The HIV and sexually transmitted infection syndemic following mass scale-up of combination HIV interventions in two communities in southern Uganda: a population-based cross-sectional study

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Summary

Background Combination HIV prevention and treatment interventions (CHIs) have led to substantial declines in HIV incidence in sub-Saharan Africa; however, population-level data on non-HIV sexually transmitted infections (STIs) in the context of CHIs are rare. We aimed to assess STI burden following scale-up of CHIs in Uganda.

Methods The Sexually Transmitted Infection Prevalence Study (STIPS) was a cross-sectional study nested within a population-based cohort among inland agrarian and Lake Victoria fishing populations in southern Uganda. STIPS enrolled consenting residents aged 18–49 years in two communities (one inland and one fishing) between May and October, 2019, and measured the prevalence of chlamydia, gonorrhoea, trichomonas, syphilis, and herpes simplex virus 2 (HSV-2).

Findings Between May 27, 2019 and Oct 25, 2019, STIPS enrolled 1825 participants. HIV prevalence was 14·0% among the inland population and 39·8% among the fishing population, with about 90% HIV viral load suppression in both communities. Among inland and fishing populations, chlamydia prevalence was 9·6% (95% CI 7·9–11·7) and 9·9% (8·1–12·0), gonorrhoea prevalence 5·0% (3·8–6·7) and 8·4% (6·8–10·5), trichomonas prevalence 9·4% (7·7–11·5) and 12·2% (10·2–14·5), and HSV-2 prevalence 43·0% (39·9–46·3) and 64·4% (61·3–67·6), respectively. In the fishing population, syphilis seropositivity was 24·2% (21·5–27·2) with 9·4% (7·7–11·5) having high-titre (rapid plasma reagin ≥1:8) infection, including 16·9% (11·9–24·0%) of men living with HIV. Prevalence of at least one curable STI (chlamydia, gonorrhoea, trichomonas, or high-titre syphilis) was 51% higher among people living with HIV (*vs* HIV negative; adjusted prevalence risk ratio [PRR] 1·51; 95% CI 1·27–1·78), including among pregnant women (adjusted PRR 1·87, 1·11–3·17), with no differences by HIV suppression status.

Interpretation Despite near universal HIV treatment, STI burden remains extremely high in southern Uganda, particularly among people living with HIV. There is an urgent need to integrate STI care with HIV services in African settings.

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Introduction

Sexually transmitted infections (STIs) are a major cause of fetal and neonatal morbidity and mortality, cervical cancer, and female infertility, and are associated with reduced quality of life.[1] Globally, the absolute number of STI cases and associated disability adjusted life years have increased between 1990 and 2019, despite reductions in HIV incidence with the scale-up of combination HIV prevention and treatment interventions (CHIs).[2,3] In 2019, the US Centers for Disease Control and Prevention (CDC) reported more than 2·5 million cases of *Chlamydia trachomatis* (chlamydia), *Neisseria gonorrhoea* (gonorrhoea), and syphilis, continuing an alarming, rapid rise in STIs since 2015.[4] Emerging data on STI trends from the USA and other high-income countries have prompted re-evaluation of the relationship between HIV and STIs in the context of CHIs.[5]

Although there are abundant data on STI burden following scale-up of CHIs in high-income countries, there are limited data elsewhere, including in Africa. Worldwide, incidence rates of chlamydia, gonorrhoea, and *Trichomonas vaginalis* (trichomonas) are highest in sub-Saharan Africa, with the majority of cases occurring among heterosexual men and women.[6] The region also bears the world's greatest HIV burden, with more than 25 million people living with HIV.[7] Since the mid-2000s, there has been substantial global investment in African HIV epidemic control.[8] CHIs, including antiretroviral

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Research in context

Evidence before this study

Sexually transmitted infections (STIs) are associated with poor reproductive health outcomes and neonatal morbidity and mortality. Decades of previous research have shown that STIs are also strongly and consistently associated with higher HIV incidence and prevalence, including in sub-Saharan Africa, where the global burden of HIV is concentrated. Although HIV incidence has declined by 43% in eastern and southern Africa since 2010 with the scale-up of combination HIV prevention and treatment programmes, population-level data on STIs since widespread implementation of these programmes are rare. Over the past decade, data from facility-based settings, predominantly antenatal care clinics, and HIV clinical trials suggest that STI burden among African women who are pregnant and of reproductive age remains high. We searched PubMed, in English only, from inception to Jan 1, 2022, using search terms such as "population-level", "population-based", and "sexually transmitted infections" we identified only two comprehensive population-level studies on STIs (ie, including assessment of multiple STIs in addition to syphilis) conducted in sub-Saharan Africa since 2010, both of which were done in KwaZulu-Natal, South Africa before universal HIV treatment access. The first study was done among people aged 15–49 years between 2014 and 2015 and found high STI burden, with overall prevalence of gonorrhea of 2·8%, chlamydia 7·1%, high-titre syphilis 1·6%, and trichomonas 9·0%. The second of these studies was done among 447 adolescents and young people aged 15–24 years in 2016, and similarly found high STI burden.

Added value of this study

We used primary data collected through an ongoing population-based surveillance cohort in southern Uganda to measure prevalence of chlamydia, gonorrhoea, trichomonas, syphilis, and herpes simplex virus 2 (HSV-2) following mass scale-up of combination HIV prevention interventions in two East African communities with high HIV prevalence. Despite successful public health efforts to treat and curb HIV spread within these communities, non-HIV STI burden was extremely high with large numbers of asymptomatic STI infections. We also found an extraordinarily high prevalence of high-titre syphilis infection (about 9%) among Lake Victoria fishing populations, at a prevalence arguably constituting a public health emergency. Despite achieving UNAIDS 95-95-95 HIV fast-track treatment targets with about 90% HIV viral load suppression, the burden of STIs was significantly higher among people living with HIV, including among pregnant women, underscoring a lack of effective integrated HIV and STI services. To our knowledge, this is the first comprehensive population-level assessment of STI burden, including measurement of gonorrhoea, chlamydia, trichomonas, syphilis, and HSV-2, in an eastern Africa setting in more than a decade, and the first done in sub-Saharan Africa since universal HIV treatment programmes were implemented.

Implications of all the available evidence

Taken together, data from this population-level study of STI burden in Uganda and those from other sub-Saharan African settings suggest that STIs remain neglected diseases in sub-Saharan Africa. The absence of affordable STI diagnostics and poorly-integrated public health services stand as major barriers to reducing STI burden in the region. Global investment in innovative approaches that simultaneously test and treat HIV and STIs within existing health infrastructure has the potential to substantially improve population health in Africa, such as integrated HIV and STI service programmes within the President's Emergency Plan for AIDS Relief programme. Controlling STI epidemics within Africa should be a global health priority given the important consequences of STIs for female reproductive and child health and the growing threat of antimicrobial resistance.

therapy (ART) and voluntary medical male circumcision (VMMC), have been successfully scaled up in many countries.[9] Although data from studies across Africa show declining HIV incidence with increasing coverage of CHIs,[10] population-level data on STI burden in the era of widespread biomedical HIV prevention are rare. Understanding the extent to which modern HIV and STI epidemics overlap could identify points of synergy for integrated disease control within African HIV treatment and prevention programmes.[11]

Here, we report results from the Sexually Transmitted Infection Prevalence Study (STIPS), a cross-sectional, population-based study of chlamydia, gonorrhoea, trichomonas, syphilis, and herpes simplex virus 2 (HSV-2) prevalence. STIPS was nested in two communities within the Rakai Community Cohort Study (RCCS), a population-based HIV surveillance cohort in Uganda. Scale-up of CHIs has led to substantial declines in HIV incidence in RCCS study communities;[12,13] however, the burden of STIs since CHI roll-out has not been characterised previously.

Methods

STIPS

STIPS was a cross-sectional study nested in the 19th survey round (R19) of RCCS, an open population-based census and HIV cohort study in 40 communities in Rakai and surrounding districts in southern Uganda done by the Rakai Health Sciences Program (RHSP).[14] As part of routine activities, the RCCS conducts a household census with no age truncation. The RCCS survey, done after the census, includes all people aged 15–49 years residing within community surveillance boundaries. Individuals providing written informed consent for the RCCS survey are administered voluntary HIV testing and counselling and a structured questionnaire through

face-to-face interview to collect sociodemographic, behavioural, and health information. The RHSP refers participants to HIV treatment and prevention services, including ART and VMMC. ART was initially made available in Uganda in 2004 through the US President's Emergency Plan for AIDS Relief, and VMMC services began in 2007. Pre-exposure prophylaxis (PrEP) roll-out began in selected communities and target populations in 2017.

All consenting RCCS participants aged 18–49 years residing in two RCCS study communities were invited to participate in the STIPS study. The two selected communities included a semi-urban trading centre and surrounding rural villages (herein referred to as inland community) and a fishing community along the Lake Victoria shoreline. These communities were selected because of their representativeness, geographical diversity, population size, and enrolment timelines within the RCCS R19 survey. All study participants provided written informed consent for STIPS in addition to the RCCS. Consent for STIPS immediately followed the consent for RCCS, and those who agreed to participate in STIPS provided written informed consent for collection of three genital swabs (for chlamydia and gonorrhoea testing, for trichomonas testing, and for storage for future studies). Clinicians collected penile meatal swabs from men and self-collected vaginal swabs were obtained from women. STIPS participants were also administered an STI module during the RCCS survey, which included survey questions on STI symptoms (current and in the past 6 months).

STIPS was approved by the Uganda Virus Research Institute Research Ethics Committee (GC/127/19/03/709) and the Johns Hopkins School of Medicine Institutional Review Board (IRB00204691). The study was also registered with the Ugandan National Council for Science and Technology (HS 364 ES).

Procedures

HIV, HSV-2, and syphilis antibody tests were performed using serum from peripheral blood samples. HIV and syphilis testing was done at the time of the RCCS and STIPS survey and HSV-2 testing after enrolment of all STIPS participants. HIV testing was done using a field-validated parallel three-test rapid HIV testing algorithm with ELISA and PCR testing for first-time diagnoses.[15] HIV viral load testing was done for all participants who were HIV seropositive using the Abbott RealTime assay (Abbot Molecular, Abbott Park, IL, USA), and an HIV viral load of more than 1000 copies/mL was classified as being viraemic. HSV-2 testing was done using the Kalon ELISA (Kalon Biological, Guilford UK) with a previously validated index cutoff value of 1·5.[16]

Syphilis antibody status was established using the SD Bioline Syphilis 3.0 (SD Biostandard Diagnostics Private, Gurgaon, India), a solid-phase immunochromatographic point-of-care assay for the qualitative detection of treponemal antibodies. The rapid plasma reagin (RPR) test (Cypress Diagnostics, Hulshout, Belgium) was done for all participants with positive antibody results on SD Bioline to determine syphilis titres. RPR testing was done within 24 h at the RHSP central laboratory in Kalisizo, Uganda, and high-titre syphilis infection was defined as an RPR titre of 1:8 or higher.

Penile meatal and vaginal swabs were tested for chlamydia, gonorrhoea, and trichomonas. Chlamydia and gonorrhoea testing was done using the Abbott m2000 RealTime CT/NG assay (Abbot Molecular) for the direct, qualitative detection of plasmid DNA of chlamydia and genomic DNA of gonorrhoea. Testing was done at the RHSP central laboratory within 7 days of sample collection according to the manufacturer's protocol. Trichomonas testing was done from genital swabs at time of survey using the OSOM Trichomonas Rapid Test (Sekisui [formerly Genzyme Diagnostics], Burlington, MA, USA) for qualitative detection of *T vaginalis* antigens.

Return of STI test results and provision of treatment

HIV, syphilis, and trichomonas rapid-test results were returned to participants immediately by on-site counsellors after testing. If results were positive, they were offered free treatment per Uganda Clinical Guidelines for treatment of STIs.[17] Individuals who reported symptomatic vaginal or penile discharge or genital ulcers at time of survey but who were not diagnosed with an STI were also offered treatment in line with WHO syndromic management guidelines.[18] Participants who tested positive for chlamydia and gonorrhoea were recontacted after the survey and were provided with counselling after testing and free treatment.

Statistical analysis

We have previously shown that HIV prevalence substantially varies between Lake Victoria fishing and inland communities in the RCCS,[14] and so we first compared the demographic, sexual behaviour, and HIV service use characteristics between STIPS participants residing in inland and fishing communities. All characteristics were described categorically using frequency counts and percentages, and statistically significant differences were determined using χ^2 tests. We next estimated the prevalence of each STI separately by gender, community type (ie, fishing *vs* inland), and HIV status using modified Poisson regression with robust variance estimators.[19] Prevalence was estimated similarly by age group (15–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years, and 45–49 years), gender, and community type. In sensitivity analyses, prevalence of each STI was estimated using inverse probability weights to account for potential biases induced by selective participation into the study by

gender, age, migration status (in-migrant *vs* long-term resident), last known HIV serostatus (HIV seropositive, HIV seronegative, or unknown), and status as head of household. Selection weights were estimated using logistic regression separately for each community.

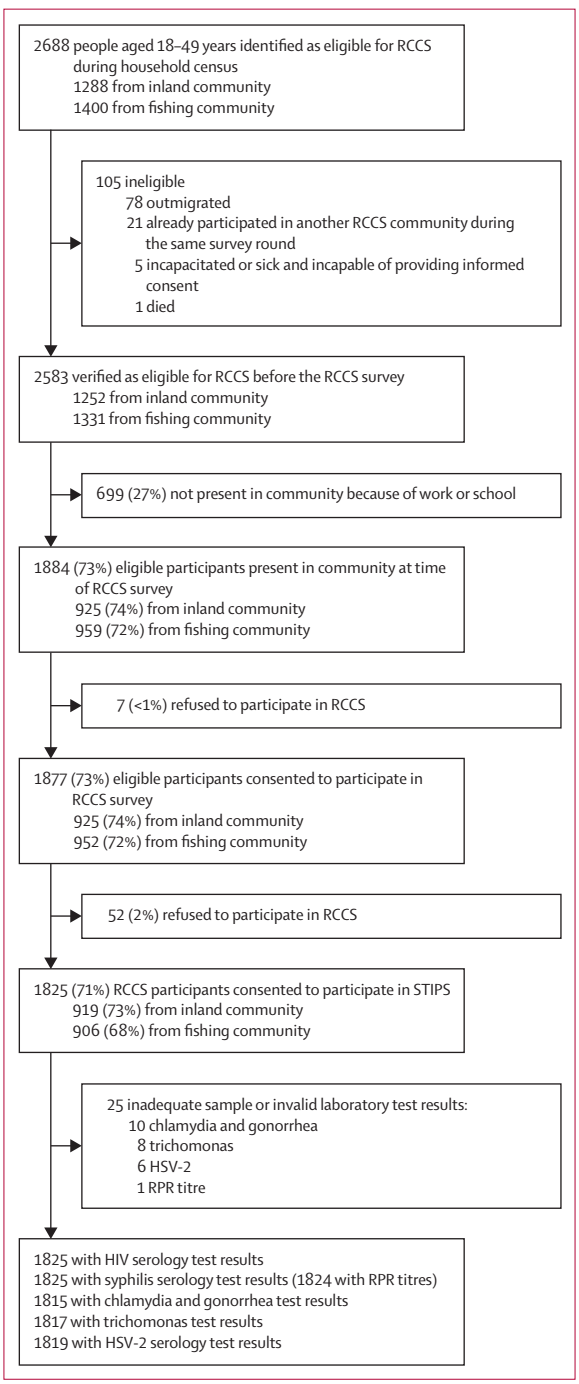

Figure 1: **Enrolment of 1825 participants into the STIPS through the RCCS**
All percentages are reported as a proportion (times 100) among those verified as eligible for the RCCS. HSV-2=herpes simplex virus 2. RCCS=Rakai Community Cohort Study. RPR=rapid plasma reagin. STIPS=Sexually Transmitted Infection Prevalence Study.

See Online for appendix

Overlap in HIV and STI epidemics was first evaluated using frequency counts of each STI with the *UpSetR* package in the R statistical software (version 4.0.3). Next, we evaluated associations between the various STIs, assessing each as both an outcome and risk factor using unadjusted and adjusted modified Poisson regression models, the latter with adjustment for gender, age and community type (ie, fishing *vs* inland). We further analysed risk factors for curable STIs, including chlamydia, gonorrhoea, trichomonas, and high-titre syphilis. Risk factors evaluated included gender, age group, marital status, educational level, number of sex partners in the past year, HIV serostatus, male circumcision, pregnancy, HIV viraemia among people living with HIV, and PrEP among people who were HIV negative. All associations were measured using unadjusted and adjusted modified Poisson regression and reported as prevalence risk ratios (PRRs) with 95% CIs.

We also evaluated the association between an STI diagnosis and incident HIV infection using longitudinal data on HIV serostatus from the RCCS. HIV incident cases were defined as participants who had a first seropositive HIV test result in the STIPS and RCCS R19 survey and a negative test result at the previous survey (median follow-up time 2·0 years) as previously described.[12] Associations between STIs and HIV incident infection were measured using Poisson regression models with an offset term for person-years of follow-up and reported as incidence rate ratios (IRRs) with 95% CI.

Lastly, we assessed the validity of self-reported current STI symptoms for diagnosis of chlamydia, gonorrhoea, and trichomonas. Clinically indicative symptoms of each STI were defined as specified in the 2016 Uganda clinical guidelines.[17] Sensitivity and specificity of each self-reported symptom, clinically indicative symptoms, and all symptoms combined were estimated using the *epiR* package in R version 4.03.

Role of the funding source

The study sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of this report.

Results

There were 2583 census-eligible participants, of whom 1884 (73%) were present in the community at the time of RCCS survey. Of those individuals present, 1825 (97%) consented to participate in STIPS between May 27, 2019 and Oct 25, 2019, including 919 participants in the inland community and 906 in the fishing community (figure 1). Study participation among census-eligible residents was significantly lower among those residing in the fishing community, younger people, men, people of unknown HIV serostatus, and recent in-migrants (appendix p 2).

The median age of study participants was 32 years (IQR 25–39) and 860 (47·1%) were men and 965 (52·8%)

	Inland, n (%)	Fishing, n (%)	χ^2 p-value
Overall	919	906	..
Sex	..	..	0·00085
Female	522 (56·8%)	443 (48·9%)	..
Male	397 (43·2%)	463 (51·1%)	..
Age, years	..	..	..
15–19	262 (28·5%)	177 (19·5%)	0·0001
25–29	156 (17·0%)	192 (21·1%)	..
30–34	136 (14·8%)	169 (18·7%)	..
35–39	162 (17·6%)	170 (18·8%)	..
40–44	123 (13·4%)	131 (14·5%)	..
45–49	80 (8·7%)	67 (7·4%)	..
Marital status	..	..	..
Currently married	605 (65·8%)	595 (65·7%)	<0·0001
Never married	169 (18·4%)	93 (10·3%)	..
Previously married	145 (15·8%)	218 (24·1%)	..
Education			
None	36 (3·9%)	97 (10·7%)	<0·0001
Primary	537 (58·4%)	607 (67·0%)	..
Secondary	251 (27·3%)	154 (17·0%)	..
Tertiary or trade School	95 (10·3%)	48 (5·3%)	..
Occupation	..	..	<0·0001
Agriculture	481 (52·3%)	35 (3·9%)	..
Transport	31 (3·4%)	23 (2·5%)	..
Fishing	4 (0·4%)	285 (31·5%)	..
Government, clerical, and teaching	60 (6·5%)	11 (1·2%)	..
Hairdresser	34 (3·7%)	19 (2·1%)	..
Housework	22 (2·4%)	89 (9·8%)	..
Student	44 (4·8%)	8 (0·8%)	..
Trader or shop keeper	131 (14·3%)	204 (22·5%)	..
Bartender or waitress	16 (1·7%)	76 (8·4%)	..
Other	96 (10·4%)	156 (17·2%)	..
Sex partners in the past year	..	..	<0·0001
None	117 (12·7%)	62 (6·8%)	..
One	571 (62·1%)	485 (53·5%)	..
Two	149 (16·2%)	190 (21·0%)	..
Three	52 (5·7%)	93 (10·3%)	..
Four or more	30 (3·3%)	76 (8·4%)	..
HIV prevalence	..	..	<0·0001
HIV negative	790 (86·0%)	545 (60·2%)	..
HIV positive	129 (14·0%)	361 (39·8%)	..
(Continued from previous column)			
Viral load suppression status among people living with HIV	..	..	0·83
≤1000 copies/mL	118 (91·5%)	326 (90·3%)	..
>1000 copies/mL	11 (8·5%)	35 (9·7%)	..
Male circumcision status*	..	..	0·48
Uncircumcised	205 (51·6%)	227 (49·0%)	..
Circumcised	192 (48·4%)	236 (51·0%)	..
Ever used PrEP if HIV-negative†	..	..	..
No	785 (99·4%)	505 (92·7%)	<0·0001
Yes	4 (0·5%)	39 (7·2%)	..
Currently pregnant if female	..	..	1
No	464 (88·9%)	394 (88·9%)	..
Yes	58 (11·1%)	49 (11·1%)	..

PrEP=pre-exposure prophylaxis for HIV. *Male circumcision status could not be clinically confirmed for 7 male participants; these men were classified as uncircumcised. †There was missing data on PrEP use for two participants.

***Table 1*: Characteristics of 1825 Sexually Transmitted Infection Prevalence Study participants in southern Uganda stratified by community of residence**

were women, of whom 107 were pregnant. HIV prevalence was 14·0% in inland communities and 39·8% in fishing communities, with about 90% HIV viral load suppression among people living with HIV in both communities. Half of men were circumcised, but few people who were HIV negative reported ever using PrEP (table 1).

There was a total of 177 chlamydia, 122 gonorrhoea, 196 trichomonas, and 98 high-titre syphilis infections detected among 478 (26%) study participants, of whom 21% (n=100) had several infections. Prevalence of STIs was substantially higher among fishing compared with inland community residents (table 2). Adjusting for age, gender, and community type, people living with HIV were 51% more likely to be diagnosed with at least one curable STI compared with people who are HIV negative (174 [35·5%] of 490 *vs* 304 [22·8%] of 1335; adjusted PRR 1·51, 95% CI 1·27–1·78; appendix p 3). The most frequently co-occurring curable STI with HIV was trichomonas followed by high-titre syphilis and then gonorrhoea (appendix p 16). With the exception of chlamydia, all STIs were positively associated with HIV serostatus (table 3).

Approximately one in ten people were diagnosed with chlamydia in both communities (table 2). Although chlamydia prevalence did not differ between participants by community or gender (appendix p 5), prevalence tended to be lower among people living with HIV compared with people who were HIV negative (6·6% *vs* 10·9%; appendix p 6). Among men and women, chlamydia prevalence was highest among those younger than 30 years, and significantly declined with increasing age (appendix p 5). Age-specific trends of chlamydia prevalence were similar between inland and fishing communities (figure 2A and B).

Gonorrhoea was diagnosed in 122 study participants, including among 46 (5·0%) of 915 inland community

	Inland community (n=919)			Fishing community (n=906)		
	n/total	Unweighted prevalence, % (95% CI)	Weighted prevalence, % (95% CI)	n/total	Unweighted prevalence, % (95% CI)	Weighted prevalence, % (95% CI)
Chlamydia	88/915	9·6 (7·9–11·7)	10·4 (8·4–12·7)	89/900	9·9 (8·1–12·0)	10·0 (8·2–12·2)
Gonorrhoea	46/915	5·0 (3·8–6·7)	5·1 (3·8–6·8)	76/900	8·4 (6·8–10·5)	8·61 (6·92–10·7)
Trichomonas	86/916	9·4 (7·7–11·5)	9·1 (7·3–11·2)	110/901	12·2 (10·2–14·5)	11·3 (9·4–13·5)
Positive syphilis serology	65/919	7·1 (5·6–8·9)	7·0 (5·5–8·9)	219/906	24·2 (21·5–27·1)	23·1 (20·5–26·1)
High-titre syphilis	13/919	1·4 (0·8–2·4)	1·6 (0·9–2·9)	85/909	9·4 (7·7–11·5)	9·3 (7·5–11·4)
Herpes simplex virus 2	393/915	43·0 (39·9–46·3)	40·2 (37·1–43·6)	582/904	64·4 (61·3–67·6)	60·2 (56·9–63·7)
Any curable STI*	195/919	21·2 (18·7–24·0)	21·9 (19·2–24·9)	293/906	31·2 (28·4–34·4)	30·7 (27·7–33·9)

STI=sexually transmitted infection. *Curable STIs included chlamydia, gonorrhoea, trichomonas, and high-titre syphilis.

Table 2: **Unweighted and inverse probability weighted estimates of STI prevalence among 1825 Sexually Transmitted Infection Prevalence Study participants in southern Uganda stratified by community of residence**

	Chlamydia	Gonorrhoea	Trichomonas	Positive syphilis serology	High-titre syphilis	HSV-2	HIV
Unadjusted PRR (95% CI)							
Chlamydia	..	2·72 (1·91–3·87)	1·63 (1·13–2·35)	1·06 (0·73–1·55)	1·86 (1·18–2·94)	0·76 (0·58–1·01)	0·60 (0·42–0·87)
Gonorrhoea	2·88 (1·96–4·25)	..	1·93 (1·26–2·96)	1·54 (1·02–2·31)	1·75 (0·98–3·14)	1·41 (0·99–2·01)	1·90 (1·34–2·68)
Trichomonas	1·62 (1·12–2·32)	1·86 (1·25–2·75)	..	2·06 (1·55–2·75)	2·22 (1·49–3·29)	2·64 (1·93–3·61)	2·00 (1·54–2·6)
Positive syphilis serology	1·06 (0·74–1·50)	1·46 (1·03–2·08)	1·95 (1·51–2·52)	..	..	2·85 (2·20–3·69)	3·42 (2·77–4·21)
High-titre syphilis	1·94 (1·18–3·20)	1·77 (0·97–3·22)	2·39 (1·52–3·76)	..	..	2·40 (1·55–3·72)	2·95 (2·02–4·33)
HSV-2	0·86 (0·73–1·02)	1·17 (1·01–1·35)	1·48 (1·35–1·62)	1·55 (1·43–1·69)	1·40 (1·23–1·59)	..	2·09 (1·94–2·24)
HIV	0·65 (0·47–0·90)	1·59 (1·27–2·00)	1·69 (1·41–2·04)	2·58 (2·24–2·97)	2·05 (1·66–2·52)	5·56 (4·36–7·09)	..
Adjusted PRR (95% CI)							
Chlamydia	..	2·45 (1·72–3·50)	1·74 (1·20–2·52)	1·22 (0·83–1·78)	1·99 (1·26–3·14)	1·06 (0·78–1·46)	0·78 (0·53–1·13)
Gonorrhoea	2·67 (1·79–3·97)	..	1·71 (1·11–2·65)	1·38 (0·89–2·12)	1·50 (0·81–2·78)	1·42 (0·95–2·11)	1·93 (1·30–2·86)
Trichomonas	1·71 (1·20–2·45)	1·62 (1·10–2·39)	..	1·89 (1·41–2·55)	2·09 (1·39–3·13)	2·10 (1·48–2·98)	1·66 (1·24–2·21)
Positive syphilis serology	1·18 (0·84–1·66)	1·31 (0·92–1·85)	1·72 (1·33–2·23)	..	..	2·11 (1·58–2·81)	2·44 (1·94–3·06)
High-titre syphilis	2·04 (1·25–3·33)	1·50 (0·82–2·76)	2·21 (1·39–3·52)	1·87 (1·12–3·11)	..	1·87 (1·12–3·11)	2·01 (1·32–3·06)
HSV-2	1·03 (0·89–1·19)	1·14 (1·00–1·30)	1·24 (1·14–1·36)	1·28 (1·18–1·39)	1·21 (1·07–1·38)	..	1·58 (1·46–1·70)
HIV	0·82 (0·62–1·09)	1·46 (1·18–1·80)	1·38 (1·16–1·63)	1·80 (1·57–2·07)	1·47 (1·21–1·78)	3·61 (2·79–5·67)	..

Row headings are STI outcomes and column headings are STI risk factors. PRR=prevalence risk ratio. STI=sexually transmitted infection. HSV-2=herpes simplex virus 2. *Adjusted models included adjustment for gender, age, and community type (fishing *vs* inland).

Table 3: **Unadjusted and adjusted associations (PRRs) between STI risk factors and outcomes among 1825 Sexually Transmitted Infection Prevalence Study participants in southern Uganda**

participants and 76 (8·4%) of 900 fishing community participants (table 2). By contrast to chlamydia, gonorrhoea prevalence was significantly higher among people living with HIV compared with people who were HIV negative (adjusted PRR 1·93, 95% CI 1·30–2·86; table 3; appendix p 3), with the exception of women in the fishing community, for whom gonorrhoea prevalence was similar irrespective of HIV serostatus (appendix p 4). There were no clear trends in gonorrhoea prevalence by age among men or women (figure 2C and D; appendix p 7).

Prevalence of trichomonas was 9·4% in the inland community and 12·2% in the fishing community (table 2). Disease burden was significantly higher among women compared to men (15·9 *vs* 5·0%; adjusted PRR 4·01, 95% CI 2·35–6·85; appendix p 9) and among people living with HIV relative to people who were HIV negative (17·0 *vs* 8·5%; adjusted PRR 1·66, 95% CI 1·24–2·21; table 3; appendix p 3). Although disease burden tended to increase with age among men in fishing communities, there were no other trends in trichomonas prevalence by age observed (figure 2E and F).

HSV-2 seropositivity was highly prevalent in both communities (393 [43·0%] of 915 in inland communities and 582 [64·4%] of 904 in fishing communities), and was strongly associated with HIV serostatus (table 3). Adjusting for age, community type, and HIV serostatus, women had significantly higher prevalence of HSV-2 than men (606 [63·1%] of 960 *vs* 369 [43·0%] of 859; adjusted PRR 1·46; 95% CI 1·34–1·58). Age-specific seroprevalence increased rapidly among women through their late twenties peaking thereafter in their early thirties. By contrast, male HSV-2 seroprevalence

continued to increase steadily through their forties (figure 3A and B).

Syphilis seroprevalence was 7·1% among inland residents and 24·2% among fishing community residents (table 2), with similar burden among men and women in both communities (appendix p 4). Syphilis seropositivity was strongly and positively associated with HIV serostatus (158 [32·2%] of 490 HIV positive *vs* 126 [9·4%] of 1335 HIV negative; adjusted PRR 2·44; 95% CI 1·94–3·06; table 3; appendix p 3), and generally increased with age (figure 3C and D). High-titre syphilis infection was substantially more common among fishing community versus inland community residents (85 [9·4%] of 905 *vs* 13 [1·4%] of 919; adjusted PRR 5·17; 95% CI 2·45–10·91; appendix p 11). Although high-titre syphilis was not associated with female age, its prevalence steadily increased with age among men through their early forties (figure 3E and F). Notably, 16 (16·9%) of 154 (95% CI 11·9–24·0) men living with HIV residing in the fishing community had high-titre syphilis infection (appendix p 4).

We did not find any statistically significant associations between HIV viral load suppression status or history of PrEP use with either chlamydia, gonorrhoea, trichomonas, or high-titre syphilis (appendix pp 5–12). Although male circumcision status was associated with significantly reduced prevalence of trichomonas (14 [3·3%] 428 *vs* 29 [6·8%] of 424, adjusted PRR 0·52, 95% CI 0·29–0·94; appendix p 10), there was substantially higher prevalence of chlamydia among circumcised men than uncircumcised men (53 [12·4%] of 428 *vs* 27 [6·4%] of 424; adjusted PRR 1·78, 95% CI 1·13–2·79; appendix p 6).

Of the 107 pregnant women in this study, 33 (31%) were diagnosed with chlamydia (ten [9·4%] of 106), gonorrhoea (seven [6·6%] of 106), trichomonas (18 [16·8%] of 107), or high-titre syphilis (three [2·8%] of 106), with five women having several infections. Overall, burden of curable STIs did not differ between women by pregnancy status after adjustment for age, community type, and HIV serostatus (adjusted PRR 0·99, 0·74–1·32). All three cases of high-titre syphilis were found among pregnant women residing in the fishing community. There were 24 pregnant women living with HIV, all of whom, but one, were HIV virally suppressed. Compared with pregnant women who were HIV negative, pregnant women living with HIV were significantly more likely to have a curable STI adjusting for age and community type (13 [54·2%] of 24 *vs* 20 [24·1%] of 83; adjusted PRR 1·87, 1·10–3·17).

There were 876 STIPS participants who tested HIV seronegative at their previous RCCS survey, contributing a total of 1746 person-years of follow-up to the HIV incidence cohort. Of these participants, 12 HIV seroconverted for an overall HIV incidence of 0·69 per 100 person-years. HIV incidence was significantly higher in the fishing community (1·26 per 100 person-years; n=8 cases per 636 person-years) than in the inland community (0·36 per 100 person-years; n=4 cases per 1110 person-years; IRR 3·49, 95% CI 1·10–13·1). Gonorrhoea and syphilis were more common among HIV incident cases at time of diagnosis than in individuals who remained HIV seronegative, and most (ten [83%] of 12) HIV incident cases had HSV-2 antibodies (IRR 6·14, 95% CI 1·62–39·92; appendix p 13).

Lastly, we evaluated the sensitivity and specificity of using self-reported STI symptoms for diagnosis of chlamydia, gonorrhoea, and trichomonas among men and women (appendix pp 14–15). Overall, sensitivity of clinically indicative symptoms for diagnosis of all three infections was low for both women (≤50%) and men (<40%). By contrast, specificity tended to vary depending on STI, symptom, and gender.

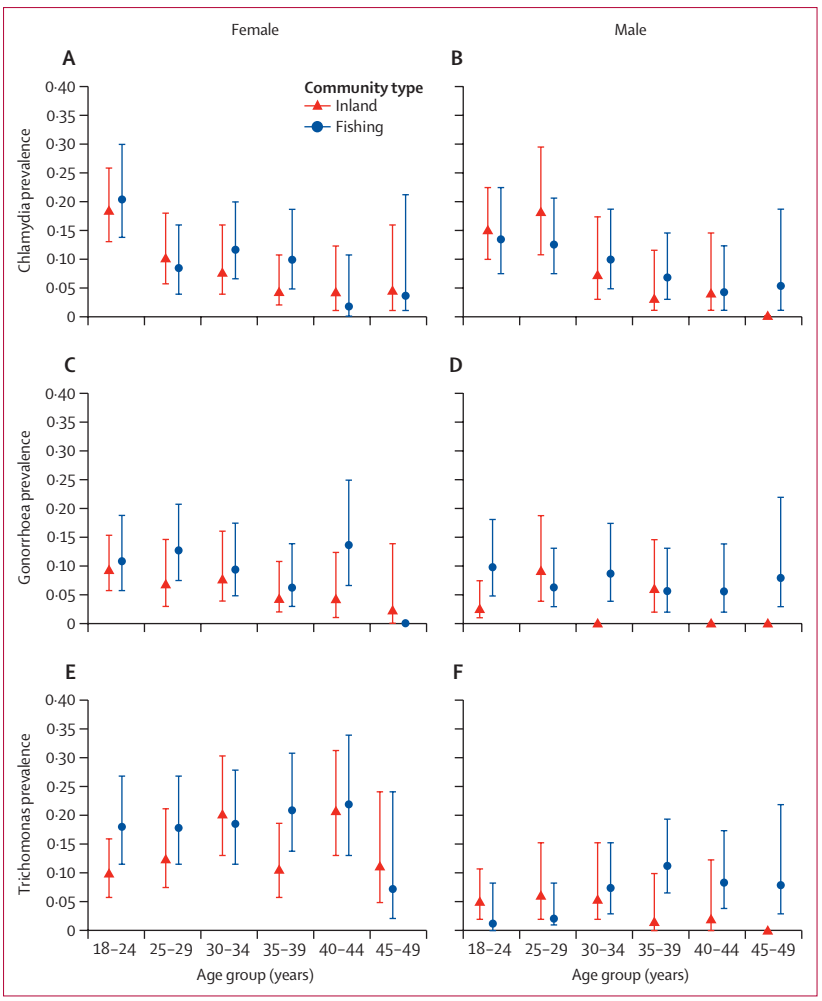

Figure 2: **Chlamydia, gonorrhoea, and trichomonas prevalence among 1825 STIPS participants in southern Uganda stratified by age, gender, and community**
Bars represent 95% CIs. STIPS=Sexually Transmitted Infection Prevalence Study.

Discussion

In this cross-sectional population-based study, we found high population-level STI burden in two Ugandan

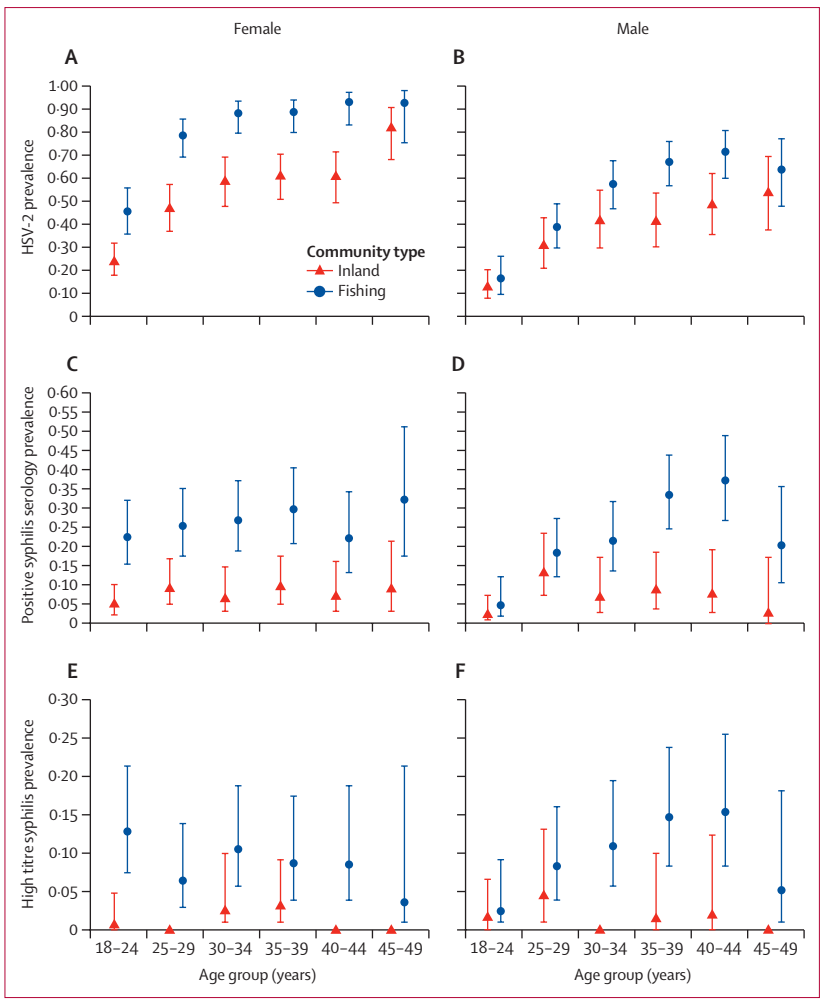

Figure 3: **HSV-2 and syphilis (positive serology and high titre) prevalence among 1825 STIPS participants in southern Uganda stratified by age, gender, and community**
Bars represent 95% CIs. STIPS=Sexually Transmitted Infection Prevalence Study.

communities exceeding UNAIDS 95-95-95 fast-track HIV treatment targets with 90% HIV viral load suppression and high VMMC coverage. Approximately 15% of our study population had either chlamydia or gonorrhoea, and participants residing in the Lake Victoria fishing community had high-titre syphilis prevalence (about 9%) that exceeded four times the prevalence of the Ugandan population nationally (about 2%).[20] Overall, STI infections were significantly more common among people living with HIV, including pregnant women living with HIV for whom STIs can cause severe adverse pregnancy complications. Most chlamydia, gonorrhoea and trichomonas infections detected in this study probably would not have been diagnosed through syndromic case management, which is currently the standard of care in most African countries. Despite rapid growth of a massive health-care infrastructure to diagnose and treat HIV across Africa and calls for integrated HIV and STI care, our results indicate that HIV programmes have failed to address non-HIV STI epidemics, especially among people living with HIV, and that these infections remain neglected diseases.

Numerous studies over the 40-year history of the HIV pandemic have linked STIs to HIV,[21] including the RCCS in which this study was nested.[22] We also found strong associations between curable STIs and HIV infection. Although recent data are scarce, syphilis and trichomonas have been strongly associated with HIV acquisition risk across a range of African settings and populations.[23,24] In addition, we also found that HSV-2 seroprevalence was nearly universal among people living with HIV and associated with a six-times higher rate of HIV incidence. Unlike gonorrhoea and syphilis, chlamydia is thought to generate a partial protective immune response.[25] So although chlamydia prevalence was significantly lower among people living with HIV, this inverse cross-sectional association might reflect high prevalence of pre-existing immunity caused by past infection, rather than a lower risk of HIV acquisition.

Of the 107 pregnant women in this study, nearly one third had a curable STI. These findings are in line with results from other recent African studies showing high prevalence of curable STIs among pregnant women, especially among women living with HIV.[26] Of note, we found three cases of high-titre syphilis among pregnant women participating in STIPS. It is unclear whether these cases were the result of screening gaps in antenatal programmes or caused by missed antenatal visits. In 2016–17, only 43% of Ugandan antenatal clinic attendees were tested for syphilis, although more than about 95% of pregnant women had attended at least one antenatal visit.[27] Given the potentially severe sequelae of untreated STIs during pregnancy, these results demonstrate an opportunity to improve both maternal and newborn health outcomes by building upon existing screenings programmes.

The strong overlap between HIV and STIs observed here and in previous studies underscores that comprehensive HIV and STI programming remains an unaddressed, but urgent public health priority.[28,29] A major barrier to integrated HIV and STI care has been a scarcity of high-quality, affordable STI diagnostics that can be easily implemented in low-resource settings.[11] As shown here, the current approach of syndromic management has low sensitivity and specificity, probably leading to substantial underdiagnosis of STIs irrespective of sex and the probably gross misallocation of antibiotic treatment. Emerging STI point-of-care diagnostics offer a new opportunity for comprehensive HIV and STI programming and more prudent distribution of antibiotic treatments.[30] Although these tests could lead to more timely and improved STI care in sub-Saharan Africa, their effectiveness and implementation needs rigorous evaluation in low-resource settings and cost remains a major barrier to roll-out. Investment in a

combination of HIV and STI programming has the potential to reduce HIV incidence, while at the same time improving female reproductive and neonatal health and reducing the growing public health threat of gonococcal resistance. For example, identifying people who are HIV negative with STIs, could help target HIV prevention interventions, including oral and long-acting PrEP, to those most at risk for HIV. Innovative implementation approaches that decentralise STI testing and care, such as self-testing solutions for HIV and STIs could potentially reduce disease burden among men, pregnant women, and key populations underserved by HIV programmes and the broader health infrastructure. Without additional resources, particularly for STI diagnostics, achieving STI epidemic control will remain out of reach for most African populations. Point-of-care STI diagnostics will be crucial for achieving integrated programme success in resource-limited settings, but must be implemented using sustainable, cost-effective approaches.

This study has limitations. First, the study was done in two communities in southern Uganda with high HIV burden, and so these results might not be generalisable to other settings, particularly those with lower HIV burden and STI risk factors. However, population-level data on STI prevalence are rare and the data generated here are in line with previous research in South Africa.[31] Second, not all census-eligible people for the study participated, with men and younger people participating substantially less. In sensitivity analyses, weighted estimates of STI prevalence to account for selective participation did not significantly differ from unweighted estimates. Third, the OSOM rapid test for trichomonas is not validated for male penile meatal swabs, which were collected and tested here. Fourth, we did not collect data on history of syphilis treatment and therefore could not establish what proportion of those with positive syphilis serology had active, latent, or resolved infection. Fifth, although we report on STIs among a small number of HIV incident cases, STIs were detected at time of first positive HIV test and might have been acquired during or after HIV acquisition. Sixth, we cannot rule out the possibility that some swabs might have been contaminated, especially for women who self-collected their own swabs. We also did not collect data on pregnancy trimester or pregnancy outcomes.

In conclusion, we found extremely high STI burden in this population-based study done in two African communities with high HIV burden and near-universal HIV treatment coverage. STIs were particularly elevated among people living with HIV, most of whom were engaged in HIV services, including pregnant women. Taken together, these data suggest a clear absence of integrated HIV and STI care.

Contributors

MKG, CAG, TCQ, GK, SJR, LWC, CK, AART, YCM, and JK conceptualised this study and contributed to the design. MKG did the formal analysis. MKG, TCQ, and CAG acquired study funding. MKG, LWC, MJW, RHG, JK, GK, DS, and RS supervised study activities. ADP, JCJ, SKi, and JM coordinated the study. GK, SKa, and RMG supervised laboratory activities. RHG, JM, ADP, RS, SKa, AN, JBK, JT, and SKi collected survey, clinical, and laboratory data. MKG, CAG, and TCQ wrote the original draft. All authors contributed to writing, reviewing, and editing of the final manuscript.

Declaration of interests

MJW and RHG are paid consultants to the Rakai Health Sciences Program and serve on its Board of Directors. These arrangements have been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. YCM has received grant support to John Hopkins University from Hologic, Cepheid, Roche, ChemBio, Becton Dickinson, and miDiagnostics, and has provided consultative support to Abbot. All other authors declare no competing interests.

Data sharing

All data and code are available upon reasonable request to the Rakai Health Sciences Program.

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