Impact of recurrent sexually transmitted infections on HIV seroconversion: results from multi-state frailty models

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Conflict of interest

The author(s) declare that they have no competing interests.

Disclaimer

The findings and interpretation of this study are those of the authors only.

Ethical approval

Ethical approval for the trials, including all study protocols and informed consent forms, were received from the University of KwaZulu-Natal Biomedical Research Ethics Committee and the South African Medical Research Council Ethics Committee as well as the various study-specific Institutional Review Boards.

Authors' contributions

HW, SN and JM drafted the concept. TR and HW pooled the dataset and performed the statistical analysis. HW drafted the manuscript. SN, JM, and TR interpreted the results and assisted in drafting the manuscript. All authors read and approved the final manuscript.

Informed consent

Study participants who enrolled in these trials provided either written or verbal consent. Participants confirmed their consent by signature or witnessed thumbprint.

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Abstract

After several decades of research, South Africa is still considered to be the epicentre of HIV epidemic. The country has also the highest burden of sexually transmitted infections(STIs) which have been frequently linked to increasing rates of HIV transmission due to biological and behavioral associations between these two pathogenesis. We investigated the cumulative impact of recurrent STIs on subsequent HIV seroconversion among a cohort of South African women. We used the "*frailty*" models which can account for the heterogeneity due to the recurrent STIs in longitudinal setting. The lowest HIV incidence rate was 5.0 /100 person-year among women who had no baseline STI and remained negative during the follow-up. This estimate was three-times higher among those who had recurrent STIs in the follow-up period regardless of their STI status at baseline (15.8 and 14.0 /100-person-year for women with and without STI diagnosis at baseline respectively). Besides younger age and certain partnership characteristics, our data provided compelling evidence for the impact of recurrent STI diagnoses on increasing rates of HIV. At the population-level, 65% of HIV infections. These results have significant clinical and epidemiological implications and may play critical role in the trajectory of the infections in the region.

Key words: HIV, South Africa, Sexually transmitted infections, frailty models

Introduction

According to World Health Organisation (WHO) estimates, globally more than 360 million people are infected with sexually transmitted infections (STIs). [1,2] Besides causing significant social stigma and shame, untreated

STIs have also been linked to adverse reproductive health conditions such as infertility, preterm and ectopic pregnancies.[3-5] A strong biological association between STIs and HIV acquisition have also been reported due to the disruption of the mucosal barriers and inflammation. [6,7] These mechanisms have been shown to facilitate HIV transmission by changing the vaginal immunity. [8,9] In addition to a biological link, HIV and STIs also have overlapping risky sexual behaviours. [10,11] In fact, along with the other established risk factors, STIs were identified as one of the most influential predictors of HIV infection and were included in risk scoring algorithms to predict those at increased risk of HIV among populations in Southern Africa where 70% of the infected people live.[12,13,15] The region also has the highest burden of STIs.[16] Therefore, providing guidance to the current and future HIV prevention programs and policymakers is essential. It is thus crucial to understand "how to weigh the STIs and their impacts on HIV acquisition" which is one of the research priorities. Consistent with this priority, the current study aimed to quantify the association between HIV and STIs among women who participated in biomedical intervention trials and resided KwaZulu-Natal, South Africa (2002-2016).[17-22] We primarily focused on quantifying the impact of recurrent STIs on HIV acquisition using transition-specific models. In our modelling approach, recurrent STIs are assumed to be the clinical *intermediate* event(s) before the HIV infection (or censoring/end of study) which was considered as a "*terminating event*". We hypothesized that women who had repeated STI diagnoses may be correlated through an "*unobserved*" heterogeneity which potentially represents the accumulation effect of STIs on HIV transmission. We also hypothesised that they may share some "*observed*" behavioral and biological characteristics which may increase their susceptibility to HIV. Therefore, we introduced transition-specific models in which the hazard functions for transitions between any two states are dependent, not only on a vector of known risk variables, but also on a random component which was considered to reflect the impact of recurrent STIs and their accumulation effect on transitions between STIs and HIV. In our setting, such a random component is termed as the "*frailty*" of the women who had recurrent STIs and is included in the models for hazard as a random component.

After several decades of research, South Africa is still considered to be the epicentre of the epidemic. The country has also the highest burden of bacterial STIs.[11,16] Therefore, understanding the association between recurrent STIs

and subsequent HIV acquisition is crucial and may have significant implications in clinical and epidemiological settings. While there is substantial research that reports significant links between STIs and HIV infection, most of these studies used cross-sectional data which may be compromising the results due to their complex bi-directional association.[23]

This is the first study with several longitudinally measured clinical outcomes in a cohort of women who resided in a region where the HIV epidemic is uniquely severe. Our transition-specific modelling approach will increase our understanding of the complex association between recurrent STIs and HIV using this cohort of women.

Materials and Methods

Study design and population

A total of 9,948 women enrolled in six HIV prevention studies (2002-2016). Main studies including descriptions of the study populations were published elsewhere. [17-22] Briefly, the inclusion criteria were similar across all the trials. They also used the similar HIV/STI testing methods. Women were tested for HIV and STIs [chlamydia (*Chlamydia trachomatis*), gonorrhoea (*Neisseria gonorrhoeae*), and trichomoniasis (*Trichomonas vaginalis*) at baseline and during the pre-scheduled visits. Women were also tested for syphilis (*Treponema pallidum*). The study team provided counselling before and after the tests. Women who were diagnosed with any STI were either provided with treatment at the research site or referred for free treatment according to the study-specific and local guidelines. Almost all the infections were recorded during the scheduled visits rather than unscheduled visits due to symptoms.

Measurements

Time to HIV seroconversion was the primary outcome of the study and was calculated using the date at baseline and date at HIV positive test result (or censoring/end of the study). Similar methodology was used to calculate "time to STI infection". Any positive STI test during the study were regarded as a new infection. We analyzed all the measurements if they were available in all studies. Participants' age was split into five categories(<20, 20-24, 25-29, 30-34, 35+ years); women's marital status was categorised as: single/not cohabiting vs.

married/cohabiting; schooling (less than secondary vs. secondary or more), age at sexual debut (younger than 20 vs. 20 years or older), multiple/concurrent sex partners in past three months (<2 vs. 2+), knowledge of partner's partner (yes/no), condom use (at last sex) (yes/no), baseline STI diagnosis (yes/no), contraceptives: oral/pill and injectables and other.

Statistical Analysis:

The baseline characteristics of the women were presented using percentages. Figures 1a and 1b presents all possible states and transitions in our models. HIV incidence was initially analysed as a two-state model by using a standard Cox regression model which was repeated for the women with and without STI diagnosis at baseline (Model 2 and Model 4 respectively). We also considered models for HIV seroconversion following recurrent STI diagnoses. We mainly focused on the models in which the hazard functions for transitions between any two states are dependent, not only on a vector of known risk factors, but also on a random person component which is referred as the "*frailty*" of the individual and is included in the models for hazard as a random component (Model 3 and Model 5). In our modelling approach, we used the following transitions:

T_{12}: Transition from State 1 (HIV seronegative) to State 2 (HIV seropositive) .

T_{13} & T_{23}: Transition from state 1 (HIV seronegative) to state 2 (HIV seropositive) following the State 3 (i.e., following recurrent STI diagnoses). Each of these transitions has a potentially different hazard function:

$h(t_{12}) = \alpha(t_{12})exp(x_1'\beta)$,

$h(t_{32}|t_{13}) = \alpha(t_{32}|t_{13})exp(x_3'\beta + U)$,

where t_{ij} is the time from the i^{th} state to the j^{th} state where $i = 1, 2, 3$ and $j = 1, 2, 3$ for the three possible transitions as described in Figure 1b. In these expressions the β are unknown vectors of regression coefficients for the risk variables in each transition. We also included unobserved random effect, U into the hazard function following recurrent STIs during the study follow-up which represents the "*frailty"* of a woman i in transition type T_{23} and $U \sim N(0, \sigma_u^2)$ In this setting, the term "*frailty*" is interpreted as the accumulated impact of repeated STI diagnoses and potentially associated with woman's susceptibility to HIV. We identified transition-specific predictors after fitting the models separately to transition T_{12} and jointly for transitions T_{13} and T_{23} with frailty

component in order to account for heterogeneity (i.e. frailty) due to the recurrent STIs. We also estimated population-level impact of baseline and recurrent STIs on HIV using a modified version of population attributable risk (PAR%) which was described in Appendix.

Assessment using a "Heat-Map"

We also provided a visual assessment to evaluate the age-specific impact of baseline and recurrent STI diagnoses on HIV seroconversion rates. In this analysis, we used a "Heat-map" to compare the HIV incidence rates visually across the four age groups (i.e. <25, 25-29, 30-34 and 35 year or older) in the following populations: overall (regardless of STI status) (transition: T_{12} in model 1); women with/without baseline STIs (transition: T_{12} in model 2 and model 4); women with/without baseline STIs as well as recurrent STI diagnoses (transition: T_{32} following transition: T_{13} model 3 and model 5 respectively).

Results

The current analysis was based on 9,948 women who were HIV negative at baseline (median age: 26). More than 50% of them had less than primary schooling (Table 1). The vast majority of them indicated their sexual debut to be < 20 years; 77% of them were not married and/or not cohabiting with their partners; only 25% of the study population were sure that their sexual partners did not have another partner. Injectable contraceptives were the most prevalent contraceptive method. Baseline STI prevalence was 18% while incidence of HIV infection was 6.7 per 100 person-year regardless of baseline and on-study STI diagnosis (Figure 1a: transition T_{12}) (Table 2). This estimate declined to 5.0 per 100 person-year (95% CI: 4.4, 5.5) among women who did not have baseline STI diagnosis and remained negative in the follow-up; while it increased to 8.7 per 100 person years in the group who had positive STI test at baseline but remained STI free during the study follow-up/censoring. (i.e. transition T_{12}, in model 2). While HIV incidence rate was more than doubled (14.0 per 100 person-year, 95% CI: 12.0, 16.0) among participants with no baseline STI, had a recurrent STI diagnosis before they seroconverted (or censored) (i.e. transition T_{32}, in model 2) (Figure 1b). This rate increased to 15.8 per 100 person-year (95% CI: 9.6, 17.2) among those who had baseline and recurrent STI diagnoses (i.e. transition T_{32}, in model 3).

Predictors of HIV seroconversion: two-state models

Results from the multivariable Cox regression analysis for model 1 was presented in Table 1. Younger women were the group at increased risk of HIV seroconversion (aHRs ranged from 1.54 for women 30-34 years old to 3.75 for women <20). Single women were also at higher risk of HIV with aHR: 1.74 (95% CI: 1.50, 2.00). In addition, those who indicated that their partners' have other partner(s) or were not sure were 63% and 82% more likely to seroconvert. Women with positive STIs at baseline were 60% more likely to seroconvert (95% CI: 1.36, 1.90), compared to those who tested negative. We also determined the predictors of HIV seroconversion after stratifying the women according to their baseline STI status. Younger age [aHR: ranged from 1.60 (30-34 years old) to 4.13 (<20 years old)], being single (aHR: 2.03, p<0.001) and those who reported using injectables (aHR: 1.30, p<0.001) were all at higher risk of HIV seroconversion than in the group without STI diagnosis at baseline and remained STI free during the study (i.e. transition T_{12}, in Figure 1b); these factors were also statistically significant among those who had at least one STI diagnosis at baseline but remained STI free during the study (i.e. transition T_{12}, in Figure 1b); while higher number of sex partners, knowing that their sexual partner has another partner and using condoms at last sex were associated with higher risk of HIV infection in women with no baseline STI diagnosis.

Predictors of HIV seroconversion: frailty models

In a stratified analysis based on the women's baseline STI status, adjusted hazard ratios for the significant risk factors were presented after accounting for accumulated effect of recurrent STI diagnoses using the Cox regression models with a "frailty" term (i.e., transition T_{23} following transition T_{13}) (Table 2). Consistent with the previous results, younger women (<30 years) were significantly at higher risk of HIV (aHR ranged: 1.63 to 2.42), 30 to 34 years of them significantly at lower risk of HIV (aHR: 0.64, p=0.038) compared to the oldest age group (35+ years). Other characteristics including single/non-cohabiting women (aHR: 2.48, p<0.001), multiple sex partners (aHR: 1.66, p=0.001) and those reported using injectable contraceptives (aHR: 1.29, p=0.006) were all significantly at risk of HIV infection. Except age groups, these characteristics were also statistically significant among the study participants with STI diagnosis at baseline. The estimated variance component of the random frailty terms were also significant in both models (θ=0.17, 95% CI: 0.02, 1.40 and θ=0.16, 95% CI: 0.06, 1.12, p<0.001, both models).

State-specific Population Attributable Risk (PAR%)

PAR% (95% CI) of STIs on HIV seroconversion rates are presented in Table 2. In overall analysis, baseline STI diagnosis was associated with 20% of HIV infections (T_{12}). In model 5, transition-specific PAR% was estimated as 41.8% (95%: 33.0%, 51.2%) among women who did not have any STI at baseline but moved to state 3 during the study follow-up i.e., $\gamma(t_{32}|t_{13})$. This proportion increased to 64.6% (95% CI: 59.5%, 69.4%) among women who had baseline/recurrent STIs (i.e., $\gamma(t_{32}|t_{13})$, in model 3.

Age-specific HIV infection rates:

Figure 2 presents age-specific visual associations between STI and HIV infection (Figure 2). The youngest age group (<25 years old) had the highest HIV infection rates regardless of STI positivity (baseline and/or recurrent STI) (incidence rates: 10 to 16 per 100 person-year). Meanwhile the older group's risk of HIV seroconversion rates were the lowest (<5 per 100 person-year) in overall study population, but was increased substantially with co-occurrence of baseline and/or recurrent STI diagnosis during the follow-up (ranged 7 to 14 per 100 person-year).

Discussion

We investigated the impact of recurrent STI diagnoses on HIV infection among South African women who consented to participate in biomedical intervention trials. Besides standard survival analysis techniques, we also used "*frailty*" models which can account for the intermediate events such as recurrent STIs. Our data provided compelling evidence for the impact of recurrent STI diagnoses on increasing HIV acquisitions. In our analysis, the lowest HIV incidence rate was 5.0 per 100 person-year among women without baseline STIs and remained negative in the study follow-up period. This estimate was almost three-times higher among those who had

recurrent STIs in the follow-up period regardless of their STI status at baseline (14.0 and 15.8 per 100 person-year for women without and with STI diagnosis at baseline). In the overall study population, women with baseline STI diagnosis were 60% more likely to be infected with HIV compared to those without STI diagnosis at baseline. Consistent with the published research, younger women (< 25 years age) were significantly more likely to seroconvert compared to the oldest age group (35 years or older). Women's marital status, and sexual partnership characteristics (higher number of sex partners, those who knew their partner had another partner) were the other significant predictors of subsequent HIV seroconversion and were also mostly significant in all models after accounting for accumulation effect of recurrent STI diagnoses. Despite several differences in populations and methods used, our findings are consistent with previous studies conducted in Southern Africa. Young women and their partnership characteristics continuously play key roles in shaping the epidemic in South Africa. [14,16,23] Despite contrary evidence from a recent clinical trial[24], in our study population women who reported using injectable contraceptives were identified as the group at increased risk of HIV regardless of baseline and recurrent STI diagnoses. In fact, in addition to single/not cohabiting women, those who reported using injectable contraceptives were the only two characteristics which were associated with increased rates of HIV seroconversion in all models. Although we cannot ascertain this, based on the high HIV infection rate in our study population this association was considered as behavioural rather than biological which was also reported previously.[25,26]

After decades of intensive efforts and widely available testing and treatment programs, South African women continue to have the highest burden of HIV as well as bacterial STIs which are potentially curable. Besides certain sociodemographic/economic factors, single young women, low levels of schooling and lack of regular income, sexual risk-taking behaviours have also been extensively reported to be associated with increasing rates of HIV.[11,16,23] These factors are collectively linked to risky sexual behaviours including high-levels of transactional sex which may decrease women's negotiation skills for condom use. [27-29]

Our analysis also provided evidence that participants who indicated using condoms at last sex were also more likely to seroconvert in most of the models. This counterintuitive result could be explained by women's correct perception about their risky sexual behaviours which may have led them to use condoms with their sexual partner. This was previously reported in sub-Saharan Africa.[30-32] For example, high-levels of consistent condom use were reported among individuals who had multiple/concurrent sex partners with the perception of being at increased risk of HIV.[30,33] However, extremely high STI and HIV incidence rates in our analysis provide strong evidence for high-levels of condomless sex which have been consistently reported among South African women.[16,23]

Results from our study will potentially provide guidance for the current and future HIV prevention programs by emphasizing the crucial role of recurrent STIs on subsequent HIV transmission among South African women. We recommend incorporating STI testing and treatment strategies into HIV prevention programs. This may potentially provide effective/cost-effective ways of reducing HIV infections.

Limitations

The results should be interpreted carefully due to the limitations associated with our stud and the data. First, the study populations were women at reproductive age who agreed to participate in biomedical intervention studies with certain exclusion/inclusion criteria such as being sexually active. As a result, they are more likely to be at increased risk of HIV compared to the population in general. There were no data available from women's partners, including their HIV and STI status. Apart from clinical/biological measurements which were collected by the study teams, rest of the factors were self-reported by participants. Therefore, we cannot rule out over/under-reporting. Finally, all the STIs were considered as new infections. We did not consider any treatment failure and assumed all the infections were treated and cured. Despite these limitations and issues, quantifying the role of curable STIs on HIV seroconversion in a longitudinal setting is crucial due to their potentially complex and bi-directional association. This is the first study to investigate recurrent STIs on increasing risk of HIV infection in a multifactorial setting using a large cohort of women with longitudinally measured clinical events.

Conclusion

Quantifying the role of curable STIs on HIV seroconversion in a longitudinal setting is crucial and potentially have significant clinical and epidemiological implications. Our findings emphasize that to have a substantial impact on HIV prevention, in addition to risky sexual behaviours and certain partnership characteristics, women with recurrent STIs should also be targeted.

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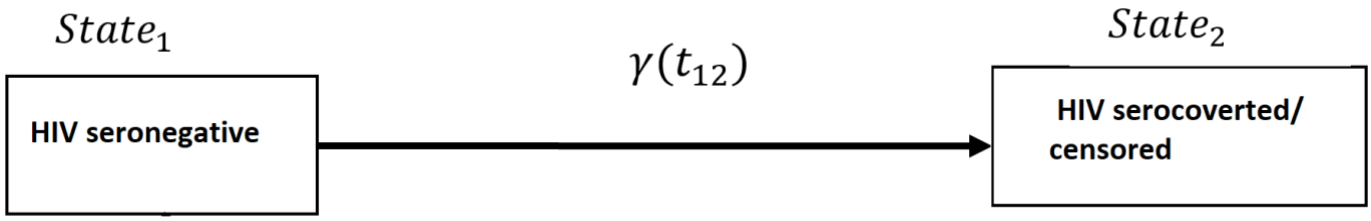
Figure 1: Survival Models: Impact of STIs on HIV infection rates:

a) Cox regression model: Two-state model (regardless of baseline and on-study STI diagnosis)



b) Frailty model: Impact of recurrent STI on HIV incidence rates during the follow-up: $State_i$ where $i = 1, 2, 3$; T_{12}, T_{23}, T_{13} transitions to HIV and STI incidence

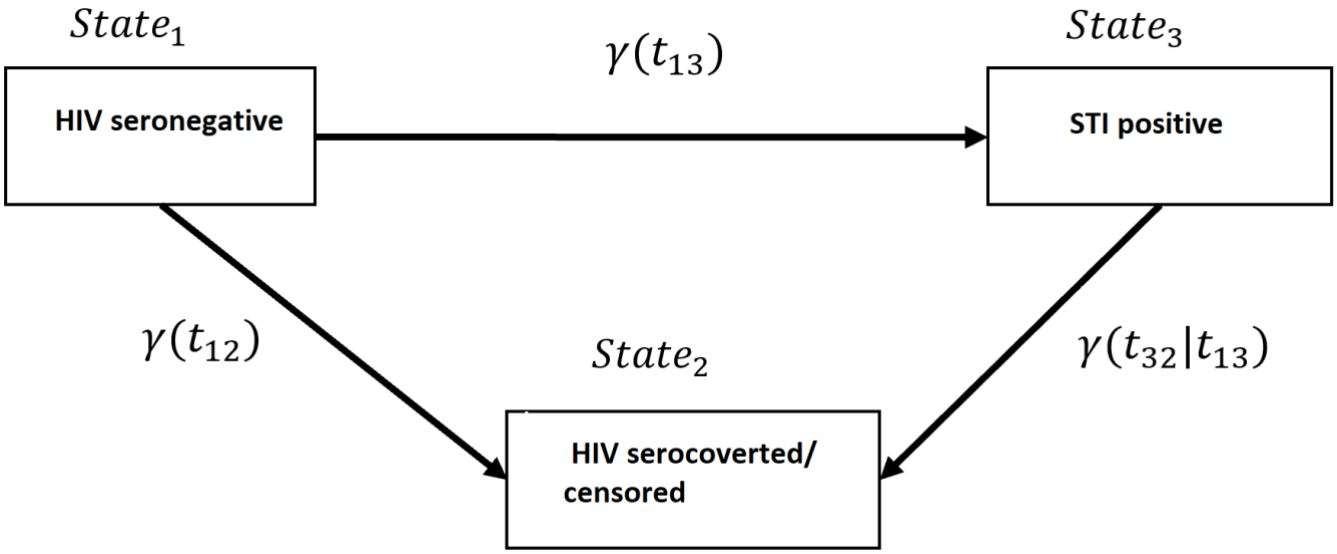


Table 2: Individual and population-level impacts of STIs

	Adjusted Hazard ratio (95% CI)		**PAR%[§] (95% CI) for STI diagnosis** (baseline or recurrent)
Model 1: $\gamma(t_{12})^{\xi}$			
STI(s) (time-dependent)	1.80 (1.47, 2.23)	<0.001	22.2% (19.2%, 25.6%)
Model 3: $\gamma(t_{32}\|t_{13})^{\xi\xi}$			
Recurrent STI(s)	2.85 (2.35, 3.46)	<0.001	64.6% (59.5%, 69.4%)
θ (variance of frailty)	0.17 (0.02, 1.40)	<0.001	-
Model 5: $\gamma(t_{32}\|t_{13})^{\xi\xi\xi}$			
Recurrent STI(s)	2.31 (1.97, 2.71)	<0.001	41.8% (33.0%, 51.2%)
θ (variance of frailty)	0.16 (0.09, 1.12)	<0.001	-

[§] adjusted PAR% from multivariable models ; [ξ] STIs Results from a standard Cox regression model when STI(s) were fitted as a time-dependent variable; [ξ ξ] with baseline STIs: results from a frailty model after accounting for repeated STI occurrences during the follow-up; [ξ ξ ξ] without baseline STIs: results from a frailty model after accounting for repeated STI occurrences during the follow-up.

Table 1: Predictors of HIV incidence for the transition-specific models: adjusted [§] hazard ratios (95% CI)

[§] All significant hazard ratios were reported from the multivariable models, while non-significant hazard ratios were reported from adjusted models where the models were adjusted for the independent predictors in each model separately; [ξ] In the past 3 months;

	%	Overall: with/without STI		With baseline STI diagnosis				Without baseline STI diagnosis			
		Model 1: $h(t_{12})$		**Model 2:** $h(t_{12})$		**Model 3:** $h(t_{32}\|t_{13})$		**Model 4:** $h(t_{12})$		**Model 5**: $h(t_{32}\|t_{13})$	
θ (for frailty)				-		**0.17 (0.02, 1.40) (p<0.001)**		-		**0.16 (0.09, 1.12) (p<0.001)**	
Age		**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
<20 years	10%	3.75 (2.81, 5.01)	<0.001	2.90 (1.60, 5.00)	<0.001	1.30 (0.67, 2.50)	0.448	4.13 (2.91, 5.90)	<0.001	2.42 (1.66, 3.52)	<0.001
20-24 years	35%	3.17 (2.47, 4.08)	<0.001	2.34 (1.41, 3.90)	0.001	1.28 (0.72, 2.27)	0.401	3.36 (2.50, 4.55)	<0.001	1.91 (1.40, 2.64)	<0.001
25-29 years	22%	2.41 (1.84, 3.17)	<0.001	1.54 (0.85, 2.81)	0.150	0.83 (0.42, 1.63)	0.586	2.71 (1.96, 3.75)	<0.001	1.63 (1.15, 2.30)	0.006
30-34 years	13%	1.54 (1.12, 2.12)	0.008	1.52 (0.76, 3.01)	0.230	0.55 (0.26, 1.14)	0.106	1.60 (1.10, 2.34)	0.016	0.64 (0.42, 0.98)	0.038
35+ years	20%	1		1		1				1	
Level of education											
Less than secondary	55%	1.10 (0.94, 1.24)	0.300	1.11 (0.83, 1.48)	0.492	1.42 (1.13, 1.79)	0.003	1.01 (0.86, 1.20)	0.890	1.13 (0.94, 1.35)	0.206
Secondary or more	45%	1		1		1		1		1	
Age at sexual debut											
20+ years old	16%	1		1		1		1		1	
<20 years old	84%	1.37 (0.90, 2.10)	0.141	1.40 (0.66, 3.00)	0.400	1.90 (1.10, 3.40)	0.030	1.30 (0.78, 2.17)	0.318	1.35 (0.77, 2.40)	0.297
Marital status											
Married/cohabitating	23%	1		1		1		1		1	
Single/not cohabiting	77%	1.74 (1.50, 2.00)	<0.001	2.50 (1.32, 5.00)	0.004	1.80 (1.20, 2.73)	0.005	2.03 (1.68, 2.45)	<0.001	2.48 (1.86, 3.31)	<0.001
Number of sex partners[ξ]											
<2	87%	1		1		1		1		1	
2+ partners	13%	1.46 (1.14, 1.87)	0.003	0.96 (0.54, 1.70)	0.883	1.60 (1.10, 2.28)	0.013	1.60 (1.21, 2.11)	0.001	1.66 (1.24, 2.22)	0.001
Condom used (last sex)											
No	33%	1		1		1		1		1	
Yes	67%	1.20 (1.04, 1.40)	0.012	1.20 (0.88, 1.64)	0.264	1.25 (0.98, 1.60)	0.075	1.30 (1.10, 1.53)	0.008	1.29 (1.08, 1.56)	0.006
Partner has partner											
No	25%	1		1		1		1		1	
Yes/Don't know	75%	1.82 (1.36, 2.42)	<0.001	1.28 (0.72, 2.27)	0.397	1.10 (0.73, 1.61)	0.678	1.94 (1.40, 2.71)	<0.001	3.10 (1.55, 6.11)	0.001
Contraceptive use											
Others	37%	1		1							
Oral Pills	10%	0.74 (1.15, 1.66)	<0.001	0.75 (0.33, 1.72)	0.500	0.67 (0.40, 1.14)	0.137	0.76 (0.52, 1.10)	0.137	0.70 (0.49, 1.00)	0.500
Injectables	53%	1.38 (1.15, 1.66)	<0.001	1.82 (1.22, 2.72)	0.003	1.48 (1.17, 2.00)	0.001	1.30 (1.10, 1.60)	0.002	1.29 (1.08, 1.56)	0.006
STI at baseline											
No	82%	1		-	-	-	-	-	-	-	-
Yes	18%	1.60 (1.36, 1.90)	<0.001	-	-	-	-	-	-	-	-

Appendix: *Transition-Specific population-level impacts of sexually transmitted infections*

In the transition-specific analysis, the population-level impacts of the baseline and recurrent STIs on HIV seroconversion rates were estimated in a multifactorial setting using the generalized version of the population attributable risk (i.e. $PAR\%$) (95% CI). All the estimates adjusted for potential confounders as well as accounted for the correlation structure of the significant predictors of HIV infection for model 1, model 2 and model 3 separately.[14] For a single risk factor:

$$PAR = \frac{p(HR-1)}{p(HR-1)+1} = 1 - \frac{1}{\sum_{s=1}^{2} p_s HR_s} \qquad (1)$$

where hazard ratio (HR) was estimated from the Cox regression models and p is the prevalence of characteristics considered in this study; where s = the levels of a characteristic considered in the model. Above equation was expanded for more than one risk factors and accounted for their multi-factorial correlation structure:

$$PAR = \frac{\sum_{s=1}^{S} p_s(HR_s-1)}{1+\sum_{s=1}^{S} p_s(HR_s-1)+1} = 1 - \frac{1}{\sum_{s=1}^{S} p_s HR_s}$$

where HR_s and p_s, $s = 1,...,S$, are the hazard ratios from the multivariable Cox regression models and the prevalence of the risk factor(s) in the population for the s th combination of the risk factors.

$$PAR = \frac{\sum_{s=1}^{S}\sum_{t=1}^{T} p_{st} HR_{1s} HR_{2t} - \sum_{s=1}^{S}\sum_{t=1}^{T} p_{st} HR_{2t}}{\sum_{s=1}^{S}\sum_{t-1}^{T} p_{st} HR_{1s} HR_{2t}} = 1 - \frac{\sum_{t=1}^{T} p_{\bullet t} HR_{st}}{\sum_{s=1}^{S}\sum_{t=1}^{T} p_{st} HR_{1s} HR_{2t}} \qquad (3)$$

where t is a unique combinations of factors which are not targeted (i.e. factors from multivariable models), $t = 1,...,T$ and HR_{2t} is the hazard ratio in combination t relative to the reference level, i.e. $HR_{2,1}$ =1.