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High prevalence and incidence of gonorrhoea and chlamydia in young women eligible for HIV pre-exposure prophylaxis in South Africa and Zimbabwe: results from HPTN 082 trial

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Abstract

Introduction: We investigated the prevalence, incidence and factors associated with STIs among young African women seeking HIV pre-exposure prophylaxis (PrEP).

Methods: HPTN 082 was a prospective, open-label PrEP study enrolling HIV-negative sexually active women aged 16–25 years in Cape Town and Johannesburg, South Africa, and Harare, Zimbabwe. Endocervical swabs from enrollment, month 6 and 12 were tested for *N. gonorrhoeae* (GC) and *C. trachomatis* (CT) by nucleic acid amplification, and *T. vaginalis* (TV) by a rapid test. Intracellular tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS) were

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AUTHORSHIP

SDM and CC designed the study, with input from NM, LGB, JMB, DD, SR and AA; SDM, NM, LGB, MM, SK, SM implemented the study; DL, contributed essential reagents or tools; CL and DD analyzed the data; SDM wrote the first draft of the manuscript; all authors provided critical review of the manuscript and approved the final version.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

measured at months 6 and 12. Associations between risk characteristics and STI outcomes were assessed using Poisson regression.

Results: Of 451 enrolled participants, 55% had an STI detected at least once. CT incidence was 27.8 per 100 person-years (py) (95% CI 23.1, 33.2), GC incidence was 11.4 per 100 py (95% 8.5,15.0), and TV incidence was 6.7 per 100 py (95% CI 4.5, 9.5). 66% of incident infections were diagnosed in women uninfected at baseline. Baseline cervical infection (GC or CT) risk was highest in Cape Town (RR 2.38, 95% CI 1.35, 4.19) and in those not living with family (RR 1.87, 95% 1.13, 3.08); condom use was protective (RR 0.67, 95% CI 0.45, 0.99). Incident CT was associated with baseline CT (RR 2.01; 95% CI 1.28, 3.15) and increasing depression score (RR 1.05; 95% CI 1.01,1.09). Incident GC was higher in Cape Town (RR 2.40; 95% CI 1.18, 4.90) and in participants with high PrEP adherence (TFV-DP concentrations ≥ 700 fmol/punch) (RR 2.04 95% CI 1.02, 4.08).

Conclusion: Adolescent girls and young women seeking PrEP have a high prevalence and incidence of curable STIs. Alternatives to syndromic management for diagnosis and treatment are needed to reduce the burden of STIs in this population.

Keywords

HIV prevention; pre-exposure prophylaxis; sexually transmitted infections; screening; adolescent girls and young women; Sub-Saharan Africa

BACKGROUND

Women in sub-Saharan Africa (SSA) bear a disproportionate burden of sexually transmitted infections (STIs), including human immunodeficiency virus (HIV)[1]. In 2019, adolescent girls and young women (AGYW) aged 15–24 years accounted for 26% of new HIV infections in eastern and southern Africa[1]. In 2016, the WHO African region had the highest prevalence and incidence for gonorrhoea and trichomoniasis in women globally [2]. Untreated gonorrhoea (GC) and chlamydia (CT) increase the risk of pelvic inflammatory disease (PID), ectopic pregnancy, chronic pelvic pain, and tubal infertility significantly [3]. Up to 15–20% of women with documented chlamydial or gonococcal PID develop infertility [4–6]. Infertility has serious social consequences for many women including poor mental health and intimate partner violence [7]. Women with secondary infertility may increase their risk for HIV in their attempts to conceive through frequent condomless sex [8]. STIs increase the risk of HIV acquisition and transmission several-fold, even if STIs are asymptomatic [9 10]. Untreated bacterial STIs are also associated with poor pregnancy and infant outcomes, including prematurity, death, and congenital infections [11]. Overall, untreated STIs and their complications result in a considerable number of disability-adjusted life years lost, particularly in women and infants in SSA [12].

Syndromic case management (SM) is still the mainstay of STI prevention and control programs in Africa and is based on the recognition of signs and symptoms associated with particular pathogens, and treatment for the most frequent causes of that syndrome[13]. While SM has some advantages over other approaches in resource-constrained settings, limitations in the diagnosis and management of cervical infections in women are well-established [13].

The vaginal discharge algorithm is a poor predictor of cervical infection, even after the addition of risk scores or simple laboratory evaluations [14–18]. As a result, high numbers of women are either overtreated or miss treatment (due to frequent asymptomatic infections) with the potential for serious long-term consequences.

Expanding pre-exposure prophylaxis (PrEP) programs in SSA provide an opportunity to strengthen failing STI prevention and control programs by providing a platform to integrate aetiologic STI testing for at-risk persons, and to link at-risk individuals to novel STI prevention interventions. To date, few data on STIs in African women taking PrEP have been available. HPTN 082 was an open-label PrEP demonstration project that assessed oral PrEP uptake and adherence among African AGYW and included laboratory testing and treatment for prevalent and incident STIs. We assessed the prevalence and incidence of chlamydia and gonorrhoea and predictors of infection in this cohort, as well as explored the relationship between PrEP adherence based on tenofovir diphosphate concentrations and subsequent STIs.

METHODS

Study population

Between October 2016 and October 2018, 451 HIV-negative women aged 16–25 years were recruited for HPTN 082 from Cape Town and Johannesburg, South Africa, and Harare, Zimbabwe (clintrials.gov NCT02732730). Women were eligible if they had vaginal or anal sex in the month prior to screening, showed interest in PrEP based on the HIV Prevention Readiness Measure (adapted from the HIV Treatment Readiness Measure) [19], had regular access to a mobile phone, were hepatitis B surface antigen negative, had creatinine clearance >60 ml/min, were not pregnant and had a score of ≥5 on the VOICE risk score [20]. VOICE risk scores ≥5 have been associated with HIV incidence >5 per 100 person-years in previous cohorts of African women seeking HIV prevention[21].

Study procedures

Details of the study procedures have been published elsewhere.[20] Briefly, consenting AGYW were eligible to enroll regardless of their decision to initiate PrEP, and those who did not initiate PrEP at enrolment were offered PrEP at each subsequent visit. Cervico-vaginal and blood samples collected at screening, month 6 and month 12 visits. Swabs were self-collected unless a pelvic examination was indicated in which case clinician-directed samples were collected. Dried blood spots (DBS) for PrEP adherence measurements were also collected at months 6 and 12. Participants with STI symptoms and signs received immediate treatment according to national syndromic management guidelines. Asymptomatic participants with positive laboratory test results were treated with appropriate antibiotics at the earliest subsequent visit. No test of cure was performed. Participants with an STI also received risk reduction counseling, condoms and were encouraged to have their partner treated (i.e., partner notification) using direct referral.

Cervico-vaginal swabs were tested for *Neisseria gonorrhoeae* (GC) and *Chlamydia trachomatis* (CT) by nucleic acid amplification test (Cepheid GeneXpert, Sunnyvale CA),

and *Trichomonas vaginalis* (TV) by rapid test (OSOM® Trichomonas Test, Seikusui Diagnostics, Burlington MA). Syphilis was assessed by Rapid Plasma Reagin (Macro-Vue RPR Test, Becton Dickinson, Sparks, MD, USA) followed by a treponemal-specific confirmatory assay (Serodia-TPPA, Fujirebio, Tokyo, Japan). DBS were assessed for intracellular tenofovir-diphosphate (TFV-DP) at the University of Colorado, using by liquid chromatography/tandem mass spectrometry [22]. Intracellular TFV-DP concentrations in red blood cells have a 17-day half-life and 25-fold drug accumulation that provides a cumulative measure of dosing and average adherence to PrEP in the prior 6 weeks based on studies of directly observed dosing of PrEP. [22 23]

The study protocol was reviewed and approved by the research ethics committees at each of the study sites. All participants provided written informed consent in English or their preferred local language. Following local regulations, participants below the legal age for consent provided assent and parent/guardian informed consent was obtained.

Statistical analysis

Descriptive statistics summarize socio-demographic, partner and risk characteristics and infection data. Multiple imputation methods were used to impute missing individual components of the Depression Score. Imputation increases statistical power and has been shown to be an appropriate approach to handling missing data for the Center for Epidemiological Studies Depression (CES-D) Scale used in this study and is preferred over assigning a zero score for missing data which would potentially underestimate levels of depression.[24] We compared participant characteristics by site to determine any significant behavioral or risk characteristics by site using linear regression for continuous variables (VOICE risk score and number of vaginal sex episodes) and chi-square tests for categorical variables.

Outcomes of interest were any cervical infection (CT/GC), as well as CT or GC alone at baseline or at either follow-up visit (months 6 and 12). STI incidence rates and 95% confidence intervals were assessed assuming a Poisson distribution. Associations between risk characteristics at baseline and over time and outcomes of interest were assessed using Poisson regression fitted using Generalized Estimating Equations assuming an exchangeable correlation structure. We developed separate models for each outcome (i.e., GC, CT or both infections) and for prevalent and incident infections. Factors considered significant at the .05 level in bivariate regression were included in the final multivariate model. To assess the association between PrEP use and subsequent STI outcomes, we included the categorical variables of any vs. no detectable TFV-DP in DBS, as well as TFV-DP ≥700 fmol/punch vs ≤700 fmol/punch, at month six or 12. The threshold of 700 fmol/punch is associated with an average of four or more PrEP doses per week in directly observed dosing studies that included both men and women, and in the iPrEx study the 700 fmol/punch threshold was associated with 100% PrEP efficacy among men who have sex with men.[22 23 25] At the time of study design, no *in vivo* data were available to support specific thresholds in women.

RESULTS

Participant characteristics at enrolment

Of 646 women screened, 451 participants were eligible and enrolled. Participant median age was 21 years (interquartile range [IQR] 19, 22) (Table 1). More than half (57%, 258/451) lived with parents and/or siblings, 33% (149/451) had a partner who was five or more years older than them, and 65% (299/451) used a long-acting reversible contraceptive (LARC). Participants reported a median of four episodes (IQR 2, 8) of vaginal sex in the prior month, with 22% (101/451) reporting transactional sex (i.e., having sex with a partner because he provided or participant expected he would provide food, clothes, cellphone airtime, etc.) and 15% (68/451) anal sex in the prior month, and 40% (140/352) used a condom at last sex. A minority (8%, 34/449) had a high HIV risk perception, even though the median VOICE risk score was 7 (IQR 5,7). Most (91%, 412/451) accepted PrEP at the enrollment visit while an additional 15 participants initiated PrEP during follow-up. Visit completion rates in this study were high with 83–97% of planned visits completed.

STIs at baseline

At baseline, 39% (174/451) of participants were diagnosed with either CT (30%, 136/174), GC (20%, 35/174), or TV (6%, 10/174,) for a total of 199 curable STI episodes (Table 1). Mixed infections were common. Among participants with CT, 14% (19/136) also had GC and 5% (7/136) had TV. Half (19/35) of those with GC also had CT, and a quarter (7/28) with TV also had CT. Syphilis was rare with reactive syphilis serology in <1% (2/451) and was therefore not included in further analyses.

Participants with a curable STI at baseline were more likely to be younger (p=0.036), from Cape Town (p=0.0001), and to use LARC (p=0.022) (Table 1). AGYW with a curable STI were also less likely to report condom use at last sex (p=0.033). STI status did not appear to influence the decision to initiate PrEP with >90% PrEP uptake across sites (p=0.501).

In multivariable analysis, AGYW living in Cape Town had a two-fold higher risk for prevalent CT compared to their peers in Harare (RR 2.41, 95% CI 1.31, 4.43), while AGYW living with non-family members also had a higher risk for prevalent CT compared to those living with family members (RR 1.93, 95% 1.14, 3.27) (Table 3). In contrast, the only significant predictor of baseline GC was the reported number of vaginal sex acts in the prior month. Risk increased by 3% for every unit increase in sex acts reported (RR 1.03, 95% CI 1.03, 1.06). When assessing risk for any cervical infection i.e. either CT or GC as baseline, risks were similar to those for baseline CT infection alone, although the strength of association weakened. Reported condom use at last sex however emerged as protective against any prevalent cervical infection (RR 0.67, 95% CI 0.45, 0.99).

Incident curable STIs

A total of 204 new curable STI infections were detected during 448.8 person- years of follow-up giving an incidence of 27.8 per 100 person-years (py) for CT (95% CI 23.1, 33.2), 11.4 per 100 py for GC (95% 8.5,15.0), and 6.7 per 100 py for TV (95% CI 4.5, 9.5) (Table 2). Of these 204 incident STIs, 66% (135/204) were in AGYW who had not had an STI at

baseline: 84% (43/51) of incident GC cases were new GC diagnoses, while 73% (22/30) of incident TV cases and 57% (70/123) of incident CT cases were new episodes.

Incident CT infection risk was significantly higher in those with an increasing depression score - every point increase on the score was associated with a 5% increase in the risk for incident CT (RR 1.05; 95% CI 1.01,1.09) – while have a baseline CT infection was associated with a two-fold higher risk of incident CT infection at follow-up (RR 2.01; 95% CI 1.28, 3.15) (Table 3). By comparison, incident GC risk was higher in AGYW who living in Cape Town compared to Harare (RR 2.40; 95% CI 1.18, 4.90) and lower in Johannesburg compared to those living in Harare (RR 0.15, 95% 0.33, 0.70). AGYW with high PrEP adherence (TFV-DP concentrations >700fmol/punch) also had a two-fold higher risk of incident GC (RR 2.04 95% CI 1.02, 4.08). This appeared to be most strongly influenced by differences in drug concentration at the week 52 visit (Supplementary table 1). This association was not observed for incident CT infections (RR 0.78, 95% CI 0.54, 1.13) or incident cervical infection (either CT or GC). Cervical infection at baseline was in fact the strongest predictor of a repeat infection at follow-up (RR 1.66, 95%CI 1.12, 2.45), while living in Johannesburg was associated with a lower cervical infection risk compared to living in Harare (RR 0.56, 95% CI 0.31,1.00) (Table 3).

Differences in characteristics of participants by site

Given the strong influence of geographic location on STI infection risk, we investigated differences in behavioral characteristics by site (supplementary table 2). Compared to participants in Johannesburg and Harare, participants in Cape Town were significantly younger (median 19, IQR 18,21), more likely to use LARC, to have a partner who was 10 or more years older than them, and to report having anal sex. They were also less likely to live with their partner, or suspect their partner of having other partners, and to report sex under the influence of drugs.

DISCUSSION

Over two-thirds of the 451 AGYW at substantial risk for HIV infection in South Africa and Zimbabwe who enrolled in a PrEP demonstration project were diagnosed with one or more curable STIs during one year of follow-up. The high prevalence and incidence of infection in this population indicates that PrEP programs can reach sexually active AGYW with ongoing risk for HIV and other STIs, and that aetiologic STI testing and treatment should be integrated with PrEP services. The finding that high TFV-DP drug concentrations in the prior month were associated with incident gonorrhoea indicates both that AGYW on PrEP continue to be at-risk and suggest based on drug levels associated with higher PrEP adherence that they have confidence in the HIV prevention benefits of PrEP and are motivated to use it. Strengthened STI prevention and control efforts in this population are therefore a priority. Mathematical modelling from South Africa provides supportive evidence that aetiologic STI testing using a GeneXpert-like test and treatment in youth 15–24 years could lead to the greatest reductions in population-wide bacterial STI incidence and prevalence over 10 years, even with low coverage levels [26].

Our data suggest that universal aetiologic STI testing rather than targeted testing based on individual risk factors may need to be implemented in PrEP programs for African AGYW. Few behavioral risk factors for prevalent or incident cervical infection, or CT and GC alone significantly discriminated AGYW with STIs from those without STIs, and those behaviors that did are very prevalent among African AGYW. For example, inconsistent condom use was associated with having any STI, as well as a higher risk of any prevalent cervical infection or CT alone but was reported by 60% of participants at baseline. Instead, we found that recruitment site was the most common factor associated with risk of both prevalent and incident cervical infection, as well as incident GC. Differences in risk behaviors and partner characteristics were observed in each of the sites. Location is likely a proxy for a range of unmeasured partner factors, sexual networks, and social norms, in addition to individual-level differences by site. A combination of individual risk behaviors, partner risk and community infection prevalence likely influenced infection risk [27]. Where targeted STI testing approaches are preferred because of resource constraints, then targeting interventions by location may be more effective than targeting individuals with particular behaviors.

One-third of incident STIs occurred in AGYW with an STI at enrolment, and those with a prevalent CT infection were twice as likely to have a repeat infection at follow-up. Given that treatment failure for chlamydia is rare, repeat infection likely reflects a high prevalence of untreated CT infection in male partners and a failure of partner notification [28]. Partner notification by direct referral is the main approach used in SSA, but only 25% of partners seek treatment [29]. Alternative strategies like provider referral or expedited partner therapy (EPT) have been shown to have much greater reach, but concerns have been raised about using these approaches in populations such as those in HPTN 082 where rates of intimate partner violence are high.[29] Notably, 16% of participants with an STI in this study reported feeling unsafe or afraid of their partner. A small non-randomized study in women in South Africa showed that EPT following point-of-care STI testing was highly acceptable, without social impacts, and with lower rates of STI detected at follow-up, supporting the evaluation of these approaches more widely. [30]

AGYW who did not live with family were almost twice as likely to have a cervical infection at enrolment as those that did; those with increasing depression scores were more likely to have incident CT infection. Taken together these findings highlight the role that social support, self-esteem, and mental health play in young women's abilities to negotiate risk reduction strategies like condom use and partner treatment, especially in relationships where power is unequal [31]. These data support the need for comprehensive, integrated services for adolescents that address their HIV, sexual and reproductive health, as well as mental health needs.

There were several limitations to this study. We did not systematically record STI symptoms in the database and cannot report on the performance of syndromic management in identifying prevalent or incident infections. However, we note in a similar study in several of the same locations that 7% of participants reported STI symptoms despite the prevalence of CT (29%) and GC (10%) being similar to prevalence observed in our study.[32] We may have underestimated GC prevalence and incidence by collecting only cervical samples, especially given that 16% reported anal sex in the month prior to enrollment. By enrolling

participants with access to a mobile phone, we may also have excluded individuals who were more economically vulnerable; this may have led to an underestimate of the STI burden. The significant differences by site point to the influence of individual, partner and sexual network characteristics on STI transmission that we did not measure, and which may limit generalizability. Despite this, the data highlight an urgent unmet need for better STI diagnosis and prevention options for at-risk African AGYW seeking PrEP.

CONCLUSION

In summary, STI prevalence and incidence in this AGYW population seeking PrEP were high and signal the need for alternatives to syndromic management. STI testing provides an important entry point for current and future STI prevention interventions like EPT, pre- or post-exposure prophylaxis for STIs, or STI vaccines that could be integrated into PrEP service delivery. Like PrEP, they could be under the control of young women. Importantly, integrated sexual and reproductive health services may also have benefits for HIV programs given the premium that many place on sexual health and may drive demand for PrEP in many settings. New approaches to STI diagnosis, treatment and prevention that go beyond syndromic management are urgently needed to reduce the burden of current infection and future disease in AGYW and respond to the threat of antimicrobial resistance (AMR). Given the success of PrEP as a sexual and reproductive health technology used by people at substantial risk for HIV infection, we must prioritize the development of novel interventions that allow PrEP users to stay both HIV and STI-free.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known on this topic?

Adolescent girls and young women in sub-Saharan Africa (SSA) experience a disproportionate burden of sexually transmitted infections, including HIV. Current approaches to the diagnosis and treatment of curable STIs are limited. Expanding PrEP programmes in SSA provide a potential platform for integrating and strengthening novel STI prevention and control approaches. Data are needed on the prevalence and incidence of STIs in populations initiating PrEP in SSA.

What this study adds

The prevalence and incidence of curable STI in adolescent girls and young women is much higher than in the general population. AGYW with high PrEP adherence based on drug concentrations had an increased risk for incident gonorrhoea. Location appeared to be a stronger influence on risk rather than individual behavioral risk factors.

How this study might affect research, practice or policy

These data provide a strong rationale for the integration of aetiologic STI testing and other novel STI prevention approaches within PrEP services in SSA.

Table 1.

Baseline characteristics, by STI diagnosis (N=451)

	N. gonorrhoeae (n=35)	*C. trachomatis* (n=136)	*T. vaginalis* (n=28)	Any STI at baseline (n=174)	No STI at baseline (n=277)	p-values
Site						**0.0001**
Cape Town, South Africa	21 (60%)	56 (41%)	7 (25%)	72 (41%)	69 (25%)	
Johannesburg, South Africa	6 (17%)	50 (37%)	10 (36%)	62 (36%)	100 (36%)	
Harare, Zimbabwe	8 (23%)	30 (22%)	11 (39%)	40 (23%)	108 (39%)	
Age (years)						**0.036**
Median (IQR)	20 (18, 21)	20 (19, 22)	21 (20, 24)	20 (19, 22)	21 (19, 23)	
Lives with						0.080
Partner	5 (14%)	24 (18%)	8(29%)	31 (18%)	67 (24%)	
Parents and/or siblings	24 (69%)	75 (55%)	14 (50%)	98 (56%)	160 (58%)	
Others	6 (17%)	37 (27%)	6 (21%)	45 (26%)	50 (18%)	
Partner age difference						0.154
Less than 5 years	29 (83%)	97 (71%)	19 (68%)	125 (72%)	177 (64%)	
>=5 and <10 years	6 (17%)	31 (23%)	7 (25%)	40 (23%)	75 (27%)	
>=10 years	0 (0%)	8 (6%)	2 (7%)	9 (5%)	25 (9%)	
Partner has made you feel unsafe, afraid, or in danger in past year	9 (26%)	20(15%)	3 (11%)	27 (16%)	63 (23%)	**0.069**
CES-D Depression Score ≥ 10 *	21 (60%)	79 (58%)	16 (57%)	102 (59%)	166 (60%)	0.765
Contraceptive method						**0.045**
Injectable Contraceptives	23 (66%)	68 (50%)	7 (25%)	87 (50%)	104 (38%)	
Implants	5 (14%)	25 (18%)	10 (36%)	35 (20%)	69 (25%)	
IUD-copper/hormone	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1%)	
Sterilization	0 (0%)	0 (0%)	1 (4%)	1 (1%)	0 (0%)	
Oral Contraceptives	1 (3%)	18 (13%)	6 (21%)	20 (11%)	34 (12%)	
Condoms, natural methods or none	6 (17%)	25 (19%)	4 (15%)	31 (18%)	66 (24%)	
Transactional sex, past month	7 (20%)	28 (21%)	12 (43%)	42 (24%)	59 (21%)	0.489
Anal sex, past month						
Yes	7 (20%)	21 (15%)	2/28 (7%)	27 (16%)	41 (15%)	0.391
No	20 (57%)	78 (57%)	17 (61%)	101 (58%)	146 (53%)	
Prefer not to answer	8 (23%)	37 (27%)	9 (32%)	46 (26%)	90 (32%)	
No. vaginal sex episodes, past month						0.307
Median (IQR)	5 (2, 10)	4 (2, 6)	6 (4, 12)	4 (2, 8)	4 (3, 8)	
Condom use at last vaginal sex **	8 (29%)	33 (31%)	7 (29%)	44 (31%)	96 (45%)	**0.033**

	N. gonorrhoeae (n=35)	*C. trachomatis* (n=136)	*T. vaginalis* (n=28)	Any STI at baseline (n=174)	No STI at baseline (n=277)	p-values
Co-infection with other STI						
C. trachomatis	19 (54%)	136 (100%)	7 (25%)	136 (78%)	0 (0%)	
N. gonorrhoeae	35 (100%)	19 (14%)	1 (4%)	35 (20%)	0 (0%)	
T. vaginalis	1 (3%)	7 (5%)	28 (100%)	28 (16%)	0 (0%)	
High self-perceived HIV risk in next year ***	1 (3%)	10 (7%)	3 (11%)	12 (7%)	22 (8%)	0.430
Modified VOICE risk score ****						0.544
Median (IQR)	7 (6, 8)	7 (5, 7)	6 (5, 7)	7 (6, 7)	7 (5, 7)	
PrEP accepted at baseline	33 (94%)	120 (88%)	27 (96%)	157 (90%)	255 (92%)	0.500

*Missing values imputed, n=9 missing responses

**Missing responses n=33 for those with STI and n= 66 those with no STI

***Missing responses n=2 for those with no STI

****Modified Risk Score does not include score for curable STI at baseline; includes age <25 years = 2 >=25 years = 0, married or living with primary partner No=2 Yes =0, partner provides material support No=1 Yes =0, primary partner has other partners Yes =2 Don't know =2 No =0

Table 2.

STI incidence over 12 months, by site

	Overall (N=451)	Cape Town (N=141)	Johannesburg (N=162)	Harare (N=148)
N. gonorrhoeae				
Events	51	32	2	17
Person-years	445.58	134.13	161.23	150.23
Event Rate (100 Person-years)	11.4	23.9	1.2	11.3
95% Exact CI for Event Rate	(8.5, 15.0)	(16.3, 33.7)	(0.2, 4.5)	(6.6, 18.1)
C. trachomatis				
Events	123	50	38	35
Person-years	441.7	135.1	155.2	151.4
Event Rate (100 Person-years)	27.8	37	24.5	23.1
95% Exact CI for Event Rate	(23.1, 33.2)	(27.5, 48.8)	(17.3, 33.6)	(16.1, 32.1)
T. vaginalis				
Events	30	6	7	17
Person-years	448.8	138	161.2	149.6
Event Rate (100 Person-years)	6.7	4.3	4.3	11.4
95% Exact CI for Event Rate	(4.5, 9.5)	(1.6, 9.5)	(1.7, 9.0)	(6.6, 18.2)

Table 3.

Baseline characteristics associated with prevalent or incident GC, CT, or combined CT/GC infection

	CT/GC		CT		GC	
	Univariate RR (95% CI)	**Multivariable RR (95%)**	**Univariate RR (95% CI)**	**Multivariable RR (95%)**	**Univariate RR (95% CI)**	**Multivariable RR (95%)**
Baseline infection						
Site						
Cape Town vs. Harare	2.10 (1.38, 3.18)	2.38 (1.35, 4.19)**	1.96 (1.26, 3.06)	2.41 (1.31, 4.43)**	2.76 (1.22, 6.22)	2.28 (0.88, 5.89)
Johannesburg vs. Harare	1.46 (0.96, 2.26)	1.13 (0.67, 1.91)	1.52 (0.96, 2.40)	1.27 (0.73, 2.22)	0.68 (0.24, 1.98)	0.52 (0.15, 1.84)
Age (years) †					0.86 (0.72, 1.02)	0.95 (0.79, 1.14)
Living arrangements						
Lives with partner vs. parents and/or siblings	0.54 (0.20, 1.44)	0.85 (0.44, 1.64)	0.84 (0.54, 1.34)	1.01 (0.51, 1.98)		
Lives with other vs. parents and/or siblings	0.68 (0.28, 1.66)	1.87 (1.13, 3.08)*	1.34 (0.90, 1.98)	1.93 (1.14, 3.27)*		
Modified risk score †					1.34 (0.96, 1.84)	1.25 (0.87, 1,79)
No. vaginal sex acts, past month †					1.04 (1.00, 1.06)	1.03 (1.00, 1.06)*
Condom use at last sex	0.66 (0.46, 0.98)	0.67 (0.45, 0.99)*	0.68 (0.46, 1.02)	0.69 (0.46, 1.05)		
Incident infection						
Site						
Cape Town vs. Harare	1.60 (1.08, 2.36)	1.14 (0.70, 1.86)	1.50 (0.94, 2.42)	1.39 (0.78, 2.48)	2.20 (1.12, 4.34)	2.40 (1.18, 4.90)*
Johannesburg vs. Harare	0.96 (0.62, 1.48)	0.56 (0.31, 1.00)*	1.22 (0.76, 1.98)	0.87 (0.48, 1.56)	0.14 (0.04, 0.64)	0.15 (0.33, 0.70)*
Age (years) †			0.94 (0.86, 1.00)	1.01 (0.91, 1.11)		
CES-D depression score †	1.02 (1.00, 1.06)	1.02 (0.99, 1.05)	1.04 (1.02, 1.08)	1.05 (1.01, 1.09)**	1.00 (0.94, 1.06)	1.00 (0.95, 1.06)
Age difference of primary partner	0.94 (0.88, 1.00)	0.94 (0.88, 1.01)	0.94 (0.88, 1.02)	0.95 (0.88, 1.02)		
Long-acting contraceptive use (baseline) §			1.42 (0.92, 2.18)	1.18 (0.69, 2.03)		
Anal sex, past month						
Yes vs. No	1.18 (0.74, 1.90)	1.34 (0.76, 2.33)				
Prefer not to answer vs. No	0.70 (0.50, 0.98)	0.75 (0.49, 1.15)				

	CT/GC		CT		GC	
	Univariate RR (95% CI)	**Multivariable RR (95%)**	**Univariate RR (95% CI)**	**Multivariable RR (95%)**	**Univariate RR (95% CI)**	**Multivariable RR (95%)**
CT/GC at baseline	1.66 (1.20, 2.32) **	1.66 (1.12, 2.45) *				
CT at baseline			1.84 (1.26, 2.66)	2.01 (1.28, 3.15) **		
Detectable TFV-DP ▫	1.00 (0.73, 1.35)		0.78 (0.54, 1.13)		1.46 (0.86, 2.49)	
TFV-DP ≥700fmol/punch ▫	1.00 (0.63, 1.58)		0.76 (0.43, 1.34)		1.96 (0.98, 3.91)	2.04 (1.02, 4.08) *

CT: chlamydia; GC: gonorrhoea; RR: relative risk; CI: confidence intervals; TDF-DP: tenofovir diphosphate

† Continuous variables

§ LARC includes injectables, implants and intrauterine devices.

▫ based on DBS collected at month 6 and/or 12

* p<0.05

** p<0.005

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