95	0.7 (0.44-1.03)	0.07
21-35 year-old males (reference)	1.0		1.0	
Adenovirus 5 titer				
> 200	1.6 (0.87-2.77)	0.14	0.9 (0.60-1.21)	0.36
≤ 200 (reference)	1.0		1.0	
Risk behaviors in previous 6 months				
Mean number of sexual partners	1.1 (0.88-1.27)	0.54	1.0 (0.85-1.08)	0.50
Unprotected vaginal sex (yes vs. no)	1.0 (0.58-1.85)	0.90	0.9 (0.60-1.21)	0.37
Exchanged sex for money or gifts (yes vs. no)	0.5 (0.13-1.86)	0.29	0.5 (0.19-1.13)	0.09
Sexually transmitted infection (self-report; yes vs. no)	1.6 (0.46-5.54)	0.47	0.8 (0.36-1.84)	0.62
Mean number of days with heavy drinking (>5 drinks/day)	1.0 (0.97-1.03)	0.84	1.0 (0.96-1.01)	0.14
Prior to unblinding, I think I received:				
Vaccine	1.0 (0.41-2.39)	0.98	1.5 (0.80-2.88)	0.20
I don't know	1.1 (0.45-2.57)	0.87	1.3 (0.68-2.47)	0.43
Placebo (reference)	1.0		1.0	
Social Harms				
Minimal disturbance	0.9 (0.27-3.34)	0.93	1.1 (0.44-3.00)	0.78
Moderate or major disturbance	1.4 (0.17-11.72)	0.75	1.4 (0.36-5.56)	0.63
No social harms reported (reference)	1.0		1.0	
Reasons for enrolling in vaccine trial[b]				
To find a vaccine that works	0.8 (0.46-1.37)	0.40	1.2 (0.88-1.69)	0.23
To help community	1.3 (0.88-1.90)	0.20	0.9 (0.70-1.23)	0.61
Free HIV tests	1.5 (0.77-2.90)	0.24	**1.7 (1.20-2.32)**	**0.002**
To be informed about HIV research	1.3 (0.85-2.00)	0.23	1.1 (0.81-1.44)	0.60
Free counseling	**0.7 (0.43-0.99)**	**0.05**	**0.7 (0.52-0.97)**	**0.03**
Know someone with HIV	1.1 (0.86-1.36)	0.52	1.0 (0.91-1.18)	0.62
To receive other tests or medical care	0.9 (0.51-1.43)	0.55	1.0 (0.76-1.31)	0.99
To help me to avoid high-risk behavior	1.0 (0.61-1.58)	0.94	1.1 (0.83-1.42)	0.55
Vaccine may protect me from HIV	0.9 (0.70-1.22)	0.58	0.9 (0.74-1.01)	0.07
To get paid	0.9 (0.66-1.20)	0.45	1.2 (0.96-1.39)	0.13

[a] Adverse event model adjusted for age and gender, study site, and free counseling. Loss to study follow-up model adjusted for age and gender, study site, free HIV tests, and free counseling.

[b] Reasons for enrolling in the vaccine trial were scored on a five point Likert scale.