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Risk Behavior among Women enrolled in a Randomized Controlled Efficacy Trial of an Adenoviral Vector Vaccine to Prevent HIV Acquisition: the Step Study

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Abstract

Objectives—Report of risk behavior, HIV incidence, and pregnancy rates among women participating in the Step Study, a phase IIB trial of MRKAd5 HIV-1 gag/pol/nef vaccine in HIV-negative individuals who were at high risk of HIV-1.

Design—Prospective multicenter, double-blinded, placebo-controlled trial

Methods—Women were from North American (NA) and Caribbean and South America (CSA) sites. Risk behavior was collected at screening and 6-month intervals. Differences in characteristics between groups were tested with Chi-square, two-sided Fisher's exact tests, and Wilcoxon rank sum tests. Generalized estimating equation models were used to assess behavioral change.

Results—Among 1134 enrolled women, the median number of male partners was 18; 73.8% reported unprotected vaginal sex, 15.9% unprotected anal sex and 10.8% evidence of a sexually

transmitted infection in the 6 months prior to baseline. With 3344 person-years (p-y) of follow up, there were 15 incident HIV infections: incidence rate was 0.45 per 100/p-y (95% CI 0.25, 0.74). Crack cocaine use in both regions (relative risk [RR]=2.4 [1.7,3.3]) and in CSA, unprotected anal sex (RR=6.4 [3.8, 10.7]) and drug use (RR=4.1 [2.1, 8.0]) were baseline risk behaviors associated with HIV acquisition. There was a marked reduction in risk behaviors after study enrollment with some recurrence in unprotected vaginal sex. Of 963 non-sterilized women, 304 (31.6%) became pregnant.

Conclusions—Crack cocaine use and unprotected anal sex are important risk criteria to identify high-risk women for HIV efficacy trials. Pregnancy during the trial was a common occurrence and needs to be considered in trial planning for prevention trials in women.

Introduction

As with other sexually transmitted infections (STIs), infection with HIV is intimately linked to risk behavior, and efforts to prevent acquisition of HIV largely involve alterations in behavior. This may include direct efforts to alter or refrain from risk-taking, or the incorporation of some strategy or product into one's sexual practices to reduce acquisition risk. Studies of HIV preventive vaccines or other prevention strategies often rely on recruitment of high-risk participants with measureable HIV incidence in order to be able to assess the efficacy of the intervention. Participation in such trials also exposes participants to frequent risk reduction messages, which are very effective in at least transiently reducing risk behavior [1, 2]. The relatively low incidence of HIV acquisition among heterosexually at risk women in the Americas makes studies of HIV prevention strategies such as a preventive vaccine challenging, and several studies have sought to better define risk behaviors associated with HIV acquisition in such women to help guide future recruitment efforts for such studies. Heterosexual transmission of HIV has been associated with non-injection drug use [3], which has in turn been associated with high risk behaviors [4], and with proximate infection with an STI in some studies [5, 6] while others failed to make such an association [7]. Pregnancy, itself a marker for unprotected sexual contact has been shown to be associated with HIV acquisition [7–9].

The current report describes risk behavior, HIV incidence, and pregnancy rates among women participating in the Step Study, a multicenter, double-blinded, randomized, placebo-controlled, phase IIB test-of-concept study of the MRKAd5 HIV-1 gag/pol/nef vaccine in HIV-1 negative individuals who were at high risk of HIV-1 acquisition. HIV incidence was too low among women participating in the Step Study to assess vaccine efficacy, the analysis of which was therefore restricted to men [10, 11]. Baseline risk behaviors in both men and women by treatment arm and adenovirus-05 (Ad5) status have been previously reported [10], as has an analysis of male risk behavior on study outcome [12]. The current analysis of risk behavior among women participants will address the effects of the trial on risk behavior change, and provide some insight into the factors influencing the observed HIV incidence.

Methods

The Step Study was a multicenter, double-blinded, randomized, placebo-controlled phase IIB test-of-concept study of three doses of the MRKAd5 HIV-1 gag/pol/nef vaccine in HIV-1 negative individuals at high risk of HIV-1 acquisition. Women were enrolled from April 2005 to March 2007. The intervention was stopped early in September 2007 for futility to show efficacy [10]. Exploratory analyses raised concerns regarding possible increased risk of HIV acquisition among male vaccinees who were uncircumcised and/or Ad5 seropositive at baseline. Because of this increased risk, participants were informed of

the study results, their treatment assignment and Ad5 serostatus beginning in mid-October 2007. Women who did not become HIV infected were followed on a 6-month visit schedule for a maximum of four years or until roll-over into a follow-up study beginning in March 2009 (Figure 1).

The study eligibility and procedures are described elsewhere[10]. Women were 18–45 years of age, HIV-1 seronegative, and at high risk of HIV-1 acquisition based on self reported risk behavior in the 6 months prior to enrollment of 1) unprotected vaginal or anal intercourse with an HIV positive man or an injection drug user (IDU); 2) exchanging sex for money, drugs, services, or gifts, or 3) using crack cocaine 3 times. Women from Caribbean sites were also included if they reported a diagnosis of syphilis or pelvic inflammatory disease within the previous 6 months. Women who were pregnant at screening were excluded, and women of childbearing potential needed to agree to use a protocol-specified effective method of contraception for at least 30 weeks after enrollment.

Vaccinations were administered at enrollment (week 0), weeks 4 and 26. Pregnancy and HIV testing, including personalized risk reduction counseling, took place at screening, weeks 0, 4, 12, and 26, and at 6-month intervals thereafter. A standardized risk behavior questionnaire was administered by trained staff at screening and at 6-month intervals after enrollment. Women were asked about the number of sexual partners they had (total and by HIV serostatus), types of sex by partner serostatus (as yes-no questions), exchange of sex for money, drugs or services, drug use, and evidence of STIs in the prior 6 months and their current method of contraception (also assessed at enrollment). Pregnancy history prior to enrollment and details on the duration of use of specific contraceptive methods were not collected.

Participants provided written informed consent and the protocol was approved by the ethics committee for each site.

Statistical methods

Because of the differences between the cohorts enrolled in the Caribbean and South America (CSA) and North America (NA), most analyses were done by region. Differences in demographics and risk behaviors between groups were tested with Chi-square, two-sided Fisher's exact tests, and for continuous data Wilcoxon rank sum tests. Score tests from generalized estimating equation (GEE) models were used to assess changes in behaviors over time, while controlling for age and race. Since knowledge of study results and treatment assignment may have influenced behavior change, behavioral data were truncated at mid-October 2007 (participant unblinding). P-values <0.05 were considered statistically significant.

For calculation of HIV incidence rates, the date of infection was estimated as the midpoint between the dates of the last negative HIV test and first positive test. Person-years were measured from first vaccination to estimated infection date for HIV infected women, or last HIV test date for non-infected women. Because of the small number of HIV infections observed, Fisher's exact tests were used to test for associations between demographic and baseline risk behaviors and HIV infection, with relative risk estimates from the 2-by-2 tables presented. Non-dichotomized variables were dichotomized for statistical testing as age 28 vs. >28 years, black vs. other race/ethnicity, number of partners <20 vs. 20, and number of HIV positive partners as 0 vs. any.

For calculation of pregnancy rates, the date of conception was estimated as 14 days after the last menstrual period date. Person-years for pregnancy incidence were calculated as the time between enrollment and last study visit, subtracting the pregnancy duration for women who

became pregnant. Women who at enrollment reported being surgically sterilized were not considered in pregnancy analyses. Women were considered as completing follow-up if they completed scheduled visits or became HIV infected.

Multivariable Cox proportional hazards models were used to assess demographic and baseline risk behaviors as predictors of time to first on-study pregnancy and time to study drop-out. Potential predictors examined were: treatment arm, site, age (in quartiles), race/ethnicity (black vs. other), number of male partners, HIV positive male partner, exchange of sex, unprotected vaginal sex (UVS), unprotected anal sex (UAS), oral sex, evidence of a STI, any recreational drug use, IDU, and crack cocaine use. In addition, for pregnancy we assessed birth control method used at enrollment (oral contraceptives, implants/injectables, condoms). For study drop-out we also assessed the time dependent variable of before or after mid-October 2007 when participants were informed of the trial results. Predictors were identified using an all-subsets model selection approach ranked by Akaike's information criterion (AIC). Final models presented contain only the statistically significant predictors identified from the AIC best-fit models.

Results

Demographics

Because the women enrolled in the study came from various sites throughout the Caribbean and South America (CSA) as well as from large urban North American (NA) cities, demographics including racial/ethnic diversity, as well as risk behaviors in the 6 months prior to screening (baseline), differ markedly by region (Table 1). The majority of the women were sex workers or reported exchanging sex for drugs, money or services. The median number of male sexual partners was 18 (CSA=8, NA=32, $P<0.001$). Overall, 73.8% of participants reported UVS, 15.9% reported UAS and 10.8% of participants reported evidence of a STI in the prior 6 months. NA women had significantly more UVS, UAS, oral sex, and reported more chlamydia and gonorrhea than CSA women. Sexual partners were mostly men with unknown HIV status, although 6.3% in CSA and 7.1% in NA reported HIV-positive partners. Drug use was much more prevalent among NA women (95.3% vs 14.5% in CSA women) and crack cocaine use in particular (59.8% in NA vs 8.4% in CSA). In CSA, crack use was reported only in Puerto Rico (PR) (45/54 women) and the Dominican Republic (DR) (7/173).

Risk Behavior at baseline and HIV Acquisition—With 3344 person-years (p-y) of follow up, there were a total of 15 incident HIV infections. The overall incidence rate was 0.45 per 100/p-y (95% CI 0.25, 0.74); for CSA, 0.38 (95% CI 0.15, 0.78, 7 infections); and for NA, 0.53 (95% CI 0.23, 1.05, 8 infections). In CSA sites, there were three infections in PR, two in Haiti, one in DR, and one in Peru. In NA, Philadelphia had four, Chicago two, New York one, and Newark one. There were seven infections in the vaccine arm and eight in the placebo arm. Only one woman from PR was diagnosed prior to study unblinding, which was the only infection occurring within the first year of follow-up. The timing of infections was: 1 in 0–1 years; 6 in >1–2 years; and 8 in >2–3 years.

Use of crack cocaine was the only baseline risk behavior predictive of HIV infection in both regions (RR=2.4, 95% CI [1.7, 3.3] for both regions combined). Three CSA infected women, all from PR, and all 8 infected women from NA reported use of crack at baseline; three of the NA women reported cessation of crack use after enrollment. There were regional differences in other baseline risk behaviors associated with HIV infection. In CSA, UAS (RR=6.4, [3.8, 10.7]), UAS with an HIV unknown status partner (RR=7.0 [4.1, 11.7] $P<0.001$), any drug use (RR=4.1 [2.1, 8.0]) and IDU (RR=10.3 [2.9, 36.2]), and for NA, UVS with a HIV positive partner (RR=5.9 [1.7, 21.1]) were also positively associated

with HIV infection. Age, race, number of sexual partners, and exchange of sex were not significantly associated with infection.

Risk behavior change—Limiting the risk behavior data to assessments prior to unblinding resulted in only 31% of the cohort having data from the 18 month assessment. Therefore, we used data from the screening (N=622 CSA/512 NA), six month (N=542/412), and 12 month reports (N=411/353) to assess behavioral change in report of more than 20 partners, UVS, UAS, exchange of sex, and crack use. Besides truncation of data at unblinding, missing data were due to study drop-out and missed visits. Since no differences in risk behaviors between treatment arms were observed at these time points, data for the two arms were combined.

Overall, there was a marked reduction in self-reported risk behaviors after enrollment for both the CSA and NA cohorts, with the largest decreases seen between the screening and 6 month visit assessment (Figure 2). For CSA women, there was a significant decline in self-reported risk behaviors between the screening visit and month 6 assessments (all p-values from GEE models <0.001, except for crack cocaine use P=0.002). For exchange of sex, there continued to be a significant decline between 6 and 12 months (P<0.001). After the initial decline, an increase in UVS was seen after the 6 month visit, although still below the baseline level at 12 months. The NA cohort also had significant declines in risk behaviors between screening and 6 months (p-values <0.001), and significant decline between 6 and 12 months for > 20 partners (P=0.006), exchange of sex (P<0.001) and crack use (P<0.001).

Contraceptive use and Pregnancy

At enrollment, the most commonly reported birth control method was condom use only (58.9% of NA and 39.1% of CSA women) followed by surgical sterilization (17.2% of NA and 13.4% of CSA women) and injectable/implant birth control method with or without condoms (NA 16.0% and CSA 24.6%). Of note, 3 of the 15 women who became HIV-infected during the trial were using injectable progesterone for contraception at the time they were diagnosed with HIV. The number of HIV infections in the trial was too small to determine if there was an association between type of contraception and acquisition risk.

Of the 1,134 women enrolled, 963 reported not being surgically sterilized at enrollment and among them, 304 (31.6%) became pregnant during the study with a total of 417 pregnancies (Table 2). The rate of all pregnancies for women in the study was 14.4 pregnancies/100p-y (95% CI 13.0, 15.8). More CSA than NA non-sterilized women became pregnant (33.8% CSA vs. 28.8% NA). The majority of the pregnancies in both groups of women (80.1%) occurred after the 3rd vaccination and 31.7% occurred >24 months into the study (Table 2). Seventy-seven women had a total of 83 pregnancies during the vaccination period, of which 25 had an early termination of the pregnancy and completed the vaccination series. Among all enrolled women, 4.6% (52/1134) became pregnant and did not complete the vaccination series.

In multivariable Cox proportional hazard models, younger women from both regions were more likely to become pregnant, but risk behaviors other than number of partners and evidence of a STI among NA women were not significant (Table 3). The median age for women who became pregnant was 24 years in CSA and 22 years in NA, compared to 28 years in CSA and 31 years in NA for non-sterile women who had no pregnancies. In NA, the median number of partners reported at screening was 157 for women who became pregnant and 26 for those who did not. In the CSA cohort, Haitian women were more likely to become pregnant than women from other sites. For unclear reasons, women who received vaccine were more likely to become pregnant than placebo recipients.

Retention

The retention rate was 85.6% overall (971/1134; 95% CI 83.6%, 87.7%), 79.9% in NA (409/512; 95% CI 76.4%, 83.4%), and 90.4% in CSA (562/622; 95% CI 88.0%, 92.7%). The difference by region was statistically significant ($p<0.0001$). Although Haiti had above average retention (92.6%), more women receiving the vaccine dropped out (12.6%) than women receiving placebo (2.1%, $p=0.001$). This was not observed at other sites. No other significant predictors of drop-out were identified for the CSA. For NA women, being of ages 29–36 (HR 2.0, 95% CI 1.3, 3.2; $p=0.002$), or having UAS (HR 1.6, 95% CI 1.0, 2.5; $p=0.03$) were predictive of drop-out. Among NA women, using recreational drugs was associated with better retention (HR 0.4, 95% CI 0.2, 0.9; $p=0.02$). The time dependent variable of being informed of trial results was not significant for either region.

Discussion

The Step Study focused on both high-risk women and high-risk MSM as target populations, and enrolled over 1100 women. However, the low observed incidence of HIV for women made analysis of vaccine efficacy among women impossible. One goal of this analysis was to understand which, if any, of the risk criteria used for screening might be predictive of HIV incidence, with the intent of improving selection criteria for future trials. While the number of incident infections was small, the analysis did yield some useful predictors. Drug use, and in particular, crack cocaine use correlated with HIV incidence, as did UAS in the CSA region. Failure to show an association with exchange of sex for drugs, money or services, a risk behavior that often accompanies crack use, may have been because exchange of sex was a selection criterion for study entry, reported by the majority (90%) of women. Crack cocaine use is well established to be associated with high-risk sexual behavior in women as well as with higher HIV prevalence [3, 13, 14]. Use of crack was therefore selected as an inclusion criterion for the trial, and a high incidence of crack use was expected. Crack use has been shown to be an independent predictor of HIV incidence among injection drug users [10, 15], and prior studies have associated non-injection drug use, including crack, with incident HIV infections among heterosexually at-risk women [7, 16], supporting continued selection of crack use as an inclusion criterion for HIV prevention research in women, and a behavior to target as a means of reducing HIV risk.

An association of UAS with HIV incidence in women observed in a prior study [7], was observed in the CSA cohort as well. In prior studies of risk behavior, UAS was associated both with crack use and Latina ethnicity as well as in women who exchanged sex for money or services, consistent with the current study [17, 18]. Anal sex was thought to substitute for lack of access to contraception, particularly in younger women [17]. which we are unable to assess since data were not collected on access to contraception.

Women participating in the Step Study reported a marked reduction in risk taking behavior while in the study. This was observed at the first follow up behavioral survey taken 6 months into the trial. There was a trend toward increasing UVS between 6 and 12 months , although never reaching the reported levels at baseline. A similar return to risk-taking behavior was reported during the Vax004 trial among women participants[1]. Frequent visits and contact with study staff, regular risk-reduction counseling, and referral to services such as drug treatment were all thought to influence behavior change in the study, as has been reported elsewhere[19, 20]. Repeated screening for HIV has been reported to have little impact on change in risk behavior, and it is unclear if it contributed to the observed change in this study[21]. However, other routine interventions that occurred at each study visit, including risk reduction counseling and free access to condoms, have demonstrated success in reducing risk behavior[22–25]. Reduction in risk behavior has not clearly been associated

with reduced HIV acquisition, although there was a trend towards reduced HIV incidence associated with increased condom use in HPTN 039 [23].

The reported reduction in risk behavior may have resulted in increased condom use, but did not translate into a reduction in pregnancies. In fact, the high rate of pregnancies in this study threatened to interfere with adherence to the vaccination schedule. The number of partners was strongly associated with pregnancy in the NA cohort, but did not hold true for the CSA cohort. Published studies indicate more consistent condom use occurs with non-primary partners [26, 27]. A limitation of the current study was not asking sexual risk questions with regard to type of partner.

Since pregnancy may adversely affect compliance with a vaccine regimen, eligibility criteria regarding birth control and provision of pregnancy counseling, condoms and ideally other forms of birth control on-site are important aspects of trial conduct. In the Phambili HIV vaccine trial women had to agree to use a hormonal and barrier contraception method until 1 month after the last vaccination and the study pregnancy rate was at the low end of the range observed in other HIV prevention trials [28]. The study also found that women enrolled at sites providing contraception on-site to be at lower risk of pregnancy. For future prevention trials in women at risk of HIV acquisition through heterosexual contact, and particularly with sex workers, when possible the effect of pregnancy in sample size calculations should be considered. For HIV vaccine trials, this would require good estimates of the timing of pregnancies from a previous trial in a similar cohort and assumptions regarding the impact of missing a specific vaccine time point on vaccine efficacy (for example, missing 1 DNA in a 3 DNA regimen might not be as important as missing a protein boost) .

Retention overall was consistent with US vaccine preparedness and vaccine studies of heterosexually at-risk women in the US and adequate for a study of this marginalized population [1, 16]. The protective effect of recreational drug use on retention may be the result of the financial compensation provided for adherence to study visits. In focus groups of study participants, cash stipends were the primary reason for initiating study participation, although altruism later becomes a motive to continue in the study (data not shown). There is no clear explanation for the lower retention observed among Haitian women who received vaccine, although a higher frequency of pain at the injection site was observed in vaccine recipients compared to placebo[10].

In conclusion, while the participation of women in the STEP Study did not contribute to answering the study question, this analysis of risk behaviors and associated incidence of HIV acquisition may help inform selection criteria for future prevention studies among women in the Americas, as well as identify at-risk women for prevention interventions. The high frequency of pregnancies in this study points to the importance of including consideration of pregnancy rates in sample size calculations in prevention research among women at risk of HIV acquisition through sexual contact. While the interventions that are included as part of the research effort appear to be highly effective in reducing risk behavior among women participants in vaccine trials in the western hemisphere, which is a laudable achievement, a consequence of this success may be an inability to assess vaccine efficacy in these women.

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Figure 1.
Study Timeline

Figure 2. Percentage of women self-reporting five risk behaviors from study entry until month 12 of follow up by region.

Table 1

Demographics and risk behaviors reported at Screening

	Caribbean/ South America	North America	Total	p-value ^a
Total Enrolled	622	512	1134	
Age				
Median	27	29	28	
25th, 75th %tile	23, 34	21, 39	22, 36	
Race/ethnicity				
Black	297/622 (47.7%)	407/512 (79.5%)	704/1134 (62.1%)	
Hispanic	227/622 (36.5%)	37/512 (7.2%)	264/1134 (23.3%)	
Mestiza	80/622 (12.9%)	0/512 (0.0%)	80/1134 (7.1%)	
Multiracial	10/622 (1.6%)	3/512 (0.6%)	13/1134 (1.1%)	
White	8/622 (1.3%)	46/512 (9.0%)	54/1134 (4.8%)	
Other	0/622 (0.0%)	19/512 (3.7%)	19/1134 (1.7%)	
Number of male sexual partners				<0.001
Median	8	32	18	
25th, 75th %tile	2, 300	5, 235	3, 261	
HIV-positive male partner(s)	39/621 (6.3%)	36/510 (7.1%)	75/1131 (6.6%)	
Male partners with unknown status				0.01
Median	8	32	15	
25th, 75th %tile	2, 300	3, 220	2, 244	
Partner pattern				<0.001
Only HIV+ partner(s)	32/621 (5.2%)	10/510 (2.0%)	42/1131 (3.7%)	
HIV+ and other partner(s)	7/621 (1.1%)	26/510 (5.1%)	33/1131 (2.9%)	
Only HIV- partner(s)	22/621 (3.5%)	46/510 (9.0%)	68/1131 (6.0%)	
Only < 20 HIV unknown status	256/621 (41.2%)	105/510 (20.6%)	361/1131 (31.9%)	
Only ≥ 20 HIV unknown status	244/621 (39.3%)	171/510 (33.5%)	415/1131 (36.7%)	
< 20 HIV unknown + some HIV-	40/621 (6.4%)	40/510 (7.8%)	80/1131 (7.1%)	
≥ 20 HIV unknown + some HIV-	19/621 (3.1%)	107/510 (21.0%)	126/1131 (11.1%)	
Exchange of sex	569/622 (91.5%)	447/509 (87.8%)	1016/1131 (89.8%)	0.048
Unprotected vaginal/anal sex	395/620 (63.7%)	442/507 (87.2%)	837/1127 (74.3%)	<0.001
Unprotected vaginal sex	392/621 (63.1%)	440/507 (86.8%)	832/1128 (73.8%)	<0.001
Unprotected anal sex	74/621 (11.9%)	105/507 (20.7%)	179/1128 (15.9%)	<0.001
Oral sex	271/618 (43.9%)	399/509 (78.4%)	670/1127 (59.4%)	<0.001
Any evidence of STD	75/622 (12.1%)	47/512 (9.2%)	122/1134 (10.8%)	
Chlamydia	7/615 (1.1%)	19/508 (3.7%)	26/1123 (2.3%)	0.005
Gonorrhea	5/615 (0.8%)	13/508 (2.6%)	18/1123 (1.6%)	0.03
Syphilis	42/618 (6.8%)	0/507 (0.0%)	42/1125 (3.7%)	<0.001
Other STD	27/619 (4.4%)	22/510 (4.3%)	49/1129 (4.3%)	
Any drug use	90/622 (14.5%)	488/512 (95.3%)	578/1134 (51.0%)	<0.001
Injection drug use	19/617 (3.1%)	72/505 (14.3%)	91/1122 (8.1%)	<0.001
Crack cocaine	52/618 (8.4%)	302/505 (59.8%)	354/1123 (31.5%)	<0.001

	Caribbean/ South America	North America	Total	p-value ^a
Speed	8/617 (1.3%)	10/504 (2.0%)	18/1121 (1.6%)	
Other drug use	48/622 (7.7%)	399/512 (77.9%)	447/1134 (39.4%)	<0.001

^a P-values are from Chi-square test, two-sided Fisher's exact tests for yes/no variables, or from Wilcoxon rank sum tests for continuous data.

Table 2**Pregnancies by Region**

	Caribbean/ South America	North America	Total
Women enrolled	622	512	1134
Not surgically sterilized	539	424	963
Women who became pregnant	182	122	304
Number of pregnancies	244	173	417
Known outcome	212	160	372
Live birth	121 (57.1%)	119 (74.4%)	240 (64.5%)
Fetal death/still birth	4 (1.9%)	7 (4.4%)	11 (3.0%)
Spontaneous abortion	44 (20.8%)	18 (11.3%)	62 (16.7%)
Therapeutic/elective abortion	43 (20.3%)	16 (10.0%)	59 (15.9%)
Unknown outcome	32	13	45
Rate per 100 person-years (95% CI)	15.0 (13.2,17.0)	13.6 (11.6, 15.7)	14.4 (13.0, 15.8)
Timing for all pregnancies			
Calendar time			
0–6 months	52 (21.3%)	39 (22.5%)	91 (21.8%)
>6 – 12 months	37 (15.2%)	37 (21.4%)	74 (17.7%)
>12 – 24 months	71 (29.1%)	49 (28.3%)	120 (28.8%)
>24 months	84 (34.4%)	48 (27.7%)	132 (31.7%)
Median	535	455	497
25th, 75th %tile	220, 836	199, 751	214, 809
Relationship to vaccination			
Before 2nd vaccination	9 (3.7%)	8 (4.6%)	17 (4.1%)
Between 2nd + 3rd vaccination	38 (15.6%)	28 (16.2%)	66 (15.8%)
After 3rd vaccination	197 (80.7%)	137 (79.2%)	334 (80.1%)

Table 3

Hazard Ratios, 95% confidence intervals (CI), and Wald p-values from multivariable region-specific models of time to first on-study pregnancy for women not surgically sterilized at enrollment

Predictor	Reference	Caribbean/South America (N=539)			North America (N=423 ^a)		
		Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Age 22	Age > 36	3.9	(2.2, 6.8)	<0.001	9.6	(4.4, 21.1)	<0.001
Age 23–28	Age > 36	3.8	(2.2, 6.6)	<0.001	7.5	(3.3, 17.0)	<0.001
Age 29–36	Age > 36	1.8	(0.9, 3.4)	0.09	3.8	(1.5, 9.8)	0.006
Vaccine	Placebo	1.4	(1.0, 1.9)	0.02	--		
Haiti	All other sites	1.5	(1.1, 2.0)	0.01	--		
Number of sexual partners	Per 100 partners	--			1.0	(1.0, 1.1)	0.004
STI	No STI	--			1.8	(1.1, 3.1)	0.03

^aOne non-pregnant woman was deleted due to missing data for number of sexual partners.