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Risk factors for HIV incidence in women participating in an HSV suppressive treatment trial in Tanzania

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Abstract

Objectives—A randomized double-blind placebo-controlled trial (RCT) of HSV-2 suppressive therapy with acyclovir 400mg b.d. conducted among women in northwestern Tanzania reported a similar rate of HIV acquisition in both trial arms (Current Controlled Trials number ISRCTN35385041). Risk factors for HIV incidence were examined in the context of three-monthly follow-up visits offering both VCT and STI care.

Design—Prospective cohort analysis of trial participants enrolled and followed for up to 30 months.

Methods—Risk factors for HIV acquisition were analysed using Cox regression.

Results—Overall 821 HSV-2 seropositive, HIV seronegative women were randomized; 400 to acyclovir and 421 to placebo; 659 (80.3%) completed follow-up. HIV incidence was 4.27 per 100 person-years. There was no overall impact of acyclovir on HIV incidence (hazard ratio (HR)=1.01; 95%CI:0.61-1.66). HIV acquisition was independently associated with younger age at enrolment (age 16-19 vs 30-35: HR=4.02; 95%CI:1.67-9.68), alcohol consumption at enrolment (≥30 drinks/week vs.none: HR=4.39, 95%CI 1.70-11.33), having paid sex within the previous 3 months (HR=1.82, 95%CI:1.09-3.05), recent infection with gonorrhoea (HR=3.62, 95%CI: 1.62-8.08) and injections in the previous 3 months (HR=3.45, 95%CI:1.62-7.34). There was some evidence of an association between HIV incidence and living in the recruitment community for less than 2 years (HR=1.75, 95%CI:0.98-3.10), and exposure to hormonal contraception (HR=1.60, 95%CI:0.93-2.76).

Conclusions—A high incidence of HIV was observed in this trial cohort, especially in young women. Interventions are needed to address the risk associated with alcohol use and to sustain control of other STIs.

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AUTHOR CONTRIBUTIONS

DWJ was principal investigator, supervised the trial and wrote the first draft of the paper. DWJ, RH, DR, TCl, and HW designed the study; KB and TCh were responsible for data management for the trial; KB and HW conducted the analysis; JC and DE supervised the laboratory work; CT supervised fieldwork; all authors commented on drafts of the manuscript and approved the final version; DWJ and RH act as guarantors for the results presented in the paper.

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Keywords

HIV; incidence; risk factors; women; high risk; Tanzania; randomized controlled trial; HSV-2

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INTRODUCTION

Sub-Saharan Africa continues to suffer a devastating HIV epidemic with HIV rates especially high in groups such as bar and hotel workers[1-5]. Risk factors for HIV acquisition may change over time as the epidemic evolves, socioeconomic factors change and prevention messages potentially impact on behavioural and biological factors. For example, a reduction in high risk sexual behaviour has been reported in Zambia[6], while recent studies have suggested a strong association between HIV acquisition and alcohol use in Africa[7].

In this paper we report factors associated with HIV incidence from the first randomized controlled trial to assess the impact of herpes suppressive therapy on HIV incidence (Current Controlled Trials number ISRCTN35385041).

METHODS

Participants

Trial procedures have been described previously[5;8]. Tanzanian women aged 16-35 years working in bars, guesthouses and similar facilities in 19 communities were interviewed, tested for HSV-2 and HIV antibodies and asked to re-attend two to three months later. At enrolment, HSV-2 seropositive participants were tested for pregnancy, interviewed and blood and genital samples collected. Women were randomized to receive a four month supply of acyclovir 400mg b.d. or matching placebo and followed three-monthly for up to 30 months depending on enrolment date.

At booked visits, pregnancy testing, family planning, STI syndromic management, HIV voluntary counselling and testing (VCT), risk reduction counselling, treatment for medical problems and condoms were provided. Participants were tested for syphilis at each visit. Vaginal and cervical specimens were collected at the 6, 12, 24 and 30 month visits. Genital examinations were performed at other visits if the participant complained of STI symptoms.

Laboratory methods

Sera were tested by HIV ELISA (Murex HIV Ag/Ab Combination ELISA, Murex Biotech, UK; Uni-FormII Ag/Ab micro ELISA system, bioMérieux, UK). Repeatedly discordant samples were tested by HIV-1 p24 Ag EIA (Biorad Genetic Systems, USA) and a line immunoassay (INNO-LIA™ HIV I/II, Innogenetics, Belgium) which was also used to confirm seroconversion samples[8]. Diagnosis of other STIs has been previously described[5,8,9].

Statistical methods

Data from the entire trial cohort were analysed, irrespective of withdrawal from tablets. Women were censored at the earliest of the date of HIV seroconversion, date last seen, or end of follow-up. Cox proportional hazards regression was used to estimate hazard ratios (HR) for HIV seroconversion which was assumed to take place midway between last negative and first positive serology results.

Potential determinants of HIV seroconversion were examined using a conceptual framework[10]. Initially, univariate age-adjusted associations were examined (Table 1). All

models included age, considered an *a priori* confounder. Baseline socio-demographic factors whose age-adjusted association reached statistical significance (p<0.20) were included in a multivariate model. Those remaining independently associated with HIV seroconversion (p<0.10) were retained in a core model. Baseline behavioural factors were added to this model one by one and significant factors (p<0.20) included in a multivariate model. Those remaining significant (p<0.10) were retained. Associations with time-varying behavioural and biological factors were determined in a similar way. The final model excluded factors one at a time until all remaining factors were significant at the p<0.10 level.

Population attributable fraction (PAF) of HIV acquisition for predictors in the final model were estimated using adjusted HRs.

Results

Sociodemographic and behavioural characteristics

In total 2719 were screened and 821 HIV-negative women were enrolled (400 randomized to acyclovir, 421 to placebo). Median age at enrolment was 28 years. At screening half of the participants reported drinking alcohol; 16.8% reported ten or more drinks per week. At enrolment, 20% used injectable depot-medroxyprogesterone acetate (DMPA) and 10% combined oral contraceptive pills (COC) for contraception. At screening and enrolment, 515 women (62.7%) accepted VCT and were given their HIV result. A further 80 (9.7%) participants accepted VCT and were tested during follow-up.

HIV incidence

Forty-five participants (5.5%) did not return after randomisation. Women were followed for 1477 person-years (pyr), with a median duration of 2.50 years (range 0–2.78 years). Overall, 659 (80.3%) completed follow-up, defined as attending until the date of seroconversion or end of study. Sixty-three women seroconverted. HIV incidence was 4.27/100 pyr (95%CI: 3.33–5.46/100 pyr) with no significant difference between acyclovir and placebo arms (HR=1.01; 95%CI:0.61-1.66). HIV incidence was 10.3/100 pyr among 16–19 year olds, falling to 2.5/100 pyr among women aged 30–35 (p-trend=0.003, Table 1).

Age-adjusted risk factors for HIV incidence

Age-adjusted factors associated with HIV incidence included living in the screening site for less than 2 years, alcohol consumption, number of partners and paying partners in the past 3 months, receiving an injection outside the trial clinic since the previous visit, injections by the trial team at the previous visit, current hormonal contraception and gonorrhoea or chlamydial infection at the current visit (Table 1). Women with a positive pregnancy test at the current visit were less likely to have seroconverted to HIV.

Multivariate analysis

In the final multivariate model (Table 2), HIV incidence was independently associated with younger age, living in the site for less than 2 years (adjusted HR=1.75, 95%CI:0.98-3.10), increasing alcohol consumption at screening (≥30 drinks/week vs. none; adjusted HR=4.39 95%CI:1.70–11.33), having a paying partner in the past 3 months (adjusted HR=1.82, 95%CI:1.09–3.05), injections outside the trial clinic since the last visit (adjusted HR=3.45, 95%CI:1.62–7.34), currently using hormonal contraception (adjusted HR=1.60, 95%CI: 0.93-2.76) and gonorrhoea (adjusted HR=3.62, 95%CI:1.62–8.08).

The estimated PAFs of HIV incidence for any alcohol use, hormonal contraception and paying partners were 40.1%, 26.2% and 20.0%, respectively. The PAFs for injections and for gonorrhoea were lower at 9.0% and 8.0%, respectively.

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Clinical symptoms in injection recipients

Clinical data on the 8 seroconverters who reported receiving an injection outside the trial clinic were examined to investigate whether seroconversion symptoms may have preceded recent injections. Four women reported receiving quinine between 2 days to 2 months prior to the first positive HIV test for an apparently positive blood smear for malaria (symptoms included fever, headache, lethargy, cough, arthralgia). Two participants, one with headache and one complaining of fever and abdominal pain, received quinine for suspected malaria one month to 6 weeks prior to the first positive HIV test. Another received penicillin for fever and joint pain 3 weeks before a positive HIV test, and one woman was given benzathine penicillin for syphilis treatment sometime between the last negative and first positive HIV test.

Discussion

HIV incidence was very high among young women in this population and we identified several potentially preventable factors strongly associated with incident HIV including consumption of alcohol. A relationship with alcohol has been observed in several recent African studies[7,11]. In our study, women consuming ten or more drinks per week were at a more than three-fold increased risk of acquiring HIV than non-drinkers. Drinking establishments in sub-Saharan Africa are known HIV high transmission sites[12]. Alcohol can lead to behavioural disinhibition with resultant risky sexual behaviour, partner violence and coercive sex, as documented in South Africa and Uganda[13,14,15]. Since alcohol may be purchased for women by their clients, it may also be a proxy marker for sex with high risk partners. Alcohol may also influence susceptibility to HIV at a biological level[16,17], possibly due to a suppressive effect on the degradation of the HIV envelope protein, gp120[18].

We found an increased risk of HIV associated with current gonococcal infection as has been seen in sex workers in Nairobi[19] but no association with trichomonasis or *C. trachomatis*, unlike recent studies[19,20]. This may have been partly because women were diagnosed in the field and offered prompt treatment and because STI were diagnosed aetiologically at selected visits, with syndromic management being offered at other visits, so reducing study power to detect an association with HIV acquisition.

Condom use was not associated with a reduction in HIV incidence. As in other studies in East Africa[21], reported condom use during the trial remained disappointingly low, despite repeated education and counselling sessions on HIV prevention. Our results indicate the need for more intensive HIV prevention programmes in this population.

Genital ulcers were not significantly associated with HIV but may have been underestimated since participants were only examined every six months unless they had symptoms. There was no significant association between HIV acquisition and cervical ectopy in contrast to a South African study where ectopy of more than 20% was associated with HIV incidence[22].

Hormonal contraception was associated with HIV incidence. This has been found in HSV-2 seronegative women in Uganda and Zimbabwe[23] and sex workers in Kenya[24] although no association between hormonal contraception and HIV incidence was observed in Cape Town[25]. Our data suggest that hormonal contraception can increase the risk of HIV in high risk women although it is possible that this association may in part be attributable to residual confounding by sexual behaviour.

VCT has been associated with self-reported behaviour change in Kenya[26]. In common with studies in Uganda and Zimbabwe, we found no difference in HIV incidence between those who accepted or did not accept VCT[27,28]. Our selected trial population, however, received

repeated risk reduction counselling irrespective of uptake of VCT which may have diluted any impact that VCT could have had as an HIV prevention tool in this setting.

Injections given outside our research clinic were also associated with HIV acquisition. Estimates of the proportion of HIV infections attributable to injections in sub-Saharan Africa range from 1-30%[29,30]. However the causal direction of this association is not straightforward. In our trial the main reason for injections was malaria treatment. Over-diagnosis of malaria is common in sub-Saharan Africa[31,32] and our clinical data suggest that, in at least seven cases, injections were given to treat symptoms possibly related to a seroconversion illness which may have been misclassified as malaria or another infection. A similar temporal association between a possible seroconversion illness and injections has been seen in Uganda[33]. If injections are given for symptoms related to seroconversion, this emphasises the necessity to maintain safe injection practices since risks of onward transmission will be high at this stage of HIV infection due to high viral load.

We could not examine the independent effect of HSV-2 on HIV incidence. However, 80% of women in this population were found to be HSV-2 seropositive at screening[5]. Our results will therefore be generalizable to many women in similar occupational settings. A further limitation is reliance on self-reported sexual behaviour since such information may be subject to social desirability bias[34,35]. Finally, with 63 seroconversions, the power of our study to detect significant associations with uncommon exposures will have been limited.

In conclusion, this prospective study has demonstrated a strong association between HIV incidence and young age, alcohol consumption, injections, payment for sex, gonococcal infection and hormonal contraception. Interventions are needed to address the risk associated with alcohol use and to sustain control of other STIs. In addition prevention messages should be targeted to young women in this population. Further work is needed to examine the effect of injections and hormonal contraception on HIV incidence in high risk settings.

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Table 1

Association between HIV incidence and socio-demographic, behavioural and biological factors

	N (%)	HIV seroconverted /pyrs	HIV incidence rate / 100 pyr	Age-adjusted HR (95% CI)
SOCIODEMOGRAPHIC FACTORS AT SCREENING				
Age (years)				P-trend=0.003
30–35	323 (39.3%)	15 / 603	2.49	1
25–29	250 (30.5%)	24 / 468	5.13	2.06 [1.08,3.93]
20–24	198 (24.1%)	16 / 328	4.88	1.96 [0.97,3.96]
16–19	50 (6.1%)	8 / 78	10.26	4.11 [1.74,9.69]
Marital status				P=0.12
Unmarried	238 (29.0%)	16 / 445	3.60	1
Married/living with partner	165 (20.1%)	11 / 283	3.88	0.58 [0.24,1.35]
Divorced/separated/ widowed	418 (50.9%)	36 / 749	4.81	1.24 [0.69,2.25]
Tribe				P=0.54
Sukuma	378 (46.0%)	35 / 737	4.75	1
Other	443 (54.0%)	28 / 740	3.78	0.85 [0.52,1.41]
Religion				P=0.53
Catholic	377 (45.9%)	36 / 699	5.15	1
Protestant	221 (26.9%)	13 / 400	3.25	0.65 [0.34,1.23]
Muslim	183 (22.3%)	11 / 302	3.64	0.72 [0.36,1.41]
Other	40 (4.9%)	3 / 76	3.97	0.85 [0.26,2.77]
Facility type				P=0.15
Local food handler	438 (53.4%)	29 / 798	3.64	1
Guesthouse	91 (11.1%)	9 / 133	6.78	2.02 [0.94,4.32]
Bar worker	103 (12.6%)	6 / 184	3.27	0.84 [0.35,2.04]
Local brew seller	57 (6.9%)	8 / 114	7.04	2.42 [1.08,5.38]
Restaurant./café/ grocery	132 (16.1%)	11 / 249	4.41	1.12 [0.56,2.25]
Education				P=0.32
Less than primary	257 (31.3%)	17 / 453	3.75	1
Primary or above	564 (68.7%)	46 / 1024	4.49	1.33 [0.76,2.33]
Literacy				P=0.93
No	203 (24.7%)	15 / 339	4.43	1
Yes	618 (75.3%)	48 / 1138	4.22	1.03 [0.57,1.85]
Lived >2 years in village				P=0.05
Yes	692 (84.3%)	47 / 1261	3.73	1
No	129 (15.7%)	16 / 216	7.42	1.83 [1.04,3.24]
BEHAVIOURAL FACTORS AT SCREENING AND ENROLMENT				

	N (%)	HIV seroconverted /pyrs	HIV incidence rate / 100 pyr	Age-adjusted HR (95% CI)
Number of drinks per week [1]				P trend<0.001
0	411 (50.1%)	18 / 737	2.44	1
1–9	272 (33.1%)	22 / 486	4.53	1.99 [1.06,3.74]
10–29	110 (13.4%)	17 / 204	8.34	3.61 [1.84,7.09]
>=30	28 (3.4%)	6 / 51	11.80	5.31 [2.07,13.61]
Hormonal contraception				P=0.54
No	574 (69.9%)	26/667	3.90	1
Yes	247 (30.1%)	37/810	4.57	1.17 [0.71, 1.93]
Age at first sex				P=0.22
<=14	121 (14.9%)	9 / 224	4.01	1
15-16	329 (40.5%)	34 / 596	5.70	1.30 [0.62,2.72]
17-18	258 (31.7%)	13 / 476	2.73	0.67 [0.29,1.57]
>18	105 (12.9%)	6 / 166	3.62	0.99 [0.35,2.79]
Ever practice vaginal washing				P=0.54
No	297 (36.2%)	26 / 505	5.15	1
1–2 times/day	226 (27.6%)	17 / 404	4.21	0.90 [0.49,1.68]
>2 times/day	297 (36.2%)	20 / 566	3.53	0.72 [0.40,1.30]
Ever practice vaginal drying				P=0.58
No	784 (95.5%)	61 / 1409	4.33	1
Yes	37 (4.5%)	2 / 68	2.94	0.69 [0.17,2.82]
Lifetime partners				P trend=0.62
0-1	33 (4.0%)	3 / 50	5.94	1
2–4	314 (38.3%)	20 / 555	3.60	0.60 [0.18,2.05]
5-9	286 (34.8%)	25 / 525	4.76	0.82 [0.24,2.80]
>=10	188 (22.9%)	15 / 346	4.33	0.77 [0.21,2.73]
Accepted VCT at baseline				P=0.57
No	306 (37.3%)	23 / 509	4.52	1
Yes	515 (62.7%)	40 / 968	4.13	0.86 [0.51,1.44]
Ever had blood transfusion				P=0.23
No	732 (89.3%)	54 / 1321	4.09	1
Yes	88 (10.7%)	9 / 153	5.87	1.59 [0.78,3.22]
Treatment arm				P=0.89
Placebo	421 (51.3%)	33 / 778	4.24	1
Acyclovir	400 (48.7%)	30 / 699	4.29	1.04 [0.63,1.70]
BEHAVIOURAL FACTORS DURING FOLLOW-UP [2]				
Same site as last visit				P=0.65
Yes	5281 (90.7%)	54 / 1312	4.12	1

	N (%)	HIV seroconverted /pyrs	HIV incidence rate / 100 pyr	Age-adjusted HR (95% CI)
No	540 (9.3%)	9 / 165	5.45	1.18 [0.58,2.41]
No. partners in past 3 m				P trend=0.02
0-1	4278 (73.5%)	38 / 1092	3.48	1
2	1095 (18.8%)	17 / 275	6.18	1.64 [0.92,2.93]
3-4	364 (6.3%)	4 / 90	4.43	1.13 [0.40,3.19]
>=5	82 (1.4%)	4 / 19	20.81	5.34 [1.88,15.15]
Paying partners in past 3 m				P=0.003
No	4340 (74.6%)	35 / 1109	3.16	1
Yes	1479 (25.4%)	28 / 368	7.61	2.21 [1.33,3.65]
Condom use with regular partner in past 3m				P=0.94
Always	956 (16.5%)	12 / 248	4.83	1
Sometimes/often	272 (4.7%)	3 / 66	4.56	0.93 [0.26,3.32]
Never/rarely	4029 (69.4%)	41 / 1021	4.02	0.90 [0.47,1.72]
No sex with reg partner in last 3m	550 (9.5%)	7 / 139	5.03	1.16 [0.45,2.96]
Anal sex in past 3 m				P=0.15
No	5805 (99.8%)	62 / 1474	4.21	1
Yes	14 (0.2%)	1 / 3	34.84	6.87 [0.94,50.45]
Blood transfusions since last visit				P=0.23
No	5803 (99.8%)	62 / 1473	4.21	1
Yes	12 (0.2%)	1 / 4	27.98	4.59 [0.62,34.22]
Injections outside trial clinic since last visit				P=0.01
No	5561 (95.6%)	55 / 1409	3.90	1
Yes	255 (4.4%)	8 / 67	11.92	3.09 [1.47,6.51]
Injections by study clinic at last visit [3]				P=0.07
No	5158 (77.7%)	43 / 1155	3.72	1
Yes	1484 (22.3%)	20 / 322	6.21	1.67 [0.98,2.84]
Current hormonal contraception use				P=0.07
No	2411 (41.4%)	19 / 618	3.08	1
Yes	3410 (58.6%)	44 / 859	5.12	1.63 [0.95,2.80]
Accepted VCT up to current visit				P=0.20
Never	1691 (29.1%)	16 / 423	3.78	1
At baseline	3774 (64.8%)	40 / 968	4.13	1.04 [0.58,1.86]
During follow up	356 (6.1%)	7 / 86	8.18	2.27 [0.93,5.57]
BIOLOGICAL FACTORS DURING FOLLOW-UP [2]				
Positive pregnancy test				P=0.08

	N (%)	HIV seroconverted /pyrs	HIV incidence rate / 100 pyr	Age-adjusted HR (95% CI)
No	5442 (93.5%)	61 / 1376	4.43	1
Yes	378 (6.5%)	2 / 101	1.98	0.34 [0.08,1.41]
Cervical ectopy (any) [4]				P=0.39
No	5426 (93.3%)	57 / 1380	4.13	1
Yes	391 (6.7%)	5 / 96	5.19	1.54 [0.61,3.89]
Cervical ectopy >20% [4]				P=0.33
No	5776 (99.3%)	61 / 1467	4.16	1
Yes	41 (0.7%)	1 / 96	10.39	3.26 [0.44,23.85]
Genital ulceration [4]				P=0.47
No	5775 (99.2%)	62 / 1466	4.23	1
Yes	44 (0.8%)	1 / 11	9.04	2.28 [0.31,16.61]
Vaginal discharge syndrome [4]				P=0.19
No	4526 (77.8%)	44 / 1155	3.81	1
Yes	1293 (22.2%)	19 / 322	5.90	1.46 [0.84,2.53]
Pelvic inflammatory disease [4]				P=0.29
No	5206 (89.5%)	54 / 1321	4.09	1
Yes	613 (10.5%)	9 / 156	5.76	1.49 [0.73,3.04]
N gonorrhoeae [4]				P=0.005
No	5639 (96.9%)	56 / 1435	3.90	1
Yes	182 (3.1%)	7 / 42	16.66	3.91 [1.76,8.69]
C trachomatis [4]				P=0.09
No	5581 (95.9%)	57 / 1418	4.02	1
Yes	240 (4.1%)	6 / 59	10.21	2.28 [0.97,5.33]
T vaginalis [4]				P=0.57
No	4834 (83.0%)	50 / 1223	4.09	1
Yes	987 (17.0%)	13 / 254	5.12	1.20 [0.65,2.21]
Bacterial vaginosis [4]				P=0.27
No	2722 (46.8%)	25 / 688	3.64	1
Yes	3099 (53.2%)	38 / 789	4.81	1.33 [0.80,2.20]
Active syphilis [5]				P=0.46
No	5513 (94.2%)	58 / 1397	4.15	1
Yes	341 (5.8%)	5 / 80	6.23	1.45 [0.57,3.65]

[1] A drink is one bottle of beer, a glass of wine or a measure of spirits)

[2] Data divided into 3 monthly intervals corresponding to booked visits. Time-varying behavioural factors defined as reported behaviour in the preceding 3 months; biological factors defined as laboratory or clinical results at each visit.

[3] Includes DMPA, ceftriaxone & penicillin injections

[4] Not recorded at every visit. Imputed using the value of the exposure recorded closest to the date halfway between the current and previous visit.

[5] RPR-positive and TPPA or FTA-positive

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Table 2

Independent factors associated with HIV seroconversion

	HIV seroconverted /pyrs	HIV incidence rate / 100 pyr	Adjusted HR[1] 95% CI
Age (years)			P trend=0.01
30-35	15 / 603	2.49	1
25–29	24 / 468	5.13	1.51 [0.78,2.91]
20–24	16 / 328	4.88	1.57 [0.77,3.2–]
16–19	8 / 78	10.26	4.02 [1.67,9.68]
Lived >2 years in village			P=0.07
Yes	47 / 1261	3.73	1
No	16 / 216	7.42	1.75 [0.98,3.10]
Number of drinks per week at screening			P trend<0.001
0	18 / 737	2.44	1
1–9	22 / 486	4.53	1.73 [0.92,3.27]
10–29	17 / 204	8.34	3.00 [1.51,5.98]
>=30	6 / 51	11.80	4.39 [1.70,11.33]
Paying partners in past 3 m			P=0.03
No	35 / 1109	3.16	1
Yes	28 / 368	7.61	1.82 [1.09,3.05]
Injections outside trial clinic since last visit			P=0.005
No	55 / 1409	3.90	1
Yes	8 / 67	11.92	3.45 [1.62,7.34]
Currently using hormonal contraception			P=0.08
No	19 / 618	3.08	1
Yes	44 / 859	5.12	1.60 [0.93,2.76]
N gonorrhoeae			P=0.007
No	56 / 1435	3.90	1
Yes	7 / 42	16.66	3.62 [1.62,8.08]

[1]Adjusted for all variables in the table