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Population prevalence of sexually transmitted infections in a high HIV burden district in KwaZulu-Natal, South Africa: Implications for HIV epidemic control

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ABSTRACT

Background: Sexually transmitted infections (STIs) and Human immunodeficiency virus (HIV) share a complex bidirectional relationship, however, population prevalence and the association between the presence of STIs and HIV in a high HIV burden district in KwaZulu-Natal, South Africa is not known.
Methods: A total of 9812 participants aged 15–49 years were enrolled in a cross-sectional population-based household survey. Participants completed a structured questionnaire and provided first-pass urine (males) or self-collected vulvo-vaginal swabs (females) for the detection of STIs.
Results: Prevalence of herpes simplex virus type-2 (HSV-2) was 57.8%, syphilis was 1.6%, *Neisseria gonorrhoeae* was 2.8%, *Chlamydia trachomatis* was 7.1%, *Trichomonas vaginalis* was 9.0%, *Mycoplasma genitalium* was 5.5% and HIV was 36.3%. HIV positive status was associated with an increased probability of having *M. genitalium* (aPR = 1.49, 95% CI 1.02–2.19) among males and syphilis (aPR = 2.54, 95% CI 1.32–4.86), *N. gonorrhoeae* (aPR = 2.39, 95% CI 1.62–3.52), *T. vaginalis* (aPR = 1.70, 95% CI 1.43–2.01) and *M. genitalium* (aPR = 1.60, 95% CI 1.15–2.22) among females. HIV viral load ≥400 copies per mL was associated with an increased probability of *N. gonorrhoeae* (aPR = 1.91, 95% CI 1.36–2.70), *C. trachomatis* (aPR = 1.52, 95% CI 1.12–2.05) and *M. genitalium* (aPR = 1.83, 95% CI 1.27–2.63).
Conclusions: The high prevalence of STIs and the association between STIs and HIV, and HIV viral load underscores the public health implications of sustained transmission risk of STIs and HIV. These findings highlight the urgent need for expanding STI surveillance and implementing interventions to monitor and reduce the STI burden.

Introduction

Sexually transmitted infections such as herpes simplex virus type 2 (HSV-2), syphilis, *Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis* and *Mycoplasma genitalium* are of major public health concern and are key epidemiological markers of unprotected sex (World Health Organization, 2016). Whilst STIs affect individuals of all ages, adolescents and young people are disproportionately affected (Dehne and Riedner, 2005). STIs contribute adversely to sexual, reproductive and maternal-child health; lead to pelvic inflammatory disease, genital malignancies and infertility (World Health Organization, 2016); and increase the risk of HIV acquisition and transmission (Wasserheit, 1992; Rottingen et al., 2001; Freeman et al., 2006; Looker et al., 2017; Unemo et al., 2017; Cohen et al., 2019).

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South Africa monitors the HIV epidemic through nationally representative population-based household surveys (Human Sciences Research Council, 2018). With a national HIV prevalence of 20.6% for among 15–49-year-olds, the epidemic in the region is characterized as generalized and hyperendemic. At the provincial level, HIV prevalence in KwaZulu-Natal was the highest at 27.0% while prevalence in the Western Cape was 12.6%. However, there are no similar surveys to monitor the STI burden and surveillance for STIs is limited to the use of convenience or clinic based sampling, limiting generalizability to groups of interest (Johnson et al., 2005; Kularatne et al., 2017; Francis et al., 2018). Notwithstanding such limitations, the studies have provided useful point estimates in select sub-populations and highlight the need for population-representative surveys to determine the burden and patterns of STIs and to reliably monitor and assess the effectiveness of STI prevention programs.

With the onset of the HIV epidemic interest in STIs has grown substantially as both share a complex, synergistic bidirectional relationship (Wasserheit, 1992; Barnabas et al., 2011; Looker et al., 2017). Evidence suggests that for HIV positive individuals, persistent high risk behaviours increase susceptibility to STIs (Erbelding et al., 2003; Chen et al., 2007; Lurie et al., 2014; Khaw et al., 2018), and advancing HIV infection may increase the frequency of STI treatment failures (Wolday et al., 2004; Unemo et al., 2017; Khaw et al., 2018). Conversely, asymptomatic or symptomatic STIs strongly predict susceptibility to HIV, enhance HIV shedding at genital mucosal sites and increase infectiousness from HIV positive individuals (Mwatelah et al., 2019). Potential biologic mechanisms that facilitate and activate HIV replication include alterations in the genital tract microbiome, localized inflammation, recruitment of CD4+ T-cells, monocytes, Langerhans' cells, and increased levels of interleukin-10 (Abdool Karim et al., 2019; Cohen et al., 2019; Mwatelah et al., 2019). Whilst these findings provide strong biological plausibility for STI control as an effective HIV prevention strategy, clinical trial evidence has produced conflicting results (Grosskurth et al., 1995; Wawer et al., 1999; Kamali et al., 2003; Hayes et al., 2010; Torrone et al., 2018). The differences in trial design, robustness of the interventions, population characteristics, stage of the HIV epidemic at the time of the study and baseline prevalence of STIs may have contributed to these mixed results (Stillwaggon and Sawers, 2015), but nonetheless, treatment of STIs remains a public health priority (Hayes et al., 2010; Cohen, 2012; Stillwaggon and Sawers, 2015).

These findings suggest that monitoring, early diagnosis and treatment of STIs may reduce STI related HIV acquisition and transmission and achieve the goal of HIV epidemic control in the region (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2017; Galvani et al., 2018).

The objectives of this study were to measure the population prevalence of STIs and to assess the association between STIs and HIV, CD4 cell counts and HIV viral load in a high HIV burden setting.

Methods

Study population, design, and procedures

The HIV incidence Provincial Surveillance System (HIPSS) was designed to measure HIV prevalence and incidence in association with the scale-up of HIV prevention and treatment efforts in a "real-world non-trial" setting in the rural Vulindlela and peri-urban Greater Edendale area in the uMgungundlovu district of KwaZulu-Natal, South Africa. The study area has a population of approximately 360 000, is predominantly Zulu speaking, and is characterized by high levels of unemployment, poverty, teenage pregnancy and high rates of HIV. Primary health-care clinics and community-based organizations provide health care and psychosocial support. The cross-sectional survey was undertaken between June 2014 and June 2015. Households were randomly selected using a multistage random sampling method to select the enumeration areas and households. One individual per household, within the age range of 15–49 years, was randomly selected from a list of eligible household members. Overall, from a total of 15,100 households, 11,289 consented for household participation and from these households a total of 9812 (86.9% response rate) individuals were enrolled. All enrolled participants provided written informed consent and/or parental consent/child assent for those participants below the age of 18 years for study participation. All participants completed interviewer administered questionnaires, had peripheral blood samples collected and first pass urine (males) and self-collected vulvo-vaginal swab (females) samples. Details of the study sampling and survey procedures have been described elsewhere (Kharsany et al., 2018).

Questionnaire measures

Structured questionnaires were administered to obtain sociodemographic and behavioural data, HIV testing history, use of antiretroviral therapy (ART), symptoms of genital ulceration and /or genital discharge, alcohol and substance use [includes use of cannabis, barbiturates, benzodiazepines, cocaine, methaqualone, opioids, whoonga (locally mixed street drugs), or tik (crystal methamphetamine)] and medical male circumcision status.

Laboratory measures

Peripheral blood samples were tested for HIV, HSV-2, and syphilis antibodies. HIV status was determined using the 4th generation HIV enzyme Biomerieux Vironostika Uniform II Antigen/Antibody Microelisa system (BioMérieux, Marcy l'Etoile, France). HIV positive samples were confirmed with the HIV 1/2 Combi Roche Elecsys (Germany) (Roche Diagnostics, Penzberg, Germany) and tested for CD4 cell counts using Becton Dickinson (BD) FACS Calibur flow cytometry (BD Biosciences, San Jose, CA, USA) and HIV viral load using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 v2.0 assay (CAP/CTM HIV-1 V2.0, Roche Diagnostics, Penzberg, Germany).

HSV-2 serostatus was determined by the detection of human IgG class antibodies using the HerpeSelect® HSV-2 enzyme-linked immunosorbent assay (Focus Diagnostics, Cypress, CA, USA) test. Syphilis serostatus was determined by a non-treponemal rapid plasma reagin (RPR) assay (Immutrep® RPR, Omega Diagnostics Ltd., Alva, UK) and a quantitative titer of 1:8 or higher was considered as positive for active syphilis.

First pass urine (males) and self-collected vulvo-vaginal swab samples (females) were tested for *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis* and *M. genitalium* using a multiplex real-time polymerase chain reaction (PCR) assay on the RotorGene 3000/6000/ Q real-time platforms (QIAGEN, Hilden Germany) (Mhlongo et al., 2010). Primers and probes targeted the *N. gonorrhoeae* cytosine-specific DNA methyltransferase gene, the cryptic plasmid of *C. trachomatis*, the *T. vaginalis* repeated DNA fragment and the *M. genitalium pdhD* gene (encoding for dihydrolipoamide dehydrogenase). Strains of *N. gonorrhoeae* (ATCC 700825), *C. trachomatis* (ATCC VR-885), *T. vaginalis* (ATCC 30001), and *M. genitalium* (ATCC 33530) were used as positive controls. Females 15–35 years were tested for a current pregnancy using beta human chorionic gonadotropin (BHCG) quantitative blood assay (Siemens Centaur XP, USA).

Ethical approvals

The protocol, informed consent and data collection forms were reviewed and approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Reference number BF269/13), the KwaZulu-Natal Provincial Department of Health (HRKM 08/14) and the Centers for Disease Control and Prevention (CDC), United States of America. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (von Elm et al., 2007) (Supplementary Table 1).

Statistical analysis

Questionnaire data and laboratory test results were linked for analysis. Statistics were weighted using survey weights to account for the sample design and non-response (Kharsany et al., 2018). As STIs were detected in some individuals who reported never having had sex, all individuals were included in the analyses unless otherwise stated. Demographic, behavioural and clinical characteristics were summarised with frequencies and proportions for categorical variables and with medians and interquartile ranges (IQR) for continuous variables. The prevalence of each STI and 95% confidence interval (CI) were calculated overall, by sex, 5-year age group, HIV, and pregnancy status (for women aged 15–35 years).

The association between pregnancy status and STI presence was tested using logistic regression adjusting for 5-year age groups. The association between the presence of STIs and HIV status was measured using log binomial regression for each of the curable STIs (syphilis, *N. gonorrhoeae, C. trachomatis, T. vaginalis* and *M. genitalium*). Crude and adjusted prevalence ratios (aPR) were estimated for each sex group. APRs controlled for factors previously identified as being associated with HIV prevalence that could possibly act as confounders to measuring the relationship between presence of curable STIs and HIV status (Kharsany et al., 2018). The factors included 5-year age group, education level (completed high-school or not), relationship status (married or living together as husband and wife, versus not), the number of lifetime sexual partners (none, one, 2–5, 6 or more, or refused to report) and male medical circumcision status (yes or no). For the sample of HIV positive individuals the association between CD4 cell count <350 versus ≥350 cells per μL) and between HIV viral load <400 (suppressed) and ≥400 (unsuppressed) copies per ml and the presence of a curable STI was measured using log binomial regression adjusting for sex and age group. HSV-2 was not included in the models as presence of antibodies does not provide an indication of recent sexual risk behaviours.

All analyses, except for log binomial regression, were performed using SAS survey procedures (SAS Institute, Cary, North Carolina, version 9.4). Log binomial regression was performed in STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

Participant characteristics

A total of 9812 participants were enrolled and assessed for the prevalence of STIs (Table 1). Females accounted for 63.9% with a median age of 27 years [Interquartile range (IQR) 21–36], whilst 36.1% were males with a median age of 26 years (IQR 20–35). About 43.5% of males and 46.7% of females had completed high school education, 63.6% of males and 63.9% of females reported a household income of <ZAR2500 and more than 80% of participants reported their relationship status as not married or living with partner as husband and wife. Of those reporting ever having had sex, 68.6% of males and 74.1% of females were currently in a sexual relationship. The median number of lifetime sex partners for males was 3 (IQR 1–6) and for females was 2 (IQR 1–3). Overall, 40.6% of males and 9.1% of females reported any lifetime alcohol use, 19.3% of males and 1.5% of females reported any lifetime substance use. Prevalence of HIV was 28.0% in males and 44.1% in females. Among HIV positive individuals 41% of males and 23.1% of females had CD4 cell counts of <350 cells per μL, whilst 36.7% of males and 45.6% of females self-reported to be ART and 41.9% of males and 54.8% of females had HIV viral load of <400 copies per mL.

Prevalence of STIs

The prevalence of laboratory diagnosed STIs overall, by sex and age is shown in Table 2. Among males compared to females respectively, prevalence of HSV-2 was 46.1% (95% CI 43.4–48.7) vs 68.8% (95% CI 66.9–70.7), syphilis was 1.5% (95% CI 1.0–2.01) vs 1.7% (95% CI 1.3–2.1), *N. gonorrhoeae* was 1.8% (95% CI 1.0–2.5) vs 3.7% (95% CI 3.1–4.3), *C. trachomatis* was 5.1% (95% CI 4.2–6.0) vs 9.0% (95% CI 8.1–9.9), *T. vaginalis* was 3.9% (95% CI 3.1–4.6) vs 13.8% (95% CI 12.3–15.2) and *M. genitalium* was 5.7% (95% CI 4.8–6.7) vs 5.2% (95% CI 4.5–6.0). Prevalence of curable STIs was higher in the younger age groups, whilst prevalence of HSV-2 was high across all age groups and peaked at 92.5% among females in the 45–49 year age group and 84.2% among males in the 40–44 year age group. Mean prevalence of STIs was higher among pregnant compared to non-pregnant females, though these differences were not significant (Supplementary Table 2).

Association between prevalent STIs and HIV, CD4 cell count and HIV viral load

Tables 3 shows the prevalence of STIs among HIV positive participants. Prevalence of HSV-2 was higher among HIV positive compared to HIV negative males (86.3%, 95% CI 83.2–89.5 vs 30.3%, 95% CI 27.9–32.8) and similarly higher among HIV positive compared to negative females (93.3%, 95% CI 92–94.5 vs 49.4%, 95% CI 47.0–51.9). Tables 4 and 5 show the association of STIs among HIV positive participants by CD4 cell counts and HIV viral load. Among males after adjusting for age, relationship status, education, number of lifetime sexual partners and medical male circumcision, being HIV positive was associated with an increased probability of having *M. genitalium* (aPR = 1.49, 95% CI 1.02–2.19). Similarly among females after adjusting for age, relationship status, education, and number of lifetime sexual partners, being HIV positive was associated with an increased probability of having syphilis (aPR = 2.54, 95% CI 1.32–4.86), *N. gonorrhoeae* (aPR = 2.39, 95% CI 1.62–3.52), *T. vaginalis* (aPR = 1.70, 95% CI 1.43–2.01).

Adjusting for sex and age, among HIV positive individuals having CD4 cell counts of <350 cells per μL was associated with an increased probability of having *N. gonorrhoeae* (aPR = 1.59, 95% CI 1.00–2.52) and *M. genitalium* (aPR = 2.01, 95% CI 1.52–2.52), whilst having an HIV viral load ≥400 copies per mL was associated with an increased probability of having *N. gonorrhoeae* (aPR = 1.91, 95% CI 1.36–2.70), *C. trachomatis* (aPR = 1.52, 95% CI 1.12–2.05) and *M. genitalium* (aPR = 1.83, 95% CI 1.27–2.63).

Discussion

This population-based survey undertaken in rural and peri-urban KwaZulu-Natal, the province with the highest HIV prevalence in South Africa (Human Sciences Research Council, 2018) showed that over half of the participants in the study area had HSV-2 infection and just under one-quarter had at least one curable STI [syphilis (1.6%), *N. gonorrhoeae* (2.8%), *C. trachomatis* (7.1%), *T. vaginalis* (9.0%), and/or *M. genitalium* (5.5%)]. Similar to the

Table 1
Characteristics of enrolled participants.

Participants characteristics	Overall (n = 9812)		Males (n = 3547)		Females (n = 6265)	
Socio demographic						
Age [median (IQR)]	27 (20–36)		26 (20–35)		27 (21–36)	
Completed high school education (n, %)	4561	45.1	1613	43.5	2948	46.7
Household income of ≤ ZAR 2500[a] (n, %)	6353	63.8	2253	63.6	4100	63.9
Relationship status: not married or living with partner as husband and wife (n, %)	8714	88.8	3306	92.1	5408	85.8
Behavioral						
Ever had sex (n, %)	8302	83.3	2855	80.8	5447	85.6
Currently in a sexual relationship (n, %)	7195	71.4	2459	68.6	4736	74.1
Concurrently in 2 or more heterosexual relationships in the last 12 months (n, %)	269	4.2	206	7.5	63	1.1
Engaged in any transactional sex with last three sexual partners (n, %)	1383	11.6	458	10.6	925	12.4
Total sex partners in the last 12 months [median (IQR)][a]	1 (0–1)		1 (0–1)		1 (0–1)	
Total lifetime sex partners [median (IQR)][a]	2 (1–4)		3 (1–6)		2 (1–3)	
Ever tested for HIV (n, %)	7265	75.5	2326	68.8	4939	81.9
Knows HIV status of all sex partners from the last 12 months[b] (n, %)	1821	25.6	521	21.0	1300	29.8
Any lifetime alcohol use (n, %)	2075	24.3	1432	40.6	643	9.1
Any lifetime substance use[c] (n, %)	830	10.1	697	19.3	133	1.5
Male condom used always during sex in the last 12 months[b] (n, %)	1587	24.5	593	26.5	994	22.7
Biological						
Any genital symptoms (n, %)	394	3.0	80	1.9	314	4.1
Medically circumcised[a] (n, %)	1102	31.9	1102	31.9	**NA**	
Ever pregnant[a] (n, %)	4391	70.7	**NA**	4391	70.7	
Currently pregnant[d] (n, %)	305	6.8	**NA**	305	6.8	
HIV positive (n, %)	3969	36.3	1014	28.0	2955	44.1
CD4 cell count <350 cells per μL[e,f]	1135	29.8	439	41.0	696	23.1
On ART[f,g]	1592	42.3	341	36.7	1251	45.6
HIV viral suppression <400 copies per mL[h]	1975	50.0	401	41.9	1574	54.8

ZAR = South African Rand.
% = population–weighted percentage calculation.
[a] Missing observations were excluded from percentage or median (IQR) calculations.
[b] Percentage for those that reported having sex in last 12 months.
[c] Includes any of cannabis, barbiturates, benzodiazepines, cocaine, methaqualone, opioids, whoonga, tik.
[d] Only women aged 15–35 years received pregnancy tests.
[e] Five men and twenty seven women were missing CD4 cell count data.
[f] As a percentage of all HIV positives.
[g] Self–report.
[h] Four men and nine women were missing viral load data.

low levels of reporting of genital symptoms among 15-to 24 year olds in rural KwaZulu-Natal (Francis et al. 2018), only 3% of our participants reported having any genital symptoms, suggesting that a majority of participants with STIs were either asymptomatic or that individuals were unable to recognize signs and symptoms of STIs, precluding them from seeking care and treatment. In addition to contributing to adverse health outcomes, STIs interact with the immune system in genital mucosa sites facilitating HIV acquisition and transmission (Wasserheit, 1992; Mayer and Venkatesh, 2011; Abdool Karim et al., 2019; Mwatelah et al., 2019). Estimates of curable STIs were higher in the younger age groups, particularly in younger females, which is the same group among whom a peak in HIV incidence occurs (Kharsany et al., 2019), thus the importance of enhanced STI surveillance (Taylor and Wi, 2019) and investment in targeted STI control programs for younger populations (Francis et al., 2018; Kharsany et al., 2019).

Globally and in the sub-Saharan African region, HSV-2 is the leading cause of genital ulceration and there is substantial overlap between the HSV-2 and HIV syndemics (Freeman et al., 2006). Prevalent HSV-2 leads to subclinical HSV-2 viral shedding (Wald et al., 2002) which may be exacerbated by incident HIV infections whilst incident HSV-2 infection has been associated with an elevated risk of HIV acquisition (Reynolds et al., 2003; Brown et al., 2007). The high prevalence of HSV-2 infection reflects either markers of risky sexual behaviours with HSV-2 and HIV acquired simultaneously (Corey, 2007) or the biological basis of the plausibility of the increased shedding of HIV during acute, early or subclinical reactivation of HSV-2 infection thus enhancing transmission of both infections (Celum et al., 2005; Cohen et al., 2019). In this study by age 24 years, 60% of females were already HSV-2- positive, which underscores the rapid speed at which HSV-2 transmission is occurring and its potential for escalating HIV risk (Looker et al., 2017). The high HSV-2 prevalence may also help to explain the magnitude of the HIV epidemic in the region (Freeman et al., 2006; Kharsany et al., 2019).

The prevalence of *T. vaginalis* was higher among females and more importantly among males and females in the older age groups, suggesting that biological factors contribute to prevalence in older individuals (Lazenby et al., 2020) and that individuals' perceptions and behaviours on sexual and reproductive health may result in sub-optimal health seeking behaviours (Rietmeijer, 2019). Furthermore, as *T. vaginalis* is strongly associated with HIV acquisition and transmission (Kissinger and Adamski, 2013), the high prevalence contributes to the spread of both infections. Similarly, the high prevalence of *N. gonorrhoeae* and *C. trachomatis* also suggests that many of these STIs remain untreated and could increase ascending genital tract infections (World Health Organization, 2016). *M. genitalium* has emerged as an important sexually transmitted pathogen with evidence of a temporal association between *M. genitalium* infection and HIV acquisition (Vandepitte et al., 2014). The prevalence of active syphilis at the population level was 3.0% in females which is higher than the 2.3% among pregnant women in KwaZulu-Natal (South African National Department of Health, 2017). Despite the successful implementation of public health programs for the management of syphilis among pregnant women during prenatal care, programmatic interventions should be aimed at the population level to diagnose, treat and prevent long-term negative sequelae of untreated syphilis and of potential congenital syphilis.

Table 2
Prevalence of sexually transmitted infections by sex and age among enrolled participants.

Age group		Overall		Males			Females		
	n/N	%	95% CI	n/N	%	95% CI	n/N	%	95% CI
Herpes simplex virus type 2 antibodies									
15–19	320/1609	16.5	14.2–18.9	55/657	8.4	6.0–10.9	265/952	24.7	21.0–28.4
20–24	935/2074	40.5	37.3–43.6	189/812	21.8	17.7–26.0	746/1262	59.0	55.3–62.8
25–29	1146/1682	63.7	60.1–67.4	306/596	51.5	45.4–57.5	840/1086	75.3	70.8–79.8
30–34	1029/1293	76.2	72.8–79.6	316/460	66.0	60.8–71.2	713/833	85.8	82.6–88.9
35–39	962/1163	80.1	76.3–83.8	297/403	73.1	67.1–79.1	665/760	86.5	83.0–89.9
40–44	865/979	87.7	84.5–91.0	261/319	84.2	79.1–89.3	604/660	90.7	87.1–94.3
45–49	872/986	86.5	83.2–89.8	220/286	77.7	71.2–84.2	652/700	92.5	90.1–95.0
Overall	**6129/9786**	**57.8**	**56.1–59.6**	**1644/3533**	**46.1**	**43.4–48.7**	**4485/6253**	**68.8**	**66.9–70.7**
Syphilis antibodies[a]									
15–19	17/1613	0.9	0.4–1.5	5/658	0.5	0.5–1.1	12/955	1.3	0.3–2.3
20–24	57/2080	2.3	1.5–3.1	17/814	1.9	0.7–3.2	40/1266	2.6	1.7–3.6
25–29	33/1688	1.5	0.8–2.2	9/602	0.9	0.1–1.7	24/1086	2.1	0.9–3.3
30–34	24/1294	1.7	0.7–2.8	8/461	1.9	0–3.9	16/833	1.5	0.5–2.5
35–39	17/1165	2.0	0.7–3.2	9/405	3.1	0.7–5.5	8/760	1.0	0.1–1.8
40–44	19/980	1.8	0.9–2.7	8/320	2.0	0.5–3.4	11/660	1.7	0.4–3.0
45–49	7/988	0.5	0–1.0	1/287	0.5	0–1.5	6/701	0.5	0.1–1.0
Total	**174/9808**	**1.6**	**1.2–2.0**	**57/3547**	**1.5**	**1.0–2.0**	**117/6261**	**1.7**	**1.3–2.1**
Neisseria gonorrhoeae									
15–19	54/1611	2.6	1.7–3.4	11/656	1.0	0.3–1.6	43/955	4.2	2.7–5.7
20–24	98/2074	4.7	3.5–6.0	21/811	2.9	1.4–4.5	77/1263	6.5	4.9–8.2
25–29	59/1683	3.6	2.3–4.8	20/600	2.8	1.1–4.4	39/1083	4.4	2.4–6.3
30–34	37/1288	2.9	1.6–4.2	11/458	2.5	0.4–4.7	26/830	3.2	1.6–4.8
35–39	21/1162	1.0	0.4–1.6	3/403	0.5	0.0–1.1	18/759	1.5	0.7–2.3
40–44	15/974	1.5	0.5–2.5	3/315	0.7	0.0–1.5	12/659	2.2	0.6–3.8
45–49	11/986	0.6	0.2–1.1	0/286	–	–	11/700	1.1	0.3–1.8
Total	**295/9778**	**2.8**	**2.3–3.3**	**69/3529**	**1.8**	**1.0–2.5**	**226/6249**	**3.7**	**3.1–4.3**
Chlamydia trachomatis									
15–19	171/1611	9.2	7.6–10.9	31/656	4.4	2.5–6.2	140/955	14.1	11.6–16.7
20–24	257/2074	12.1	10.3–13.9	67/811	8.6	6.2–11.0	190/1263	15.6	13.1–18.2
25–29	163/1683	8.6	6.9–10.4	52/600	7.5	5.1–10.0	111/1083	9.7	7.3–12.2
30–34	74/1288	5.4	3.6–7.1	23/458	5.5	2.5–8.5	51/830	5.2	3.5–6.9
35–39	45/1162	3.0	1.8–4.2	10/403	1.3	0.4–2.2	35/759	4.5	2.5–6.6
40–44	22/974	1.9	1.0–2.9	4/315	1.1	0.0–2.3	18/659	2.6	1.1–4.1
45–49	11/986	0.7	0.2–1.3	1/286	0.4	0.0–1.3	10/700	1.0	0.2–1.7
Total	**743/9778**	**7.1**	**6.5–7.7**	**188/3529**	**5.1**	**4.2–6.0**	**555/6249**	**9.0**	**8.1–9.9**
Trichomonas vaginalis									
15–19	113/1611	6.0	4.6–7.3	6/656	0.6	0.0–1.1	107/955	11.4	9.0–13.8
20–24	210/2074	7.3	6.0–8.7	14/811	1.8	0.7–3.0	196/1263	12.8	10.3–15.2
25–29	204/1682	8.3	6.5–10.1	24/599	3.2	1.5–5.0	180/1083	13.2	10.5–15.8
30–34	129/1288	7.7	5.9–9.6	17/458	4.3	1.7–6.9	112/830	11.0	8.2–13.8
35–39	174/1162	12.1	9.2–15.1	29/403	6.6	3.3–9.9	145/759	17.3	13.4–21.1
40–44	161/974	13.6	10.7–16.6	46/315	11.2	7.4–15.1	115/659	15.6	11.7–19.5
45–49	166/986	14.2	11.3–17.1	19/286	6.5	2.9–10.1	147/700	19.5	15.4–23.5
Total	**1157/9777**	**9.0**	**8.1–9.9**	**155/3528**	**3.9**	**3.1–4.6**	**1002/6249**	**13.8**	**12.3–15.2**
Mycoplasma genitalium									
15–19	69/1611	3.6	2.5–4.7	17/656	1.9	0.8–3.0	52/955	5.3	3.4–7.2
20–24	138/2074	5.8	4.4–7.1	29/811	3.2	1.8–4.5	109/1263	8.4	6.2–10.5
25–29	130/1683	8.1	6.4–9.7	52/600	9.2	6.3–12.1	78/1083	7.0	5.0–8.9
30–34	80/1288	6.9	4.8–8.9	47/458	10.4	6.9–13.8	33/830	3.6	2.0–5.1
35–39	65/1162	6.4	4.5–8.4	33/403	8.2	4.9–11.4	32/759	4.8	2.6–7.0
40–44	37/974	3.3	2.0–4.5	19/315	4.4	1.9–6.9	18/659	2.3	1.1–3.5
45–49	13/986	1.7	0.5–2.9	7/286	2.6	0.0–5.3	6/700	1.1	0.1–2.1
Total	**532/9778**	**5.5**	**4.8–6.1**	**204/3529**	**5.7**	**4.8–6.7**	**328/6249**	**5.2**	**4.5–6.0**

[a] Rapid plasma reagin (RPR) assay with a quantitative titer of 1:8 or higher was considered as positive for active syphilis.

The findings on the association of HIV positive status and curable STIs have important implications for the region. Recent studies have delineated the role and biologic mechanisms of STIs with disturbances in the vaginal microbiome, inducing mucosal inflammation, yielding unique cytokine profiles that evoke an influx of HIV receptor cells in genital mucosal epithelium (Abdool Karim et al., 2019; Mwatelah et al., 2019). The regression analyses revealed that HIV positive status increased the prevalence of curable STIs, though risk behaviours of more than 80% of sexually active participants reported not being married or living with partner as husband and wife, low levels of condom use, concurrent heterosexual partnerships, high number of lifetime sex partners and high levels of alcohol and substance use at a population level could worsen and contribute to sustaining both STI and HIV epidemics in the region. Even though our analysis adjusted for sexual risk behaviors, these behaviours might have been underestimated as survey procedures may not have adequately assessed the characteristics of the individual's sexual networks or that participants may underreport on sexual risk-taking behaviours.

Among HIV positive individuals the association of CD4 cell counts of <350 cells per mL with *N. gonorrhoeae* and *M. genitalium* suggests that even with advancing HIV disease, susceptibility to STIs remains elevated. HIV-positive individuals tend to increase condom use at ART initiation (Risher et al., 2016), so it was not surprising that in this study HIV-positive individuals who were virally suppressed had a lower prevalence of curable STIs, suggestive of practicing safer sex behaviours.

Table 3
Prevalence of sexually transmitted infections by sex, age and HIV status.

Age group	Males					Females				
	HIV negative % (95% CI)		HIV positive % (95% CI)		P value	HIV negative % (95% CI)		HIV positive % (95% CI)		P value
Herpes simplex virus type 2 antibodies										
15–19	7.6	5.1–10.1	24.1	7.2–41	0.0051	20.4	16.8–24.0	58.2	46.2–70.2	<0.0001
20–24	17.3	13.5–21.0	62.3	48.9–75.7	<0.0001	45.2	40.4–50.0	87.8	83.5–92.1	<0.0001
25–29	38.2	31.9–44.5	86.6	79.9–93.4	<0.0001	57.4	50.5–64.3	93.3	90.7–96.0	<0.0001
30–34	50.5	42.3–58.8	85.7	78.8–92.6	<0.0001	63.0	55.6–70.5	97.4	95.9–98.9	<0.0001
35–39	51.4	41.5–61.3	93.5	88.4–98.6	<0.0001	67.8	59.2–76.4	95.9	93.3–98.6	<0.0001
40–44	70.2	60.0–80.3	93.7	89.4–98.1	<0.0001	78.9	71.0–86.9	98.4	96.5–100	<0.0001
45–49	64.9	55.3–74.6	99.2	98.1–100	<0.0001	88.4	84.4–92.3	98.3	96.8–99.8	<0.0001
Total	**30.3**	**27.9–32.8**	**86.3**	**83.2–89.5**	**<0.0001**	**49.4**	**47.0–51.9**	**93.3**	**92.0–94.5**	**<0.0001**
Syphilis antibodies[a]										
15–19	0.8	0.1–1.4	1.6	0–4.7	0.5012	0.7	0.2–1.1	8.4	1–15.9	<0.0001
20–24	2.3	0.3–4.2	8.0	1.8–14.2	0.019	3.5	1.7–5.2	8.5	5.5–11.4	0.0013
25–29	1.8	0–3.9	4.4	0–9.0	0.2415	2.1	0.3–3.9	5.1	2.4–7.8	0.0753
30–34	2.9	0–6.3	2.3	0.2–4.5	0.7531	1.4	0–2.8	3.5	1.4–5.5	0.0938
35–39	4.4	0–8.9	3.3	0.5–6.1	0.6684	1.5	0–3.1	1.7	0.5–3.0	0.8095
40–44	2.1	0–4.3	3.6	0.5–6.7	0.4451	2.6	0–5.7	3.8	1.8–5.8	0.5756
45–49	2.8	0.6–4.9	2.3	0–5.5	0.8142	3.3	1.1–5.5	0.6	0–1.4	0.0132
Total	**2.1**	**1.2–2.9**	**3.5**	**2.2–4.9**	**0.0659**	**2.1**	**1.4–2.7**	**4.2**	**3.3–5.1**	**<0.0001**
Neisseria gonorrhoeae										
15–19	0.8	0.2–1.5	3.5	0–8.3	0.0578	3.1	1.6–4.6	12.7	5.3–20.1	0.0002
20–24	2.6	1–4.3	5.4	0–11.0	0.2451	4.0	2.2–5.8	11.9	7.9–15.8	0.0001
25–29	1.7	0.2–3.1	5.7	0.7–10.8	0.0468	3.5	0.8–6.2	5.2	2.6–7.8	0.3831
30–34	3.4	0–7.0	1.4	0.1–2.8	0.2143	0.5	0–1.0	4.6	2.2–6.9	<0.0001
35–39	0.4	0–1.0	0.5	0–1.6	0.808	0.6	0–1.4	1.9	0.8–3.0	0.0821
40–44	1.3	0–3.3	0.2	0–0.6	0.0965	1.6	0–4.4	2.6	0.5–4.6	0.6249
45–49	–	–	–	–		0.6	0–1.3	1.6	0.2–3.1	0.1638
Total	**1.7**	**0.9–2.5**	**2.0**	**0.9–3.1**	**0.5706**	**2.6**	**2.0–3.3**	**5.1**	**4.1–6.1**	**<0.0001**
Chlamydia trachomatis										
15–19	4.6	2.6–6.5	–	–		14	11.2–16.8	15.3	6.7–23.9	0.7724
20–24	8.7	6.2–11.2	7.9	0–16.6	0.8772	16.5	13.1–19.9	13.9	9.7–18.0	0.3631
25–29	6.4	3.9–8.9	10.6	4.4–16.7	0.1561	7.7	4.8–10.6	11.8	8.1–15.5	0.0715
30–34	8.3	3.2–13.4	1.8	0.4–3.3	0.0006	3.5	1.1–5.9	6.1	3.9–8.4	0.1527
35–39	1.9	0.4–3.5	0.8	0–1.7	0.2101	2.6	1.1–4.2	5.5	2.6–8.4	0.0393
40–44	–	–	1.9	0–3.8	–	2.3	0.1–4.4	2.8	0.7–5.0	0.7281
45–49	–	–	1.2	0–3.5	–	0.7	0–1.5	1.3	0–2.7	0.4375
Total	**5.7**	**4.5–6.8**	**3.5**	**2.0–5.0**	**0.048**	**9.8**	**8.6–11.1**	**7.9**	**6.5–9.2**	**0.0371**
Trichomonas vaginalis										
15–19	0.5	0–1.1	1.6	0–4.7	0.289	10.9	8.3–13.5	15.1	7.7–22.4	0.2662
20–24	1.7	0.4–2.9	3.5	0–7.4	0.2603	10.0	7.3–12.7	18.5	14.3–22.7	0.0001
25–29	1.4	0.4–2.4	8.2	2.4–13.9	0.0001	7.1	4.6–9.5	19.3	14.8–23.8	<0.0001
30–34	4.2	0.4–7.9	4.5	0.7–8.2	0.9078	6.5	3.3–9.7	13.3	9.7–16.9	0.0051
35–39	5.0	1.8–8.2	8.1	2.2–14.0	0.3344	11.0	6.2–15.7	20.5	15.3–25.7	0.0107
40–44	10.2	5–15.3	12.0	6.2–17.7	0.6566	11.1	5.7–16.6	18.6	13.6–23.5	0.0467
45–49	6.7	1.4–12	6.1	2–10.2	0.8596	17.6	12.1–23.1	22.0	16.4–27.7	0.2632
Total	**2.6**	**1.8–3.3**	**7.3**	**5.1–9.4**	**<0.0001**	**10.3**	**8.9–11.8**	**18.1**	**16.0–20.2**	**<0.0001**
Mycoplasma genitalium										
15–19	1.7	0.6–2.7	6.6	0–14.7	0.0375	4.8	2.8–6.8	9.5	3.6–15.4	0.0747
20–24	2.7	1.4–4	7.3	1.4–13.3	0.0353	6.6	4.3–9	12.0	8.2–15.9	0.0069
25–29	9.1	5.5–12.6	9.7	5–14.4	0.8208	5.3	2.8–7.8	8.7	5.4–11.9	0.1083
30–34	7.2	3–11.4	14.5	8.4–20.6	0.0544	3.1	0.6–5.6	3.8	1.8–5.9	0.6673
35–39	5.8	1.8–9.9	10.4	4.9–15.9	0.2126	1.7	0–3.6	6.4	3.3–9.5	0.0172
40–44	3.3	0–7.2	5.2	2.5–7.9	0.4453	1.4	0–3.2	2.8	1.2–4.5	0.3104
45–49	2.6	0–6.6	2.8	0.2–5.3	0.9365	0.9	0–2.4	1.3	0–2.7	0.7629
Total	**4.4**	**3.3–5.5**	**9.2**	**7.2–11.2**	**<0.0001**	**4.4**	**3.3–5.4**	**6.4**	**5.2–7.5**	**0.0086**

[a] Qualitative detection of antibodies suggestive of a past or current infection.

In the absence of ART, STIs augment HIV viral shedding (Johnson and Lewis, 2008). A meta-analysis of 39 studies showed that STIs that elicit a leukocyte response in the genital tract was associated with almost a three-fold increase in HIV viral shedding promoting potential sexual transmission of HIV (Johnson and Lewis, 2008). However, HIV positive individuals using ART correctly and consistently benefit by achieving HIV viral suppression to prevent onward transmission (Abdool Karim, 2019). However, whilst ART itself has no impact on STIs (Champredon et al., 2015), and as STIs remain untreated, HIV viral shedding persists in genital secretions including semen (Cohen et al., 2019) though shedding may be transient or intermittent (Chun et al., 2013). Our findings on the association of HIV viral load ≥400 copies per mL and STIs highlights the sustained potential elevated risk of onward HIV transmission. It is critical that combination HIV prevention programs include the early diagnosis and treatment of STIs to reduce HIV viral shedding towards the goal of achieving HIV epidemic control (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2017; Galvani et al., 2018).

Strengths and limitations of this study

The strength of this study was the use of biological measurements of STIs on self-collected genital samples rather than relying on signs and symptoms of STIs. Despite the robust sampling strategy, given

Table 4
Adjusted prevalence ratios for the association of curable sexually transmitted infections and HIV positive status.

	Males				Females			
	STI prevalence				STI prevalence			
	HIV positive % (95% CI)	HIV negative % (95% CI)	PR	aPR[a] (% CI)	HIV positive % (95% CI)	HIV negative % (95% CI)	PR	aPR[b] (% CI)
Syphilis	2.1 (1.1–3.1)	1.3 (0.7–1.9)	1.62	1.15 (0.46–2.86)	2.5 (1.8–3.2)	1.0 (0.7–1.4)	**2.50**	**2.54 (1.32–4.86)**
N. gonorrhoeae	2.0 (0.9–3.1)	1.7 (0.9–2.5)	1.18	1.73 (0.67–4.5)	5.1 (4.1–6.1)	2.6 (2.0–3.3)	**1.96**	**2.39 (1.62–3.52)**
C. trachomatis	3.5 (2.0–5.0)	5.7 (4.5–6.8)	0.61	0.96 (0.57–1.63)	7.9 (6.5–9.2)	9.8 (8.6–11.1)	0.81	1.01 (0.82–1.25)
T. vaginalis	7.3 (5.1–9.4)	2.6 (1.8–3.3)	2.81	1.50 (0.93–2.41)	18.1 (16.0–20.2)	10.3 (8.9–11.8)	**1.76**	**1.70 (1.43–2.01)**
M. genitalium	9.2 (7.2–11.2)	4.4 (3.3–5.5)	**2.09**	**1.49 (1.02–2.19)**	10.3 (8.9–11.8)	4.4 (3.3–5.4)	**2.34**	**1.60 (1.15–2.22)**

PR = prevalence ratio; aPR = adjusted prevalence ratio; 95% CI = 95% confidence interval.
[a] Adjusted for age, relationship status, education, number of lifetime sexual partners and medical male circumcision status.
[b] Adjusted for age, relationship status, education and number of lifetime sexual partners.

Table 5
Adjusted prevalence ratios for the association of curable sexually transmitted infections among HIV positive participants stratified by CD4 cell counts and HIV viral load.

	STI prevalence				STI prevalence			
	CD4 cell count <350 per μL % (95% CI)	CD4 cell count ≥350 per μL % (95% CI)	PR	aPR* (% CI)	HIV viral load ≥400 copies per mL % (95% CI)	HIV viral load <400 copies per mL % (95% CI)	PR	aPR[a] (% CI)
Syphilis	2.6 (1.5–3.7)	2.2 (1.6–2.9)	1.16	1.26 (0.82–1.94)	3.2 (2.1–4.2)	1.5 (0.9–2.2)	2.06	1.71 (0.97–3.02)
N. gonorrhoeae	4.6 (2.8–6.4)	3.7 (2.9–4.5)	**1.26**	**1.59 (1.00–2.52)**	5.5 (4.3–6.7)	2.3 (1.5–3.1)	**2.39**	**1.91 (1.36–2.70)**
C. trachomatis	4.3 (2.7–5.9)	7.1 (5.9–8.3)	0.61	0.72 (0.47–1.11)	8.0 (6.6–9.5)	4.5 (3.2–5.7)	**1.80**	**1.52 (1.12–2.05)**
T. vaginalis	13.6 (11–16.2)	14.3 (12.5–16.1)	0.95	1.11 (0.92–1.35)	13.2 (11–15.3)	15.0 (12.9–17.1)	0.88	1.01 (0.83–1.21)
M. genitalium	11.7 (9.4–14.1)	5.6 (4.5–6.7)	**2.10**	**2.01 (1.52–2.66)**	10.1 (8.3–11.9)	4.7 (3.4–6)	**2.16**	**1.82 (1.27-2.63)**

PR = prevalence ratio; aPR = adjusted prevalence ratio; 95% CI = 95% confidence interval.
[a] adjusted for sex and age.

the cross-sectional design of the study, temporality of any associations cannot be inferred, and generalizability of our findings are limited to the study area or to similar high HIV burden settings. As the sociodemographic, behavioural and clinical data were self-reported, these could potentially be prone to social desirability bias. The data on sexual partnerships were reported over the previous 12 months or further and may be subject to recall bias. Even though participants were guided on the self-collection method of obtaining genital samples, some samples may have been of inadequate quality resulting in an underestimation of the prevalence of STIs.

Conclusions

The high prevalence of STIs and the association with HIV and HIV viral load ≥400 copies per mL underscores the public health implications of sustained onward transmission risk of STIs and HIV. STIs remain a threat towards realizing the goal of achieving HIV epidemic control in this high HIV burden region.

Data sharing statement

Data are available upon reasonable request. Kindly contact Professor Ayesha BM Kharsany at Ayesha.kharsany@caprisa.org.

Author contributions

ABMK is the principal investigator of the study and wrote the manuscript. ABMK, LRM and LL were responsible for analysis and interpretation of the data. TCG contributed with the preparation of the tables and the literature review. ABMK, CC and DK were responsible for the field work and quality assurance; DVM was responsible for the laboratory measurements and quality assurance, SB, KG and GG contributed to the household and individual level data collection tools and interpretation of the data; DK, CC and ABMK were responsible for community and stakeholder engagement activities; KAA and CT contributed to the interpretation of the data. All authors critically reviewed and approved the final version of the manuscript.

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The funders of the survey contributed to the survey design and study monitoring and did not interact with human subjects or have access to identifiable data or specimens for research purposes. ABMK and LL had full access to all the data. ABMK, CC and DK had final responsibility for the decision to submit for publication.

Competing interest

All authors declare that they have no competing interests.

Disclaimer

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Appendix A. Supplementary data

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