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Risk factors for HIV-1 infection in a longitudinal, prospective cohort of adults from the Mbeya Region, Tanzania

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Abstract

Background—To control the global HIV epidemic targeted interventions to reduce the incidence of HIV infections are urgently needed until an effective HIV vaccine is available. This study describes HIV-1 incidence and associated risk factors in a general population cohort of adults from Mbeya Region, Tanzania, who participated in a vaccine preparedness study.

Methods—We conducted a closed prospective cohort study with six-monthly follow-up from 2002–2006, enrolling adults from the general population. HIV-1 incidence and risk factors for HIV-1 acquisition were analysed using Cox regression.

Results—We observed 2,578 sero-negative participants for a mean period of 3.06 PY (7,471 PY in total). Overall HIV-1 incidence was 1.35 per 100 PY (95% confidence interval [CI]=1.10–1.64/100 PY). The highest overall HIV-1 incidence was found in females from Itende village (1.55 per 100 PY, 95%CI=0.99–2.30/100 PY), the highest age-specific incidence was

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observed in semi-urban males aged 30-34 years (2.75 per 100 PY, 95%CI=0.75-7.04). HIV-1 acquisition was independently associated with female gender (hazard ratio [HR]=1.64, 95%CI=1.05-2.57), younger age at enrolment (age 18-19 vs. 35-39: HR=0.29, 95%CI=0.11-0.75), alcohol consumption (almost daily vs. none: HR 2.01, 95%CI=1.00-4.07), education level (secondary school vs. none: HR 0.39, 95%CI=0.17-0.89) and number of lifetime sex partners (more than five vs. one: HR 2.22, 95%CI=1.13-4.36).

Conclusions—A high incidence of HIV was observed in this cohort, and incident infection was strongly associated with young age, alcohol consumption, low school education level and number of sex partners. Targeted interventions are needed to address the elevated risk associated with these factors.

Keywords

HIV-1; incidence; risk factors; cohort study; Tanzania; Africa

Introduction

Despite advances in HIV prevention, treatment and care, HIV/AIDS continues to be a significant cause of morbidity and mortality worldwide, particularly in Africa 1. To halt the spread of HIV-1 it will require further advances on all achieved efforts and additional biomedical interventions like a safe and effective HIV vaccine.

Understanding the dynamics of HIV infections in a community risk setting is essential both for planning such interventions and to evaluate their impact on the population. Most such data derives from trends in HIV-1 prevalence that should be interpreted only with caution 2. The most reliable method to monitor the pandemic is direct HIV incidence measurement. Characterization of recent seroconverters is critical to the design of better targeted preventive interventions. However, these data are rare for general populations in Africa as prospective cohort studies are costly and difficult to execute.

We report HIV-1 incidence rates and associated risk factors from a vaccine preparedness cohort study in the Mbeya Region, Tanzania determining the ability to recruit and retain people from the general population at risk for HIV infection and identifying the factors important for the design of future HIV vaccine efficacy trials.

Methods

Ethical Considerations

Laboratory and field work was done in accordance with the Helsinki Declaration of 1975 as revised in 2000 and was also approved by the ethics committees of the Mbeya Referral Hospital, the Tanzanian National Institute of Medical Research (NIMR) and the Medical Center of the University of Munich (LMU) as well as the institutional review board of the Walter Reed Army Institute of Research. All participants provided written informed consent before enrolment.

Recruitment

Between September 2002 and April 2003, we used two different approaches to recruit 3,096 volunteers of both sexes from Mbeya Region in South-western Tanzania. Volunteers from Ghana ward, an urban area in Mbeya Town, and from Itende, a small semi-urban village close to Mbeya town, were recruited in a door-to-door campaign. A third subgroup of volunteers was recruited by advertisement in all wards of Mbeya Town. During the door-to-door campaign trained staff visited all households in the designated study areas to inform

them about the planned cohort study and to invite all eligible household members to community meetings. The “advertisement” recruitment strategy involved use of IRB approved banners, fliers, posters and public announcements in Mbeya town in order to also invite potential participants to our community meetings. During these meetings, the research team provided more details about participation in the study. At the end of each meeting, individuals aged 18–45 years were encouraged to report to our designated research facilities that were fully incorporated into the Mbeya Referral Hospital and the Itende Health Centre. These research facilities served for enrolment and follow-up evaluations throughout the whole study.

Enrolment and study procedures

We included residents of Mbeya town and Itende Village between 18 and 45 years of age, who were planning to stay in the area for at least three years and who were willing and able to provide informed consent and to adhere to study procedures including blood specimen collection.

During the first study-visit potential participants were consented, pre- and post-test counselled, tested for HIV-1 and also underwent a clinical examination. Data on socio-demographic background, relevant behaviour and knowledge about HIV/AIDS were collected in face-to-face-interviews using standardized questionnaires.

Over a four-year period, we collected venous blood samples for HIV-1 testing and storage by phlebotomy during each of the six-monthly follow-up visits. At each visit, participants received voluntary counselling about HIV-1 transmission and prevention, and free condoms (male and female). Participants with STIs received free treatment according to Tanzanian national guidelines. Those who were HIV-1 infected at enrolment, or became infected during the study, were referred to the Mbeya Referral Hospital. Provision of antiretroviral treatment by the hospital started in 2005. Throughout the duration of the study, our research clinics provided free and comprehensive outpatient care according to Tanzanian national guidelines to all participants. This included referral to the specialty clinics of the Mbeya Referral Hospital, if needed.

Laboratory tests

Venous blood samples were tested for HIV-1 with a dual enzyme-linked immunosorbent assay strategy (HIV-Determine; Abbott Laboratories, Abbott Park, Illinois, USA and Enzygnost HIV-1/2 plus; Behring, Liederbach, Germany) which was confirmed by HIV-1 Western blot (HIVblot 2.2 Genelabs/Abbott, Wiesbaden, Germany) if discordant. The last sero-negative samples of incident HIV-1 cases were re-examined with PCR to close the diagnostic windows.

Statistical analysis

We summarized demographic and behavioural characteristics at baseline. HIV-1 incidence was calculated as the number of seroconversions per 100 person years (PY). Seroconversion was assumed to have taken place midway between the dates of the last negative and the first positive serology result. We defined the time at risk for HIV-1 infection as the time elapsed after the date of enrolment. Participants who seroconverted exited at the time of seroconversion, participants who remained sero-negative were censored at the date of the last follow-up visit they attended. Univariable and multivariable Cox proportional hazard models were used to assess the association of potential risk-factors with HIV-1 seroconversion employing a modified conceptual framework approach 3. Initially, single factors adjusted for age, sex and study location which we considered as *a priori* confounders were examined one by one in univariable analyses. Socio-demographic factors (e.g. marital

status, household size or occupation) with a univariable p-value below 0.2 were included in a multivariable model and retained if their p-value in this multivariable core-model was below 0.1. Baseline behavioural factors (e.g. condom use, age at sexual debut or age of partner) were added to this model one by one and included in a multivariable model if their univariable p-value was below 0.2. Those with a p-value below 0.1 were again retained. Biological factors (e.g. circumcision, pregnancy or self-reported symptoms for sexually transmitted infections) were examined using the same approach. All retained factors were analyzed with a stepwise backward regression model excluding them one at a time until all remaining factors had a p-value below 0.15. The probability of HIV-1 infection over time was calculated and graphically displayed using Kaplan-Meier failure estimates. Stata version 10 SE (Stata Corp., College Station, TX, USA) was used for all statistical analyses.

Results

Characteristics of the sero-negative study population during enrolment

In total, we enrolled 2,578 sero-negative participants, 864 in Ghana ward in Mbeya, 846 in the advertisement group and 868 in semi-urban Itende (Table 1). Forty-four percent were men and 46% were aged <25 years. The mean age at enrolment was 27.2 (standard deviation [SD]=7.9) years; no difference was observed between male and female participants' age (male = 27.3 [SD=7.9] years; female = 27.2 [SD=7.8]; $p=0.552$ [chi-square-test]). There also was no significant difference in age distribution between urban participants from Mbeya and semi-urban participants from Itende ($p=0.137$). Ninety percent of participants had attended primary school and more than 85% had completed primary school. Education levels differed between the two sites and recruitment strategies. Semi-urban participants were mostly farmers, while half of the urban participants worked as occasional workers or were unemployed. The higher unemployment rate in Mbeya town can thus be attributed to the fact that subsistence farming is impossible in an urban setting. Table 1 summarizes the demographic and social characteristics of the participants during enrolment.

Retention

At the first follow-up visit, 137 out of 2,578 initially sero-negative participants (5.3%) did not return and could therefore not be included in the analysis of HIV-1 incidence. All remaining participants were followed for 7,471 PY overall, with a mean duration of 3.06 years (range 0.32–3.83 years). Overall, 1,776 participants (68.9% of the enrolled) completed follow-up defined as participating until the date of seroconversion or until the end of the study. Participants who were lost to follow up were more likely to be male, of younger age, from the urban site and recruited by advertisement (p -value for trend <0.01 for all mentioned variables), whereas not belonging to a religious group and having a low school education level was positively associated with compliance over the whole study period (p -value for trend <0.01 for both variables).

Incidence of HIV-1 infection

One-hundred-and-one participants seroconverted during the course of the study resulting in an HIV-1 incidence rate of 1.35 per 100 PY (95% confidence interval [CI] 1.10-1.64/100 PY). The highest overall HIV-1 incidence was found in females from Itende (1.55 per 100 PY, 95%CI=0.99-2.30/100 PY), the highest age and sex specific incidence among males aged 30 to 34 years from the semi-urban setting (2.75 per 100 PY, 95%CI=0.75-7.04). Figure 1 shows the incidence of HIV seroconversion (point estimates) for males and females, stratified by recruitment site and age. When combining participants in two age groups (18 to 29 and 30 to 45 years) of both sexes, young women had the highest incidence rate of 1.86 per 100 PY (95%CI=1.38-2.46) compared to young men (1.33 per 100PY, 95%CI=0.88-1.94), elder women (0.81 per 100PY, 95%CI=0.43-1.39) and elder men (0.94

per 100PY, 95% CI=0.47-1.69). The almost even distribution of probability of HIV-1 infection over time of the Kaplan-Meier survival functions indicates that there is almost no cohort effect in this distinct study population (Figure 2).

Age-, sex- and residence-adjusted risk factors for acquiring HIV-1 infections

Female sex (hazard ratio [HR]=1.22, 95% CI 0.82-1.84), current residence in Itende village (HR=1.10, 95% CI 0.73-1.66) and younger age (age 40-45 vs. 18-19: HR= 0.21, 95% CI 0.06-0.71) showed some association with HIV-1-seroconversion when adjusted for the other two variables respectively (Table 2). Although only the association with age was statistically significant at the 5% level of confidence, we included age, sex and residence in all models as potentially important *a priori* confounders.

Other risk factors for HIV-1 incidence that were significant in the univariable analysis included having no religion (HR=2.15, 95% CI 1.03-4.50), low school education level (finished primary school vs. none: HR=0.56, 95% CI 0.32-0.98), alcohol consumption (almost daily vs. none: HR 3.48, 95% CI 1.73-7.02) and number of sex partners (more than five vs. one: HR 2.68, 95% CI 1.41-5.11). There was no significant difference in HIV-1 incidence between the two recruitment strategies that were used in Mbeya town (HR of advertisement vs. door-to-door cohort: 1.41; 95% CI 0.82-2.40).

The final multivariable model included all variables shown in Table 2. Female sex (HR=1.64, 95% CI 1.05-2.57) and younger age at enrolment (age 18-19 vs. 35-39: HR=0.29, 95% CI 0.11-0.75), were independently associated with HIV-1 incidence, whereas living in Itende did not show an association (HR=0.90, 95% CI 0.53-1.52). Furthermore alcohol consumption (almost daily vs. none: HR 2.01, 95% CI 1.00-4.07), school education level (secondary school vs. none: HR 0.39, 95% CI 0.17-0.89) and number of sex partners (more than five vs. one: HR 2.22, 95% CI 1.13-4.36) were independently associated with HIV-1 incidence. There was also some (non-significant) evidence of an association between HIV incidence and having no religion (HR 1.78, 95% CI 0.87-3.66).

Discussion

In our study population HIV-1 incidence (1.35 per 100 PY) was four times as high as recent estimates from Tanzanian household-based prevalence data for the whole country (0.34/100 PY) 4. Cohort studies from northern Tanzania report an incidence between 0.39 and 1.20 per 100 PY depending on year of data collection and study site 5,6. The difference between our and the national estimates can partially be explained by the differences in HIV-1 prevalence; the HIV-1 prevalence in our study (14.8% for males and 21.2% for females in Mbeya; 11.5% for males and 13.4% for females in Itende) 7 was almost twice the national average 8. Even though estimating incidence from cross-sectional prevalence data is well established 9, incidence measured in cohort studies remains the gold standard for accuracy, especially for intervention trials. In the Step study 10 which assessed the efficacy of a cell-mediated immunity vaccine no increased HIV incidence was observed during the trial, even though cross-sectional data prior to the study indicated that women were at high risk.

The main burden of new infections in our study is concentrated in women, both in urban and semi-urban settings. This is consistent with the above mentioned prevalence survey from Tanzania and other African countries 4. An elevated risk due to casual partnerships with older men 11,12 during early sexual experience which could have explained this pattern was not observed in our study (data not shown). A possible explanation for the higher incidence in women could be the increased HIV-1 susceptibility of women which has been reported in many previous studies 13.

The age distribution differs considerably between our urban and rural populations: while in Mbeya town most of the infections occurred prior to the age of 25 years, Itende showed a peak incidence rate in the group of 25-29 year old females and 30-34 year old males. The age distribution of HIV-1 infected participants from Itende is similar to that of a rural cohort study close to Mwanza 6. Differences in behaviour and socioeconomic status between urban and rural settings itself could explain this delayed acquisition of HIV-1 in Itende, as well as the steady spread of HIV from urban settlements into the rural population 14. Important for the planning of recruitment strategies in future phase III vaccine trials is that a similar HIV-1 incidence was found in the two groups from Mbeya who were recruited by advertisement and by door-to-door campaign. Our data thus do not provide evidence that advertisement leads to an increase in response bias.

We did not observe a significant decline in seroconversions over time attributed to a closed cohort effect like other studies 15,16, even though we performed regular health education sessions, offered counselling and promoted free condom use.

Most studies on risk factors for HIV infection are based on prevalent rather than incident cases. Hence, their results also take account of the time after HIV-1 acquisition and are biased by determinants of disease duration. Our approach of analyzing incident cases for association excludes this bias.

We identified risk factors that are potentially preventable by public health interventions. We observed a strong association between alcohol consumption and newly acquired HIV infection which has already been described in other studies from Africa 3,17, and we were able to demonstrate that the incidence rate was positively associated with frequency of alcohol consumption. This is usually explained by the effect of alcohol to reduce inhibition and to diminish perception of exposure to risky sexual behaviour, violence, forced sex and rape 18,19 Tanzanians consume alcohol frequently in restaurants, bars and local brew establishments where they also encounter new sex partners 20. In a previous cohort study of female bar workers in Mbeya region, 67% of the participants were HIV-1 sero-positive at enrolment 21, demonstrating the high risk potential for HIV acquisition in their clients.

Another notable result is the association between the risk of HIV-1 acquisition and the number of lifetime sexual partners which – in the absence of data regarding concurrent sexual partnerships and frequency of sexual intercourse - we use as a proxy for current sexual behaviour 22. A similar association was found in a cross-sectional study of prevalent HIV infection in Northern Tanzania 23. Indeed, there is no evidence that Africans typically have more sexual partners than elsewhere in the world 24, but still sexual behaviour might be an important risk factor since having more than one concurrent partnership seems to increase the risk of HIV acquisition 25 and is in addition more frequently found in Africa 24.

While in the early phase of the epidemic HIV risk was linked to higher educational attainment 26,27 some studies in Africa observed a similar shift towards reduced risk among higher educated people as found in our study 28-30. Staying in school for a longer time plays an important role for being more frequently and intensively exposed to health and basic education. Subsequently, better educated people seem to understand and adapt health education messages faster, leading to behavioural changes like delay in sexual debut, reduction of sexual partners or increased condom use 28,31. Furthermore educational status is likely to reflect socio-economic-status which is also negatively related to HIV incidence 32.

Lastly, we found that study participants without religious denomination were at higher risk of HIV-1 acquisition. This finding could be explained by the role of religious communities

as influential social networks that can influence health promotion messages 33. Previous studies addressing correlations between religious beliefs, behaviour and risk for HIV-1 infections often focused on Muslim populations, with a particular interest in male circumcision which is a known protective intervention 34,35. Our results indicate such a correlation as well (23% risk reduction in the adjusted univariable analysis, HR=0.77, 95% CI 0.34-1.77), even though male circumcision did not reach statistical significance in the final multivariable model.

Our study and this analysis have certain limitations

The main objective of the CODE study was to explore the best recruitment strategy for future HIV vaccine trials, thus our different recruitment strategies might have caused some sampling bias. However, the results of the two urban strata did not differ significantly, thus we consider them as representative for the urban population of this age group in Mbeya. However, choosing a semi-urban setting in walking distance of the urban centre of Mbeya might be another source of selection bias because the population in this setting might closely resemble the urban population. Secondly, losses to follow-up might have influenced our results, although we attained a very high retention rate and identified characteristics for discontinuation of the study. The exact bias is difficult to assess because we were unable to collect information about reasons for loss to follow-up. It should however be noted that our losses to follow-up (31% over the study period including participants who died) are relatively low for a study in sub-Saharan Africa with a duration of four years. Third, our risk analysis only relies on data collected during enrolment because this was the most complete dataset. It is therefore possible that some of our co-variables changed over time which is not reflected in this analysis. Fourth, the validity of our data obtained during face-to-face interviews is subject to underreporting bias, especially for socially sensitive behaviours. Our study participants might have felt pressure to please our study staff in addition to the normal pressure to underreport sensitive behaviours 36. A method to overcome this bias – namely audio-computer-assisted self-interviewing – was not considered to be appropriate in this setting. Lastly, as in other closed cohorts we might have encountered a cohort attrition effect, leading to a reduced incidence rate towards the end of the study. However, the relatively stable HIV-1 incidence over time that we found does not indicate that this applies.

In conclusion, this study enhances knowledge for understanding of the ongoing HIV epidemic in East Africa and for implementing further public health actions in this setting. We observed a relatively high incidence of HIV, indicating an ongoing dynamic - especially among young women who are at higher risk - despite huge preventive efforts in the past decades. Alcohol consumption, low school education level and number of sex partner represent key risk factors; not belonging to a religious group seems to be a risk factor as well. To reduce HIV infection rates behavioural interventions towards the reduction of alcohol intake and safer sex practices should be intensified in these communities. The association with a low school education level that we found indicates that health education programs should be strengthened and go beyond formal schooling. Existing structures of social networks (e.g. religious groups) should be used and new networks should be identified to increase the catchment population for preventive measures. Finally, prevention programmes should empower young women since they are the group with the highest risk of HIV-1 infection in this region.

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Figure 1. HIV-1 incidence

Incidence of HIV seroconversion (point estimates) for males and females, stratified by recruitment site and age.

Figure 2. Kaplan-Meier cumulative Rates of Infection

The first follow-up visit was held approximately 6 months (± 2 months) after enrolment, the last one after 46 months. The graph shows probability of HIV-1 infection (solid line) and 95% confidence intervals (shaded gray). Numbers indicate the number at risk for each study year and the number of seroconversions.

Table 1

Baseline demographic and social characteristics of sero-negative participants in percent

<i>Characteristic/ Category</i>	<i>Itende (semi-urban) N=868</i>	<i>Total Mbeya^a (urban) N=1710</i>	<i>Ghana/ Mbeya (urban sub-strata) N=864</i>	<i>Advertisment/ Mbeya (urban sub-strata) N=846</i>	<i>Overall Total^b N=2578</i>
<i>Sex:</i>					
Males	43.5	44.4	44.3	44.6	44.1
Females	56.5	55.6	55.7	55.4	55.9
p-value	0.665 ^c			0.922 ^d	
<i>Age (years):</i>					
18-19	18.9	19.0	14.1	23.9	18.9
20-24	24.9	28.8	29.8	27.8	27.5
25-29	19.6	20.0	22.2	17.7	19.9
30-34	13.4	12.6	14.0	11.2	12.9
35-39	10.5	9.8	9.8	9.8	10.1
40-45	12.8	9.8	10.1	9.6	10.8
p-value	0.137 ^c			<0.001 ^d	
<i>Employment category:</i>					
Unemployed	6.1	25.0	26.0	24.1	18.7
Farmer/gardener	74.3	10.2	4.8	15.8	31.8
Occasional worker	8.1	25.0	22.8	27.2	19.3
Pupil	2.1	10.2	10.8	9.6	7.5
Others	9.5	29.6	35.7	23.3	22.8
p-value	<0.001 ^c			<0.001 ^d	
<i>Educational level:</i>					
None	23.7	3.2	2.3	4.0	10.1
Primary unfinished	8.5	4.5	3.6	5.4	5.8
Primary finished	64.2	61.3	57.9	64.8	62.3
Higher than primary	3.6	31.1	36.2	25.8	21.8
p-value	<0.001 ^c			<0.001 ^d	
<i>Marital status</i>					

Characteristic/ Category	Itende (semi-urban) N=868	Total Mbeya ^a (urban) N=1710	Ghama/ Mbeya (urban sub-strata) N=864	Advertisement/ Mbeya (urban sub-strata) N=846	Overall Total ^b N=2578
Single	33.2	41.8	41.8	41.7	38.9
Married	60.7	50.9	51.3	50.5	54.2
divorced/widowed	6.1	7.4	6.9	7.8	6.9
p-value	<0.001 ^c		0.787 ^d		
Religion:					
Catholic	8.4	22.2	21.3	23.2	17.6
Protestant	66.5	64.5	61.5	67.5	65.1
Muslim	0.5	11.9	16.6	7.1	8.0
None	24.7	1.4	0.6	2.1	9.2
p-value	<0.001 ^c		<0.001 ^d		

^aUrban Ghana- and urban advertisement-group combined

^ball three subgroups combined (Itende, Ghana + advertisement)

^{c,d}Probability values according to Chi-square or Fisher's exact test for differences between ^c total Mbeya- and Itende-group/ ^d Ghana- and advertisement-group

Table 2

Factors independently associated with HIV-1 seroconversion ^a.

Characteristic/ Category	HIV seroconverted/ PY	HIV incidence/ 100 PY	Univariable analysis		Multivariable analysis	
			HR ^b (95% CI)	p	HR ^c (95% CI)	p
Sex						
Male	38/3191	1.19	Ref.	0.33	Ref.	0.03
Female	63/4280	1.47	1.22 (0.82-1.84)		1.64 (1.05-2.57)	
Residence						
Mbeya (urban)	61/4757	1.28	Ref.	0.65	Ref.	0.69
Itende (semi-urban)	40/2714	1.47	1.10 (0.73-1.66)		0.90 (0.53-1.52)	
Age (years)						
18-19	20/1303	1.53	Ref.	<0.01	Ref.	<0.01
20-24	36/1934	1.86	1.22 (0.71-2.11)		0.93 (0.51-1.69)	
25-29	21/1474	1.42	0.95 (0.52-1.77)		0.68 (0.35-1.30)	
30-34	14/1028	1.36	0.88 (0.45-1.74)		0.54 (0.26-1.12)	
35-39	7/805	0.87	0.56 (0.24-1.33)		0.29 (0.11-0.75)	
40-45	3/927	0.32	0.21 (0.06-0.71)		0.09 (0.03-0.32)	
Religion						
Catholic	19/1281	1.48	Ref.	0.15	Ref.	0.28
Protestant	59/4867	1.21	0.84 (0.50-1.41)		0.96 (0.57-1.63)	
Muslim	4/571	0.70	0.47 (0.16-1.39)		0.54 (0.18-1.61)	
No religion	18/742	2.43	2.15 (1.03-4.50)		1.78 (0.87-3.66)	
Education						
No school education	16/787	2.03	Ref.	0.69	Ref.	0.01
Primary unfinished	9/447	2.01	1.01 (0.44-2.34)		1.01 (0.43-2.35)	
Primary finished	63/4675	1.35	0.56 (0.32-0.98)		0.66 (0.38-1.14)	
Secondary or more	13/1550	0.84	0.32 (0.14-0.74)		0.39 (0.17-0.89)	
Alcohol consumption						
Never	56/5121	1.09	Ref.	<0.01	Ref.	0.02
occasionally, less than weekly	16/735	2.18	2.27 (1.29-4.02)		1.83 (1.02-3.30)	
occasionally, weekly	19/1069	1.78	2.31 (1.33-4.00)		1.64 (0.91-2.94)	

Characteristic/ Category	HIV seroconverted/ PY	HIV incidence/ 100 PY	Univariable analysis		Multivariable analysis	
			HR <i>b</i>	95% CI	HR <i>c</i>	95% CI
Almost daily	10/545	1.83	3.48	(1.73-7.02)	2.01	(1.00-4.07)
<i>Lifetime sex partners</i>						
None	8/859	0.93	0.80	(0.34-1.88)	0.85	(0.35-2.07)
1	28/2977	0.94	Ref.		Ref.	
2	30/1460	2.05	2.62	(1.55-4.42)	2.28	(1.34-3.90)
3 or 4	19/1112	1.71	2.41	(1.32-4.41)	1.97	(1.07-3.64)
More than 5	16/1062	1.51	2.68	(1.41-5.11)	2.22	(1.13-4.36)

PY = person years; HR = hazard ratio; CI = confidence interval; p = probability value for trend, adjusted p-value for each variable when introduced into the model as a continuous predictor; Ref. = reference category for hazard ratios calculations

^a Variables that did not reach the significance level of 5% are omitted.

^b adjusted for age, sex and study location

^c adjusted for all variables in the table