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Age patterns of HSV-2 incidence and prevalence in two Ugandan communities: a catalytic incidence model applied to population-based seroprevalence data

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Background Herpes simplex virus type 2 (HSV-2) is an incurable STI associated with increased risk of acquiring and transmitting HIV. HSV-2 prevalence is extremely high in sub-Saharan Africa, but population-level estimates of HSV-2 incidence are sparse. We quantified HSV-2 prevalence, risk-factors for infection, and age-patterns of incidence in south-central Uganda.

Methods We measured HSV-2 prevalence from cross-sectional serological data among men and women aged 18-49 in two communities (fishing/inland). We identified risk-factors for seropositivity, and inferred age-patterns of HSV-2 with a Bayesian catalytic model.

Results HSV-2 prevalence was 53.6% (n=975/1819, 95%CI 51.3%-55.9%). Prevalence increased with age, was higher in the fishing community, and among women, reaching 93.6% (95%CrI 90.2%-96.6%) by age 49. Factors associated with HSV-2 seropositivity included more lifetime sexual partners, HIV positive status, and lower education. HSV-2 incidence increased steeply in late adolescence, peaking at age 18 for women and 19-20 for men. HIV prevalence was up to ten-fold higher in HSV-2-positive individuals.

Conclusions HSV-2 prevalence and incidence were extremely high, with most infections occurring in late adolescence. Interventions against HSV-2, such as future vaccines or therapeutics, must reach young target populations. Remarkably higher HIV prevalence among HSV-2-positive individuals underscores this population as a priority for HIV prevention.

Keywords: HSV-2, catalytic model, prevalence, incidence, population-based study (up to 5)

Funding: NIH, Wellcome Trust

INTRODUCTION

Herpes simplex virus type 2 (HSV-2) is a sexually transmitted infection (STI) that is prevalent in half a billion people worldwide (1). Burden is highest in sub-Saharan Africa, where population prevalence is estimated at 37% (35%-40%) (2). Once acquired, infection is lifelong and is the leading cause of genital ulcer disease (GUD) (3).

HSV-2 infection is associated with threefold higher risk of acquiring HIV, and five times higher among those recently HSV-2 infected (4). Increased HIV risk is due to a combination of biological factors and shared underlying sexual risk factors. HSV-2 and HIV acquisition share common determinants of infection including position within sexual networks and behavioural factors, such as condom use and frequency of partner change (5,6). Numerous biological hypotheses for how HSV-2 increases HIV acquisition include increased HSV-2 induced genital ulcers and recruitment of CD4+ T cells and dendritic cells to the mucosa that express CCR5 (7–9). The relationship between HSV-2 and risk of HIV infection has important consequences in

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areas with co-circulating epidemics, and has been estimated to account for more than a third of new HIV infections in the WHO African region each year (10,11).

The increased risk of HIV infection associated with acute HSV-2 infection underlies the importance of understanding patterns of HSV-2 incidence at the population level to better target HIV prevention measures towards the most at-risk groups. Of particular interest is quantifying how HSV-2 incidence varies with respect to age, sex, and location, with a view towards ameliorating HSV-2 related morbidity and transmission, including via therapeutics or future vaccines. Despite the importance of HSV-2 and HIV prevention efforts in areas of high burden, serological studies of HSV-2 incidence are generally lacking, in part due to the substantial administrative and financial cost of population-based studies. However, the lifelong nature of HSV-2 infection means seroprevalence data can be leveraged to infer incidence from how prevalence changes with age (12).

In this study, we describe determinants of HSV-2 infection among men and women in two distinct communities in Rakai, south-central Uganda. The region reported the first cases of HIV in East Africa (13), and continues to have the highest burden of HIV nationally (14). The HSV-2 seroprevalence study was embedded within the long-running Rakai Community Cohort Study (RCCS) (15). We analyse patterns of HIV and HSV-2 infection and fit a parametric catalytic model of infection to age-specific seroprevalence to estimate age-patterns of HSV-2 incidence.

METHODS

Data

We analysed data from the Sexually Transmitted Infection Prevalence Study (STIPS), a community-based cross-sectional study of STI prevalence among adults in south-central Uganda undertaken between May and October 2019. The study was nested within the Rakai Community Cohort Study (RCCS), a long-running population-based cohort conducted by the Rakai Health Sciences Program (RHSP) (16). The RHSP refers participants for HIV treatment and prevention services, including ART, voluntary medical male circumcision (VMMC), and pre-exposure prophylaxis (PrEP) which has been rolled out to high-risk populations since 2017 (17). Detailed study methods for STIPS have been described previously (18). Briefly, STIPS was conducted among consenting RCCS participants aged 18-49 years from two communities: a Lake Victoria fishing community, and an inland community comprising a semi-urban trading centre and surrounding agrarian villages. The communities were chosen to reflect the substantial differences in HIV prevalence and sexual behaviours present in the region, based on geographic diversity, population size and enrolment timeline within the wider RCCS survey (16). RCCS eligibility is based on household census of people resident for ≥6 months in inland communities and ≥1 month with intention to stay longer in fishing communities. While the RCCS enrols participants aged 15 and above, resource limitations did not allow the inclusion of under-18s in STIPS.

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Enrolled participants were surveyed about STI symptoms and treatment seeking. Circumcision status for male participants was self-reported, then clinically confirmed. History of PrEP-usage was self-reported. Participants provided genital swabs; penile swabs were collected by clinicians while vaginal swabs were self-administered, which has been shown to be more acceptable to women without impacting test sensitivity (19).

Following standard RCCS methodology, sera from peripheral blood samples were tested for HSV-2 using the Kalon ELISA (Kalon Biological Ltd, Guildford UK) with an index cutoff value of 1.5, which gave optimal test sensitivity and specificity in a Ugandan population in previous validation (20). All HSV-2 tests were performed at the RHSP central laboratory in Kalisizo, Uganda. HIV serological testing used a field-validated parallel three-test rapid algorithm (21). Syphilis seropositivity, defined by treponemal antibody status, was determined using the SD Bioline Syphilis 3.0 (SD Biostandard Diagnostics Private Limited, Gurgaon, Haryana, India). Syphilis titers were determined at the RHSP central laboratory for all participants with positive serology, using the rapid plasma reagin (RPR) non-treponemal test (Cypress Diagnostics, Hulshout, Belgium). High-titer syphilis infection was defined as RPR-titer ≥1:8. Genital swabs were tested for trichomonas, chlamydia, and gonorrhea. Trichomonas tests were performed using the OSOM Trichomonas Rapid Test (Sekisui, Burlington, MA). Chlamydia and gonorrhea tests were performed at the RHSP central laboratory, using the Abbott m2000 RealTime CT/NG assay (Lake Forest, Illinois, USA).

HIV, syphilis, and trichomonas point-of-care test results were returned by on-site counsellors. Participants who tested positive and their partners were treated in line with Uganda Clinical Guidelines and United States Centers for Disease Control and Prevention (CDC) guidelines for treatment of STIs (22,23). Partners were identified via passive referral. Participants diagnosed with chlamydia and gonorrhoea were recontacted and provided with counselling, etiologic treatment, and referrals for their sexual partners, who were invited to obtain presumptive STI treatment. Participants who tested negative but reported STI symptoms (genital discharge or lesions) were nevertheless offered antibiotic treatment in line with both Ugandan national guidelines for syndromic management of STIs (23).

Ethics

STIPS was approved by Uganda Virus Research Institute Research Ethics Committee (GC/127/19/03/709), the Johns Hopkins School of Medicine Institutional Review Board (IRB00204691), and was registered with the Ugandan National Council for Science and Technology (HS 364 ES) (18). All study participants provided written informed consent for STIPS in addition to the RCCS. The consent for STIPS was read to all participants by a research assistant; where participants were illiterate, a literate community member (of the participant's choice but typically the training community health worker) was present to witness the consent process, with consent confirmed via the participant's thumbprint in the place of a signature. All

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participants regardless of their literacy received a copy of the signed consent form for future reference.

Statistical methods

We compared demographic and behavioral characteristics of STIPS participants in inland and fishing communities using chi-squared tests. We estimated HSV-2 seroprevalence in men and women, and used modified Poisson regression (24) to estimate the association between HSV-2 infection and risk factors, specifically: community type (inland/fishing), age group, marital status, educational level, number of sex partners in the last year, lifetime number of sex partners, HIV serostatus, HIV viral load suppression status (defined as <1000 copies/ml, as per WHO guidelines (25)), history of PrEP usage, male circumcision status, and infection with a curable STI (trichomonas, chlamydia, gonorrhea, and syphilis). We measured all associations using unadjusted and adjusted prevalence risk ratios (PRR; adj PRR) with 95% confidence intervals (CI). Adjusted models controlled for age group, community type, marital status, educational level, and HIV serostatus.

Model structure and calibration

To infer HSV-2 incidence by age from seroprevalence data, we fitted a catalytic model to HSV-2 test data separately for men and women in inland and fishing communities (12). We represented prevalence at each age using the cumulative distribution function of a shifted generalised gamma distribution (26,27). We implemented the model in a Bayesian framework using the probabilistic programming language Stan (28) and used an adaptive Hamiltonian Monte Carlo (HMC) no U-turn sampler to estimate model parameters for each location and gender separately. Since infection with HSV-2 is lifelong, modelled incidence rates are given by the probability density function specified by the fitted model parameters. Full details of the model structure and calibration can be found in the supplementary material.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study population characteristics

Of the 2,583 RCCS-eligible individuals aged 18-49 years, 73% (1,884) were present in the community at the time of the census, of whom 97% (1,825) agreed to participate in STIPS. The

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study population comprised 522 women and 397 men in the inland community and 443 women and 463 men in the fishing community (Table 1). Invited individuals who did not participate in the STIPS study were significantly more likely to be men, younger aged, reside in the fishing community, have unknown HIV serostatus, or be recent in-migrants (18). In both communities, men were less likely to be HIV seropositive than women but reported more sexual partners both in the last year and over their lifetime. More than half of men were circumcised: 52% inland and 57% in the fishing community. Very few participants in the inland community had ever taken PrEP (1/522 women, and 3/397 men). PrEP usage was relatively higher in the fishing community, comprising only 8.5% of women and 6.5% of men. Data on curable STI positivity have been previously reported by Grabowski et al (18).

Risk factors associated with HSV-2 seropositivity

Prevalence of HSV-2 in the study population was 53.6% (95%CI 51.3%-55.9%). Prevalence was higher in women (63.1%; 95%CI 60.0%-66.2%) than in men (43.0%; 95%CI 39.6%-46.3%)), and higher in the fishing community than inland (64.4% (95%CI 61.2%-67.5%) vs. 43.0% (95%CI 39.7%-46.2%)). Women in the fishing community were 1.23 (95%CI 1.11-1.36) times more likely to have HSV-2 than women inland (Table 2). Among men, crude prevalence was also higher in the fishing community (51% vs 34%), but the difference was not significant after adjusting for confounders. The seroprevalence of HSV-2 increased rapidly with age. In the oldest age group (45-49 years), women were 1.90 (95%CI 1.55-2.32) times and men were 2.26 (95%CI 1.49-3.42) times more likely to be seropositive than those 15-24 years.

Marital status was not significantly associated with HSV-2 prevalence. However, reporting more lifetime sexual partners was associated with higher seroprevalence in women: 81% of women reporting four or more partners had HSV-2, compared to 30% of women reporting only one partner (adjPRR 1.81; 95%CI 1.39-2.35). Men with tertiary education had much lower prevalence of HSV-2: 23% compared to 46% among men with primary education only (adjPRR 0.51; 95%CI 0.32-0.82).

Individuals living with HIV were significantly more likely to be HSV-2 seropositive, with a pronounced difference in both men (76% vs 33%; adjPRR=1.58, 95%CI 1.37-1.83) and women (94% vs 50%; adjPRR=1.39, 95%CI 1.28-1.50). HIV viral load suppression status was not significantly associated with HSV-2 prevalence. Circumcised men had lower HSV-2 seropositivity (37% vs 63%; PRR 0.75, 95%CI 0.65-0.88); however, the difference was smaller and not significant after adjusting for age and other confounders (adjPRR 0.90, 95%CI 0.78-1.04). For women, history of PrEP-use was associated with risk of HSV-2, although the association was not significant after adjusting for confounders that may reflect underlying sexual risk.

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Associations between curable stis and HSV-2 seroprevalence by gender

Adjusting for age, community type, HIV status, educational level, and marital status, neither gonorrhea, chlamydia nor high-titer syphilis infection (non-treponemal antibody titer ≥ 1:8) were significantly associated with HSV-2 infection (Supplementary Table 1). Trichomonas was associated with HSV-2 infection in women (adjPRR 1.22; 95%CI 1.12-1.34), but not in men (adjPRR 0.95; 95%CI 0.71-1.28), whereas syphilis treponemal seropositivity (regardless of titer) was associated with HSV-2 infection in men, (adjPRR 1.26; 95%CI 1.08-1.46) but not in women (adjPRR 1.05; 95%CI 0.96-1.15).

HIV prevalence by HSV-2 serostatus

HIV prevalence was significantly higher among men and women with HSV-2 across all age groups. Among women, 54.1% (95% CI 44.8%-63.2%) of HSV-2 seropositive women aged 30-35 were also HIV-positive, compared to only 4.8% (95% CI 0.6%-16.2%) of HSV-2 seronegative women (Figure 1). Among men, 41.7% (95% CI 30.2%-53.9%) of HSV-2 seropositive men aged 30-35 were also HIV-positive, compared to only 13.2% (95% CI 6.2%-23.6%) of HSV-2 seronegative men.

Catalytic model, HSV-2 seroprevalence and incidence

In results from the catalytic model, HSV-2 prevalence by age was markedly higher in women than in men and higher in the fishing community than inland (Figure 2). HSV-2 acquisition was younger for women than men in both inland and fishing communities. By age 20, 22.1% (95%CrI 15.3%-29.4%) of inland women had acquired HSV-2 and almost double that, 42.9% (95%CrI 32.3%-53.5%), in the fishing community, compared to 11.3% (95%CrI 5.5%-17.6%) and 10.7% (95%CrI 4.1%-19.2%) of men in inland and fishing communities, respectively. By age 49, HSV-2 prevalence among women in the fishing community was 93.6% (95%CrI 90.2%-96.6%), compared to 70.1% (95%CrI 63.7%-76.8%) inland. In men, prevalence by age 49 was 72.5% (95%CrI 65.9%-79.5%) in the fishing community and 51.5% (95%CrI 43.8%-59.9%) inland.

Incidence of HSV-2 infection rose rapidly in late adolescence. The age-pattern of infection was similar between women in both locations, annual incidence peaked at age 17.9 (95%CrI 16.5-19.0) in the fishing community and 18.1 (95%CrI 16.5-19.7) inland (Figure 3). However, annual incidence reached much higher levels in the fishing community: 15.6% (95%CrI 8.6%-25.9%) compared to 7.3% (95%CrI 4.2%-12.1%) inland. After the peak, annual incidence fell steeply to a similar level in both communities by age 30: 1.3% (95%CrI 1.0%-1.8%) in the fishing community and 1.6% (95%CrI 1.2%-2.2%) inland. The mean age of infection for women was 18.3 in the fishing community and 21.0 inland. Annual incidence in men peaked lower and at older ages compared to female peers, reaching 6.1% (95%CrI 4.1%-8.5%) by age 20.3 (95%CrI 18.4-22.4) in the fishing community and 4.4% (95%CrI 2.5%- 6.6%) by age 19.0 (95%CrI 17.0-

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21.4) inland. The mean age of HSV-2 infection for men was 21.1 in the fishing community and 23.4 inland.

DISCUSSION

HSV-2 prevalence and incidence were extremely high in two distinct communities in south central Uganda, with marked heterogeneities by gender, community, and age. While the two communities studied were not selected to be representative of Uganda as a whole, the overall HSV-2 seroprevalence in our study was similar to national estimates from a recent meta-analysis (53.6% (95%CrI 51.3%-55.9%) vs 50.5% (95%CI 44.2%-56.8%))(2). Both estimates were notably higher than the 41.9% (95%CI 38.4%-45.3%) prevalence estimated for the wider East Africa region. We found a clear difference in HSV-2 prevalence by sex, with women around 1.5 times more likely to have HSV-2. This ratio mirrored the meta-analysis findings sub-Saharan Africa, which estimated 43.1% (95%CI 39.8%-46.5%) prevalence for women compared to 29.1% (95%CI 25.7%-32.6%) for men.

Risk of acquiring HSV-2 infection peaked at very young ages, especially for women. HSV-2 prevalence was higher in women than in men in the same community at all ages, and we estimate incidence increased earlier. The mean age of infection was around 18 to 21 years in women and 21 to 23 years in men. The steep increase in incidence rates in late adolescence suggests that many people acquire infection soon after becoming sexually active; however, incidence rates remain high into early adulthood. Our findings are similar to those among women in Kilifi, Kenya, where Nyiro and colleagues observed “a rapid rise in HSV-2 seroprevalence from mid-late teenage years upwards, coincident with onset of sexual activity” (29). However they contrast with incidence patterns estimated in a meta-analysis of the whole sub-Saharan Africa region, where incidence was higher in those aged 25 and older (2). The age-patterns of HSV-2 incidence were much younger than those seen for HIV in Rakai: the mean age of infection with HIV was 25 years for women and 29 years for men (30). This age-gap, combined with the increased risk of HIV seen among HSV-2 seropositive individuals, presents an important opportunity for prioritising HIV prevention to a population with high HIV epidemic potential (31).

While the age-profile of HSV-2 incidence was similar in the two communities studied, there were stark differences in the magnitude of the epidemics, with prevalence much higher in the fishing community than inland: 64% vs 43%. The higher burden of infection in the fishing community population aligns with previous findings on the extraordinarily high risk of STIs in this community, including four times greater prevalence of active syphilis than the national population (18).

At all ages, HIV prevalence was remarkably higher among those with HSV-2 than without, underscoring those with HSV-2 infection as a priority population for HIV prevention, either due to their position in sexual networks, of which HSV-2 serostatus is a marker, or increased risk of

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HIV acquisition associated with recent HSV-2 infection. Despite evidence that PrEP may offer partial protection against HSV-2 acquisition (32,33), women with history of PrEP were more likely to be HSV-2 positive; although the association disappeared when the model was adjusted for confounders that may reflect underlying sexual risk, which could cause both higher HSV-2 prevalence and higher likelihood of PrEP eligibility. Furthermore, PrEP use within the cohort was quite low overall. While being circumcised was not significantly associated with reduced risk of HSV-2 after adjusting for confounders, interestingly the 25% point-estimate of the reduction in risk was fairly close to the 28% found in a trial of voluntary medical male circumcision (VMMC) against HSV-2 acquisition (34).

The catalytic model has several key assumptions which should be considered when interpreting the results. Firstly, since it is not possible to distinguish age and cohort effects from cross-sectional data, our catalytic model implicitly assumes that age-patterns of HSV-2 incidence have not changed over time. While it has been estimated that HSV-2 incidence in sub-Saharan Africa is declining at 2% annually due to the impact of HIV prevention (2), our estimate of 33.5% HSV-2 prevalence among inland men was essentially identical to that found in 2003, when 33.8% of men in the same community were found to be HSV-2 positive during enrolment for a randomised controlled trial (35). Any population-level projections of future HSV-2 incidence trends should therefore consider the impact of cohort in addition to age. Secondly, stratified analysis by community type assumed that migration was not correlated with differential HSV-2 seroprevalence. Thirdly, we assumed that HSV-2 infection does not affect mortality. HSV-2 infection alone is unlikely to impact life expectancy, but its association with HIV may lead to higher mortality among HSV-2 positive individuals, biasing population HSV-2 prevalence at older ages. However, excess HIV mortality is now very low in the RCCS population, where 90% of people living with HIV are virally suppressed (36). Fourthly, we assumed there is no HSV-2 infection before people become sexually active, with the age of initiation of risk determined by model fitting in each population group. Although neonatal transmission of HSV-2 is an important public health concern associated with high infant mortality, it is estimated to occur in fewer than 2 in 10,000 live births across Africa (37), so population prevalence of infection in childhood is likely very low. The assumption of zero prevalence in childhood is therefore reasonable and unlikely to substantively impact the results.

Finally, our analysis is based on seroprevalence data from age 18 onwards, slightly older than the peak age of incidence we inferred for women. Due to the lack of data informing the left tail of the age-distribution of infection, we had to make informative prior assumptions about the minimum age of infection. Future studies collecting seroprevalence data down to age 15 would provide greater resolution on patterns of HSV-2 infection at younger ages.

Despite estimates that the WHO Africa region has the highest HSV-2 burden globally, population-level studies of HSV-2 prevalence are sparse. Improved understanding of HSV-2 incidence patterns is vital to inform the design of intervention packages against HSV-2, which in turn could help reduce transmission of HIV by providing a marker of epidemic potential (31).

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These results particularly inform the optimal age of delivery and which communities to prioritise. In the communities studied, HSV-2 infection likely occurs soon after commencement of sexual activity. Interventions against HSV-2 should therefore be targeted towards young people before they become sexually active. While there is not yet a vaccine against HSV-2, the WHO has identified the development of both therapeutic and prophylactic vaccines as an urgent priority (38). In the meantime, interventions such as promoting condom use and VMMC have been shown to reduce HSV-2 incidence (34). Further synergies with HIV interventions may also be possible: building on earlier reports of *in vitro* activity of tenofovir against HSV-2, a study in serodiscordant heterosexual couples in Kenya and Uganda found that daily oral PrEP could reduce the risk of HSV-2 infection by 30% (1%-49%) (39). We note that while the long-running HIV-prevention programme run by RHSP has achieved substantial reductions in HIV incidence with biomedical interventions (15), the lack of equivalent HSV-2 prevention measures has made reductions in infections harder to achieve, as evidenced by stable HSV-2 prevalence over 20 years (35). In addition to quantifying underlying patterns of HSV-2 infection in two high-prevalence communities, our model provides a framework which can be applied more widely to improve our overall understanding of patterns of HSV-2 prevalence at a population-level. Such estimates will be vital to design future interventions, such as vaccination.

Contributors: The study was conceived by JWE, LKW and MKG. The model was designed by JWE and LKW and implemented by LKW. Analysis was performed by LKW and MKG. The data were originally collected by JM, ADP, and RS. MKG, TCQ, and CAG acquired study funding. All authors had access to the data and accept responsibility for submission for publication. The report was drafted by LKW and revised by all authors.

Declaration of interests: 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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Table 1 Characteristics of study population by community type and gender

	Inland (n=919)		Fishing (n=906)	
	Women (n=522)	Men (n=397)	Women (n=443)	Men (n=463)
Age, median year (IQR)	32 (24-39)	30 (23-39)	31 (26-38)	32 (26-30)
Marital status		*p<0.0001*		*p<0.0001*
Never married	67 (13)	102 (26)	22 (5.0)	71 (15)
Currently married	350 (67)	255 (64)	306 (69)	289 (62)
Previously married	105 (20)	40 (10)	115(26)	103 (22)
Educational status		*p=0.15*		*p=0.04*
None	25 (5.6)	11 (2.8)	56 (13)	41 (8.9)
Primary	292 (56)	245 (62)	277 (63)	330 (71)
Secondary	145(28)	106 (27)	83 (19)	71 (15)
Tertiary	60 (11)	35 (8.8)	27 (6.1)	21 (4.5)
Sex partners in the last year		*p<0.0001*		*p<0.0001*
0	75 (14)	42 (10.6)	37 (8.4)	25 (5.4)
1	406 (78)	165 (42)	332 (75)	153 (33)
2	32 (6.1)	117 (29)	54 (12)	136 (29)
3	8 (1.5)	44 (11)	11 (2.5)	82 (18)
≥4	1 (0.2)	29 (7.3)	9 (2.0)	67 (15)
Lifetime sex partners		*p<0.0001*		*p<0.0001*
0	20 (3.8)	22 (5.5)	4 (0.9)	10 (2.2)
1	99 (19)	14 (3.5)	34 (7.7)	9 (1.9)
2	155 (30)	29 (7.3)	60 (14)	10 (2.2)
3	132 (25)	41 (10)	108 (24)	27 (5.8)
≥4	116 (22)	291 (73)	237 (53)	407 (88)
HIV serostatus		*p=0.02*		*p<0.0001*
HIV seronegative	436 (84)	354 (89)	236 (53)	309 (67)
HIV seropositive	86 (16)	43 (11)	297 (47)	154 (33)

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HIV suppression status*		*p=0.22*		*p=0.36*
≤1000 copies/ml	81 (94)	37 (86)	190 (92)	136 (88)
>1000 copies/ml	5 (6)	6 (14)	17 (8)	18 (12)
Current or prior history of PrEP use**		*p=0.48*		*p=0.58*
No	434 (99)	351 (99)	216 (92)	289 (94)
Yes	1 (0.2)	3 (0.8)	19 (8.1)	20 (6.5)
Male circumcision status***				
Uncircumcised	-	189 (48)	-	199 (43)
Circumcised	-	208 (52)	-	264 (57)

IQR=interquartile range; Total number of participants and percentage (%) shown unless otherwise noted; * Analysis restricted to HIV seropositive participants; **Analysis restricted to HIV-seronegative participants; two participants had missing data. ***Analysis restricted to male study participants.

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Table 2 Risk factors associated with HSV-2 seropositivity

	Women (N=960)*			Men (N=859)*		
	No. HSV-2 positive/Total (%)	PRR (95%CI)	adjPRR (95%CI)	No. HSV-2 positive/Total (%)	PRR (95%CI)	adjPRR (95%CI)
Community type						
Inland	260/518 (50)	Ref.	Ref.	133/397 (34)	Ref.	Ref.
Fishing	346/442 (78)	**1.56 (1.41-1.72)**	**1.23 (1.11-1.36)**	236/462 (51)	**1.52 (1.29-1.80)**	1.11 (0.94-1.32)
Age group (years)						
15-24	77/235 (33)	Ref.	Ref.	30/203 (15)	Ref.	Ref.
25-29	116/183 (63)	**1.94 (1.56-2.40)**	**1.44 (1.19-1.75)**	59/164 (36)	**2.43 (1.65-3.56)**	**1.53 (1.03-2.29)**
30-34	122/164 (84)	**2.27 (1.85-2.78)**	**1.55 (1.29-1.88)**	72/140 (51)	**3.48 (2.41-5.03)**	**1.94 (1.32-2.86)**
35-39	129/174 (84)	**2.26 (1.85-2.77)**	**1.65 (1.37-2.00)**	88/156 (56)	**3.82 (2.67-5.46)**	**2.15 (1.46-3.15)**
40-44	99/131 (76)	**2.31 (1.87-2.84)**	**1.59 (1.31-1.94)**	76/122 (62)	**4.21 (2.95-6.03)**	**2.25 (1.52-3.33)**
45-49	63/73 (86)	**2.63 (2.15-3.23)**	**1.90 (1.55-2.32)**	44/74 (60)	**4.02 (2.75-5.89)**	**2.26 (1.49-3.42)**
Marital status						
Never married	22/88 (25)	**0.40 (0.28-0.58)**	0.75 (0.56-1.00)	25/173 (15)	**0.30 (0.20-0.40)**	0.75 (0.51-1.12)
Currently married	406/652 (62)	Ref.	Ref.	270/543 (50)	Ref.	Ref.
Previously married	178/220 (81)	**1.30 (1.19-1.42)**	1.04 (0.95-1.14)	74/143 (52)	1.04 (0.88-1.25)	1.02 (0.85-1.22)
Educational status						
None	66/81 (82)	**1.18 (1.05-1.33)**	1.01 (0.90-1.13)	32/52 (62)	**1.33 (1.06-1.68)**	0.98 (0.78-1.24)
Primary	39/565 (69)	Ref.	Ref.	265/574 (46)	Ref.	Ref.
Secondary	108/227 (48)	**0.69 (0.59-0.80)**	0.91 (0.80-1.03)	59/177 (33)	**0.72 (0.58-0.91)**	0.82 (0.66-1.01)
Tertiary	42/87 (48)	**0.70 (0.56-0.88)**	0.91 (0.74-1.12)	13/56 (23)	**0.50 (0.31-0.82)**	**0.51 (0.32-0.82)**
Sex partners in the last year						
0	64/112 (57)	0.92 (0.77-1.09)	0.98 (0.86-1.11)	9/67 (13)	**0.30 (0.16-0.56)**	0.80 (0.48-1.33)
1	457/733 (62)	Ref.	Ref.	143/318 (45)	Ref.	
2	61/86 (71)	1.14 (0.98-1.32)	1.02 (0.89-1.17)	110/252 (44)	0.98 (0.81-1.17)	0.99 (0.83-1.17)
3	17/19 (90)	**1.44 (1.22-1.69)**	**1.23 (1.04-1.46)**	67/126 (53)	1.18 (0.96-1.45)	**1.22 (1.00-1.47)**
≥4	7/10 (70)	1.12 (0.75-1.69)	0.76 (0.57-1.01)	40/96 (42)	0.93 (0.71-1.21)	0.92 (0.71-1.19)
Lifetime sex partners						
0	0/24 (0)	-	-	0/32 (0)	-	-
1	39/130 (30)	Ref.	Ref.	1/23 (4.3)	Ref.	Ref.
2	115/214 (54)	**1.79 (1.34-2.39)**	**1.63 (1.24-2.13)**	10/38 (26.3)	6.05 (0.83-44.3)	4.13 (0.57-30.10)
3	167/239 (70)	**2.32 (1.77-3.07)**	**1.79 (1.38-2.32)**	34/68 (35.3)	**8.12 (1.16-56.7)**	4.04 (0.58-28.03)
≥4	285/353 (81)	**2.69 (2.06-3.52)**	**1.81 (1.39-2.35)**	334/698 (47.9)	**11.0 (1.62-75.0)**	4.33 (0.63-29.76)
HIV serostatus						

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HIV seronegative	332/667 (50)	Ref.	Ref.	219/662 (33)	Ref.	Ref.
HIV seropositive	274/293 (94)	**1.88 (1.73-2.04)**	**1.39 (1.28-1.50)**	150/197 (76)	**2.30 (2.01-2.63)**	**1.58 (1.37-1.83)**
HIV suppression status**						
≤1000 copies/ml	255/271 (94)	Ref	Ref	133/173 (77)	Ref.	Ref
>1000 copies/ml	19/22 (86)	0.92 (0.78-1.09)	0.91 (0.76-1.10)	17/24 (71)	0.92 (0.70-1.21)	0.98 (0.76-1.27)
Current or prior history of PrEP use†						
No	316/645 (49)	Ref	Ref	208/639 (33)	Ref.	Ref
Yes	15/20 (75)	**1.53 (1.17-2.00)**	1.00 (0.77-1.29)	11/23 (48)	1.47 (0.95-2.28)	1.08 (0.67-1.75)
Male circumcision status						
Uncircumcised	-	-	-	193/388 (63)	Ref.	Ref
Circumcised	-	-	-	176/471 (37)	**0.75 (0.65-0.88)**	0.90 (0.78-1.04)

PRR=Prevalence Risk Ratio; adjPRR=adjusted prevalence risk ratio models adjusted for age, community type, marital status, educational level, and HIV serostatus. *There were six study participants with missing HSV-2 results (n=5 women; n=1 man); ** Analysis restricted to HIV-seropositive participants; †Analysis restricted to HIV-negative participants. Bold text shows statistically significant results.

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Figure captions

Figure 1 Comparison of HIV prevalence by age stratified by HSV-2 serostatus and gender. Bars show HIV prevalence in each age group, with lines showing 95% binomial confidence intervals.

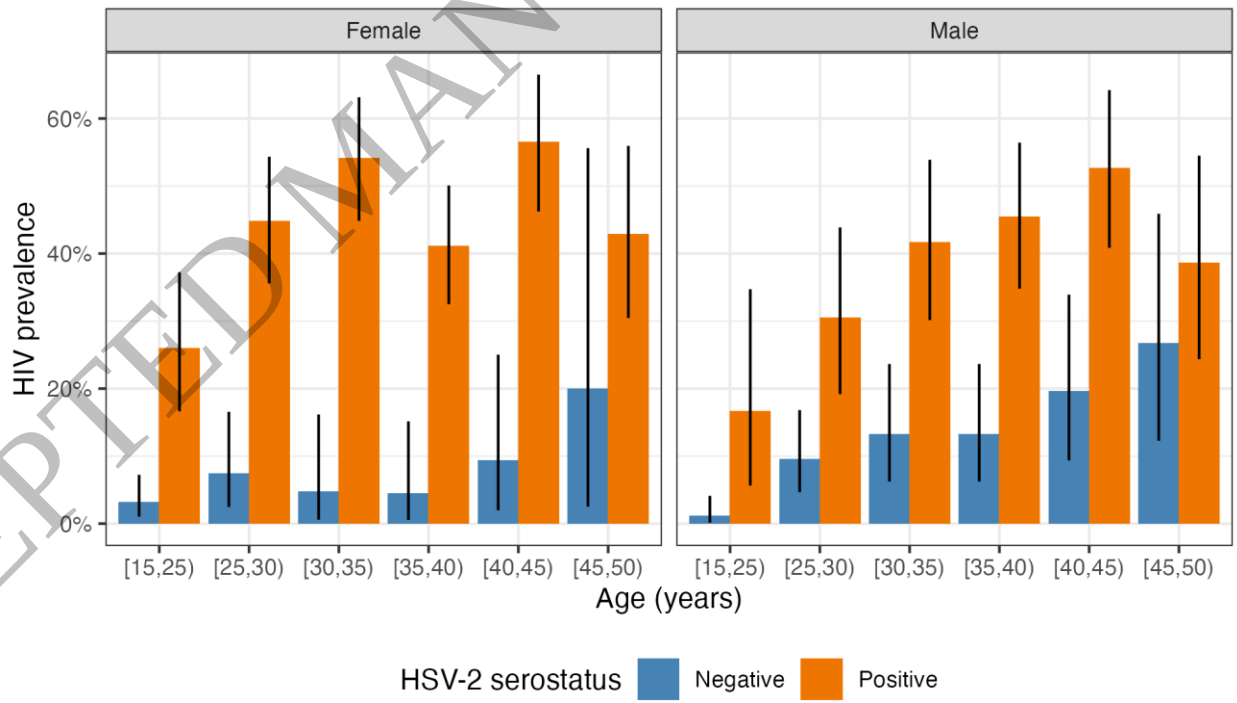

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Figure 2 HSV-2 prevalence by age in men and women in fishing and inland communities. The solid red line depicts the maximum a posteriori estimate of prevalence by age, the surrounding shaded red area shows the 95% credible interval. The black points represent the HSV-2 prevalence by age observed in the STIPS data, vertical error bars show 95% binomial confidence intervals for each data point.

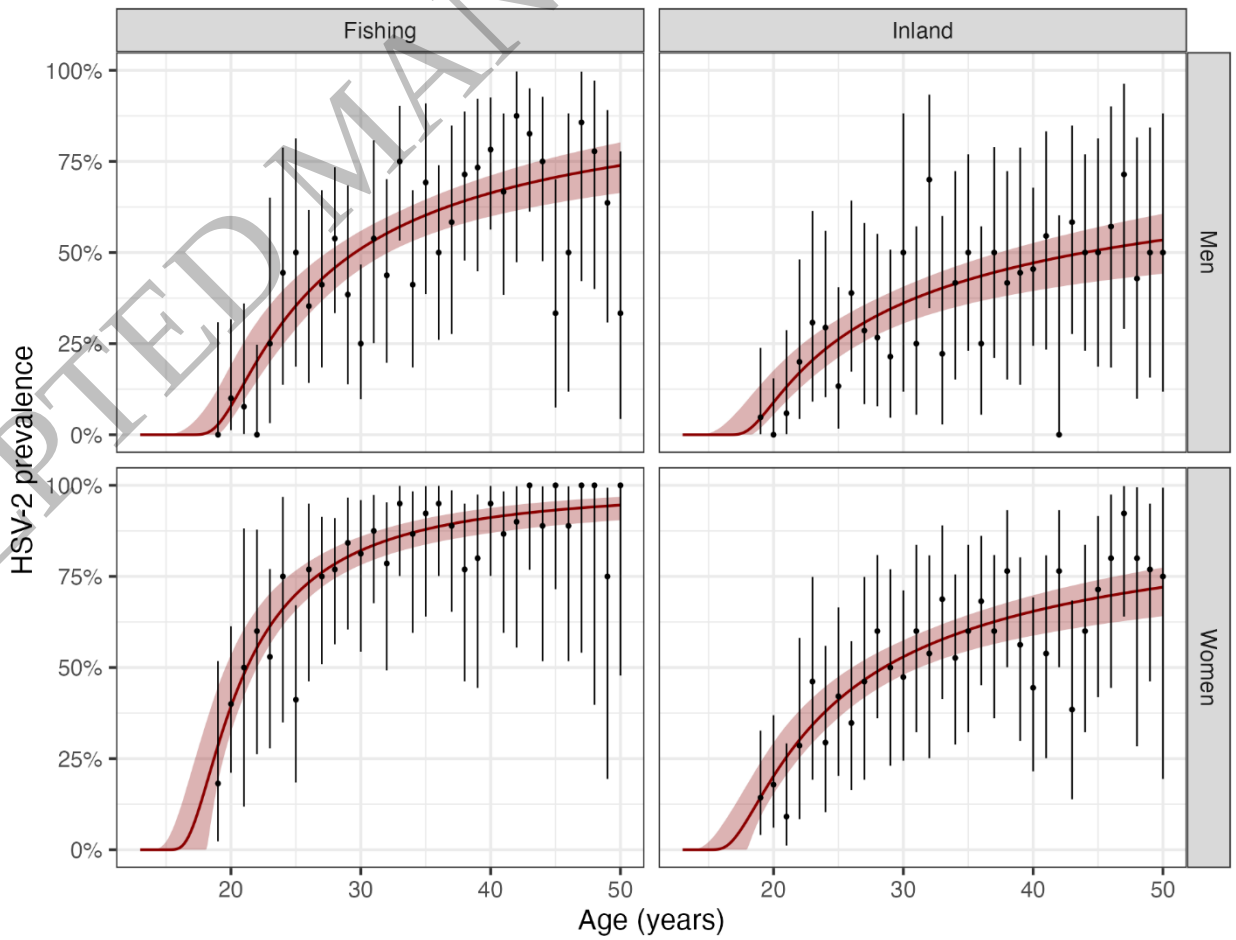

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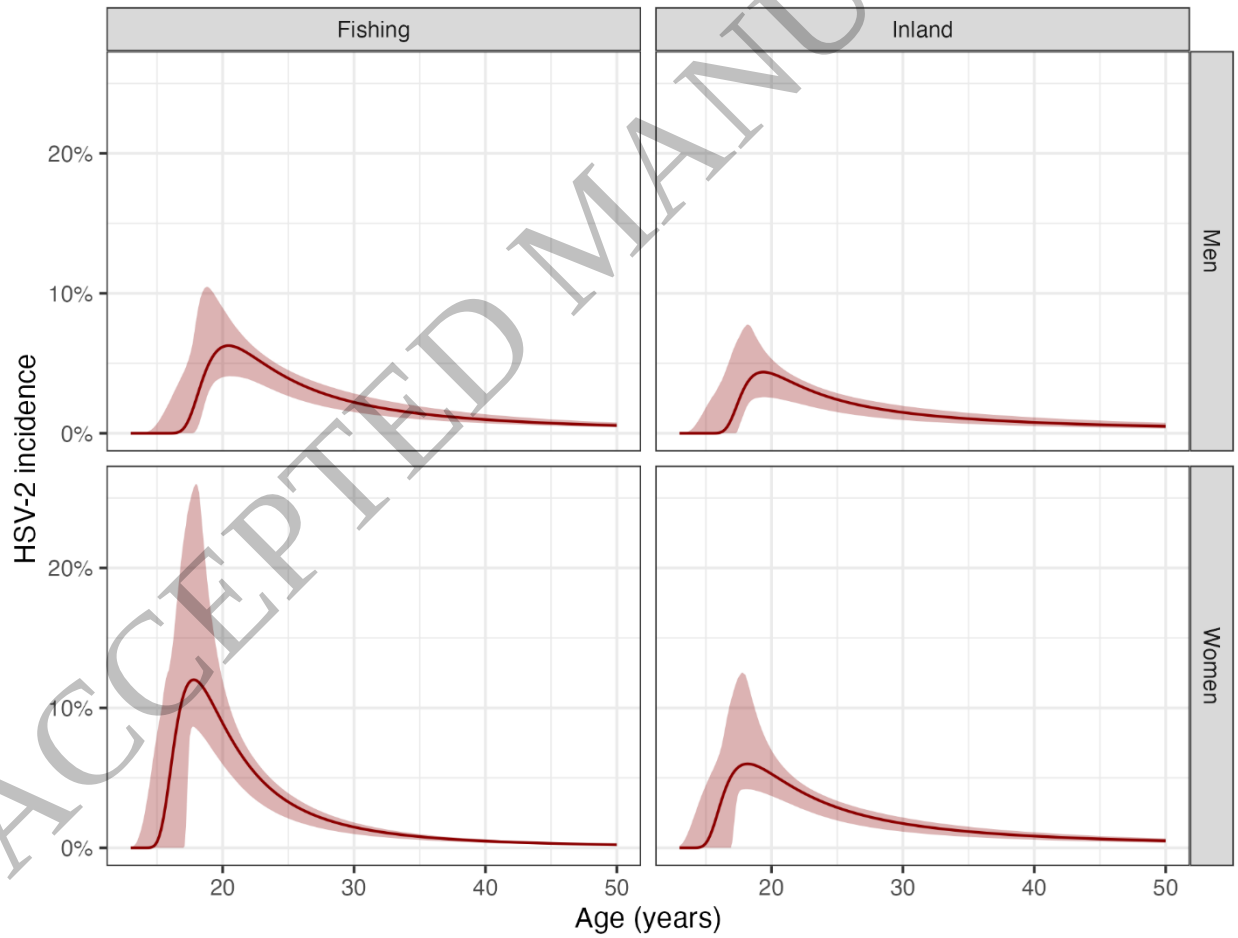
Figure 3 Modelled HSV-2 incidence per year by age in men and women in fishing and inland communities. The solid red line depicts the maximum a posteriori estimate of prevalence by age, the surrounding shaded red area shows the 95% credible interval



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