Published in final edited form as:
J Infect Dis. 2009 April 1; 199(7): 945–949. doi:10.1086/597074.

Factors Associated with the Prevalence and Incidence of Herpes Simplex Virus Type 2 Infection among Men in Rakai, Uganda

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Abstract

Little is known about risk factors for incident herpes simplex virus type 2 (HSV-2) infection among men in Africa. In a trial in Rakai, Uganda, 6396 men aged 15–49 years were evaluated for serological evidence of HSV-2, human immunodeficiency virus (HIV), and syphilis infections at enrollment and at 6, 12, and 24 months. The prevalence of HSV-2 infection was 33.76%, and the incidence was 4.90 cases per 100 person-years. HSV-2 incidence increased with alcohol use with sexual intercourse (adjusted incidence rate ratio [adjIRR], 1.92 [95% confidence interval {CI}, 1.46–2.53]), decreased with consistent condom use (adjIRR, 0.56 [95% CI, 0.36–0.89]) and male circumcision (adjIRR, 0.70 [95% CI, 0.55–0.91]), and was not significantly affected by enrollment HIV status. Education on modifiable behavioral changes may reduce the acquisition of HSV-2.

Herpes simplex virus type 2 (HSV-2) infection is one of the most common sexually transmitted infections (STIs) and is a major cause of genital ulceration worldwide [1]. Individuals who are serologically positive for HSV-2 have a lifelong risk of infecting their sex partners [1], and pregnant women may transmit HSV-2 during delivery. HSV-2 seropositivity is also associated with a 3-fold increased risk of acquiring HIV-1 in observational studies [1], but trials of HSV suppression with acyclovir failed to show reductions in HIV acquisition [2]. It has been proposed that the increased risk of HIV acquisition associated with HSV-2 infection may be due to breaches of the mucosal barrier and recruitment of $CD4^+$ T cells expressing CCR5 and immature dendritic cells to areas of HSV-2 replication with both clinical and subclinical reactivation of mucosal lesions [1,3,4]. However, epidemiologic studies are vulnerable to confounding by unmeasured sexual behaviors. It is also difficult to determine the temporal order of HIV and HSV-2 infection in cross-sectional studies. Even in prospective studies, the higher infectivity of HSV-2 makes it more likely to be contracted before HIV, so one cannot conclude that the association is causal. However, there is an association between genital ulcer

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Potential conflicts of interest: none reported.

ClinicalTrials.gov identifiers: NCT00425984 and NCT00124878.

disease (GUD) and HIV acquisition and transmission [5]. Thus, it is plausible that herpetic ulceration would increase the risk of HIV acquisition.

Genital herpes is a major health problem in Africa, and it has been proposed that management of HSV-2 needs to shift from short-term syndromic GUD management to prevention among those most at risk [6]. Although previous studies have evaluated risk factors for incident HSV-2 infection among high-risk individuals [7], little is known about HSV-2 infection in the general population. Knowledge of HSV-2 risk factors is important for prevention of primary HSV-2 infection and potentially for trials of HSV-2/HIV interventions aimed at reducing HIV transmission and progression. It has been recently demonstrated that male circumcision significantly reduces both HIV and HSV-2 acquisition in men [8,9]. It has been hypothesized that the protection against HIV acquisition afforded by male circumcision could in part be mediated by a decreased frequency of HSV-2–associated genital ulcers. Thus, it is important to understand the risk factors for both prevalent and incident HSV-2 infection. Here, we report the results of the first study to evaluate the risk factors for incident HSV-2 infection among a general population in sub-Saharan Africa.

Methods

Six thousand three hundred ninety-six men aged 15–49 years were enrolled into 2 trials of male circumcision for HIV and STI prevention in Rakai, Uganda. The design and results of the trials have been reported elsewhere [8,9]. In brief, eligible persons were informed of study procedures and risks, provided written informed consent before screening, and provided additional written consent for enrollment. Men were excluded from the trial if they had anemia, active genital infections, anatomical abnormalities (e.g., hypospadias), or medical indications or contraindications for surgery (e.g., severe phimosis). Men were randomly assigned to receive immediate circumcision or circumcision delayed for 24 months. Serological testing for HIV, HSV-2, and syphilis and physical examinations and interviews to ascertain sociodemographic characteristics and sexual risk behaviors were conducted at baseline and repeated at 6-, 12-, and 24-month follow-up visits. Samples were collected by trained staff, and serum was stored at −70°C. At each visit, all subjects were provided free HIV counseling and testing, health education, and condoms. All participants found to be HIV positive were referred to an HIV treatment program funded by the President’s Emergency Fund for AIDS Relief.

The trials were approved by 4 institutional review boards: the Science and Ethics Committee of the Uganda Virus Research Institute (Entebbe, Uganda), the HIV Subcommittee of the National Council for Research and Technology (Kampala, Uganda), the Committee for Human Research at Johns Hopkins University Bloomberg School of Public Health (Baltimore, MD), and the Western Institutional Review Board (Olympia, WA). The trials were overseen by independent data safety monitoring boards [8,9] and were registered with ClinicalTrials.gov (identifiers NCT00425984 and NCT00124878).

HSV-2 infection was determined by HSV-2 ELISA (Kalon Biological). The assay was performed according to the manufacturer’s protocol with minor modifications. Test samples were run in duplicate, and the mean index value was used to classify HSV-2 status. On the basis of prior evaluation of test performance among Ugandan serum samples, HSV-2–positive individuals were defined as those with an index value of ≥1.5 [10]. HSV-2 seroconversion was defined as negative serological results (index value <0.9) at enrollment followed by positive serological results during follow-up.

HIV status was determined using 2 separate ELISAs and was confirmed by HIV-1 Western blot, as described elsewhere [8]. Active *Treponema pallidum* infection was determined by a positive rapid plasma reagin test result (Becton Dickinson) or a toluidine red unheated serum

test result (New Horizons Diagnostics) followed by a positive *T. pallidum* particle agglutination assay result (Serodia-TP PA Kit; Fujirebio).

For exploratory analyses, covariates associated with prevalent HSV-2 infection were assessed by characteristics and behaviors at enrollment. Because the timing of the initial HSV-2 infection was unknown and could have preceded enrollment by several years, we assessed long-term risk behaviors (such a lifetime number of sex partners) rather than behaviors reported in the year preceding enrollment. For analyses of incident HSV-2 infection, we assessed associations with fixed covariates (such as age, marital status, and education at enrollment) and by time-varying covariates (such as sexual risk behaviors— e.g., number of partners, nonmarital relationships, condom use, and alcohol use with sexual intercourse) reported at follow-up visits. Symptoms of STIs (such as GUD) reported at follow-up visits were not included in regression models of predictors of HSV-2 infection because these are likely to be consequences of HSV-2 infection rather than causes of HSV-2 acquisition. Risk factors with $P < .15$ in univariate analysis were entered into the multivariable model to adjust for possible confounding. The multivariable model adjusted for all covariates shown.

Prevalence ratios (PRs) were used to measure the associations between prevalent HSV-2 infection and the potential risk factors at enrollment. A Poisson model was used to estimate adjusted PRs (adjPRs).

Incidence rate ratios (IRRs) were used to evaluate the association between HSV-2 acquisition among individuals with a baseline Kalon index value <0.9. For incidence-rate and person-time calculations, it was assumed that HSV-2 infection occurred at the middle time point between the last negative and first positive serological test result. Time from enrollment was accumulated for the 24-month follow-up visit or the visit at which the last sample was available, and HSV-2 incidence was estimated per 100 person-years. Adjusted IRRs (adjIRRs) were estimated for fixed and time-varying covariates (to account for changes in risk behaviors over time).

Results

Of the 6396 men enrolled, 2159 (33.76%) were HSV-2 seropositive at baseline (table 1). In multivariate adjusted analysis, HSV-2 prevalence was increased with older age, current or previous marriage, and higher lifetime number of sex partners. The PRs associated with age declined markedly after adjustment, suggesting substantial confounding; therefore, we evaluated potential associations with other covariates. The increasing HSV-2 prevalence associated with a higher lifetime number of sex partners was highly correlated with age ($P <$ .001). HSV-2 was associated with HIV infection (adjPR, 1.53 [95% CI, 1.43–1.64]) and syphilis (adjPR, 1.09 [95% CI, 1.01–1.18]) at enrollment. There were no associations between HSV-2 prevalence and religion, age at first sexual intercourse, nonmarital relationships, sex partners from outside the community, or use of family planning in the past year.

During the 2-year follow-up of initially HSV-2–uninfected men, the HSV-2 incidence rate was 4.90 cases per 100 person-years (284 seroconverters per 5793.75 person-years) (table 2). In unadjusted analyses, covariates significantly associated with incident HSV-2 infection included older age, current or prior marriage, higher number of sex partners, condom use, alcohol use with sexual intercourse during the follow-up interval, and uncircumcised status. Transactional sexual intercourse was infrequent and did not influence HSV-2 acquisition. There was no association between incident HSV-2 infection and syphilis or HIV serostatus at enrollment. In multivariate Poisson regression, the IRRs for HSV-2 acquisition were increased with alcohol use with sexual intercourse (adjIRR, 1.92 [95% CI, 1.46–2.53]) and were decreased with consistent condom use (adjIRR, 0.56 [95% CI, 0.36–0.89]) and male

circumcision (adjIRR, 0.70 [95% CI, 0.55–0.91]). Number of sex partners and nonmarital relationships were not associated with HSV-2 acquisition.

Discussion

The prevalence (33.76%) and incidence (4.90 cases per 100 person-years) of HSV-2 infection is high among men in Rakai, Uganda. HSV-2 prevalence was strongly associated with lifetime number of sex partners and HIV infection (table 1). HSV-2 incidence was increased with the lack of consistent condom use and alcohol use with sexual intercourse and was reduced in men circumcised during the trial (table 2). We believe this to be the first study to evaluate risk factors for incident HSV-2 infection in a rural African population.

The risk factors differed between prevalent and incident HSV-2 infection. HSV-2 prevalence increased with older age, nonstudent occupation, current or previous marriage, higher lifetime number of sex partners, and HIV-positive status, similar to findings of previous studies [11, 12]. However, none of the risk factors for prevalent HSV-2 infection were associated with HSV-2 incidence. Although the number of sex partners was associated with increased HSV-2 incidence in the unadjusted analysis, no significant association was found after adjustment. However, only sexually active individuals were included in the adjusted analysis, because data on sexual behavior were not collected for individuals who were not sexually active.

In developing countries, it is difficult to define HSV-2 seroconversion because the serological assays appear to differ in sensitivity and specificity from that determined for European and North American populations [10,13]. It has been hypothesized that the decreased specificity may be due to increased cross-reactivity of antibodies to HSV-1 with those of other pathogens. Although it has been previously demonstrated that use of the Kalon HSV-2 IgG ELISA with an index value of 1.5 optimizes both sensitivity and specificity for rural Ugandan serum [10], detection of HSV-2 seroconversion may be a limitation of the present study.

We previously demonstrated that male circumcision decreased HSV-2 acquisition among HIV-negative men in Rakai, Uganda [9], as was observed in the present analysis that included HIV-positive men. Although the present study is primarily an observational analysis nested within a trial, male circumcision status was determined by randomization, and half of the men were circumcised shortly after enrollment. Consequently, there is less confounding with the finding that male circumcision decreases HSV-2 acquisition. However, whether HSV-2 acquisition is affected by possible incomplete keratinization of scar tissue is unknown.

Observational studies have suggested that HSV-2 prevalence and incidence are associated with HIV infection [7,12,14,15]. In the present study, both HIV infection and active syphilis at enrollment were associated with prevalent HSV-2 infection. HSV-2 incidence was increased slightly among HIV-positive individuals, but this was not statistically significant. There were only 9 men who were HIV positive at enrollment and then seroconverted to HSV-2, an unsurprisingly low number given that the large majority of HIV-positive individuals at baseline were also HSV-2 positive. This constrained study power. Although it is has been hypothesized that HIV infection may increase the risk of HSV-2 acquisition because of an immunocompromised state, HIV and syphilis are most likely markers of increased sexual activity.

Promotion of consistent condom use, male circumcision, and policies to reduce alcohol consumption remain pillars in the current effort to stem the spread of HIV infection. Our findings highlight the importance of these measures, which could synergistically reduce the spread of 2 viruses, HSV-2 and HIV.

Acknowledgments

We appreciate Andrew Redd's suggestions. We are most grateful to the study participants and the Rakai Community Advisory Board, whose commitment and cooperation made this study possible.

Financial support: National Institutes of Health (grant U1AI51171 to the trials); Bill and Melinda Gates Foundation (grant 22006.02 to the trials); Fogarty International Center (grants 5D43TW001508 and D43TW00015 to the trials); Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health (support to this study).

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Table 1

Sociodemographic characteristics, risk behaviors, and symptoms of sexually transmitted diseases among men with prevalent herpes simplex virus type 2 (HSV-2) infection.

Category, parameter	HSV-2 positive, proportion (%)	Unadjusted analysis		Adjusted analysis[b]	
		PR (95% CI)	P^a	PR (95% CI)	P^a
All participants	2159/6396 (33.76)				
Age			<.001		<.001
15–19 years	167/1487 (11.23)	1.00 (referent)		1.00 (referent)	
20–24 years	370/1618 (22.87)	2.04 (1.72–2.41)		1.24 (1.01–1.51)	
25–29 years	471/1248 (37.74)	3.36 (2.86–3.94)		1.56 (1.26–1.93)	
30–49 years	1151/2043 (56.34)	5.01 (4.33–5.82)		1.93 (1.56–2.39)	
Education			<.001		.086
None	183/402 (45.52)	1.00 (referent)		1.00 (referent)	
Primary	1547/4298 (35.99)	0.79 (0.70–0.89)		0.95 (0.86–1.04)	
Secondary or higher	429/1696 (25.29)	0.56 (0.49–0.64)		0.88 (0.79–0.99)	
Occupation			<.001		.054
Nonwage	1750/4675 (37.43)	1.00 (referent)		1.00 (referent)	
Wage	334/893 (37.40)	1.00 (0.91–1.10)		0.98 (0.90–1.07)	
Student	75/828 (9.06)	0.24 (0.19–0.30)		0.72 (0.56–0.94)	
Marital status			<.001		<.001
Never married	391/2636 (14.83)	1.00 (referent)		1.00 (referent)	
Currently married	1487/3258 (45.66)	3.08 (2.79–3.40)		1.47 (1.28–1.68)	
Previously married	281/502 (55.98)	3.77 (3.35–4.25)		1.44 (1.24–1.68)	
Lifetime no. of sex partners			<.001		<.001
None	49/561 (8.73)	1.00 (referent)		1.00 (referent)	
1–2	252/1337 (18.85)	2.16 (1.62–2.88)		1.24 (0.90–1.69)	
3–6	768/2345 (32.75)	3.74 (2.85–4.93)		1.54 (1.13–2.10)	
7–10	463/1003 (46.16)	5.29 (4.01–6.96)		1.74 (1.27–2.39)	
≥11 or unknown	627/1150 (54.52)	6.24 (4.75–8.20)		1.85 (1.35–2.53)	
Drink alcohol			<.001		.074
No	629/2727 (23.07)	1.00 (referent)		1.00 (referent)	
Yes	1530/3669 (41.70)	1.81 (1.67–1.96)		1.07 (0.99–1.15)	
Prior receipt of voluntary counseling and testing			<.001		.965
No	1364/4533 (30.09)	1.00 (referent)		1.00 (referent)	
Yes	795/1863 (42.67)	1.42 (1.32–1.52)		1.00 (0.94–1.06)	
Enrollment syphilis status[b]			<.001		.022
Negative	1840/5600 (32.86)	1.00 (referent)		1.00 (referent)	
RPR and TPPA positive	147/248 (59.27)	1.80 (1.62–2.01)		1.09 (1.01–1.18)	
Enrollment HIV status			<.001		<.001
Negative	1546/5533 (27.9)	1.00 (referent)		1.00 (referent)	
Indeterminate	2/7 (28.6)	1.02 (0.32–3.30)		1.32 (0.45–3.90)	
Positive	611/856 (71.4)	2.55 (2.41–2.71)		1.53 (1.43–1.64)	

NOTE. CI, confidence interval; PR, prevalence ratio; TPPA, *Treponema pallidum* particle agglutination assay.

[a] Overall *P* value for risk factor category.

[b] Adjusted model evaluated 5848 men because 548 men had missing rapid plasma reagin (RPR) results.

Table 2

Risk factors for incident herpes simplex virus type 2 (HSV-2) infection.

Category, parameter	Seroconverters/PY	Incident HSV-2 infections/100 PY	Unadjusted analysis		Adjusted analysis[b]	
			IRR (95% CI)	*P*[a]	IRR (95% CI)	*P*[a]
All participants	284/5793.75	4.90				
Age				<.001		.019
15–19 years	69/1950	3.54	1.00 (referent)		1.00 (referent)	
20–24 years	108/1712.75	6.31	1.78 (1.32–2.41)		1.21 (0.83–1.77)	
25–29 years	61/1050.25	5.81	1.64 (1.16–2.32)		0.94 (0.59–1.50)	
30–49 years	46/1080.75	4.26	1.20 (0.83–1.75)		0.65 (0.39–1.09)	
Education				.043		.710
None	13/251.5	5.17	1.00 (referent)		1.00 (referent)	
Primary	202/3733	5.41	1.05 (0.60–1.83)		1.12 (0.61–2.07)	
Secondary or higher	69/1809.25	3.81	0.74 (0.41–1.34)		0.99 (0.51–1.92)	
Occupation				<.001		.071
Nonwage	216/3884.25	5.56	1.00 (referent)		1.00 (referent)	
Wage	38/795.25	4.78	0.86 (0.59–1.22)		0.78 (0.53–1.13)	
Student	30/1114.25	2.69	0.48 (0.32–0.71)		0.53 (0.29–0.98)	
Marital status				.008		.149
Never married	136/3235	4.20	1.00 (referent)		1.00 (referent)	
Currently married	129/2322	5.55	1.32 (1.04–1.68)		0.83 (0.59–1.18)	
Previously married	19/236.75	8.02	1.91 (1.18–3.10)		1.36 (0.78–2.40)	
Nonmarital relationships				.176		
No	179/3868	4.63	1.00 (referent)		…	…
Yes	105/1925.75	5.45	1.18 (0.93–1.50)		…	…
No. of sex partners during past year				<.001		.420
None[b]	34/1146	2.97	1.00 (referent)			
1	141/2966	4.75	1.62 (1.11–2.35)		1.00 (referent)	
≥2	109/1681.75	6.48	2.21 (1.50–3.25)		1.12 (0.85–1.48)	
Condom use during past year				<.001		.004
None	115/2130.75	5.40	1.00 (referent)		1.00 (referent)	
Inconsistent use	108/1530.5	7.06	1.31 (1.00–1.71)		1.121 (0.90–1.63)	
Consistent condom use	27/986.5	2.74	0.51 (0.33–0.77)		0.56 (0.36–0.89)	
Alcohol use with sexual intercourse				<.001		<.001
No	123/3586	3.43	1.00 (referent)		1.00 (referent)	
Yes	161/2207.75	7.29	2.14 (1.69–2.71)		1.92 (1.46–2.53)	
Prefer sexual intercourse with partner's vagina				.224		
Wet during intercourse	248/4500.5	5.51	1.00 (referent)		…	…
Dry during intercourse	2/121.75	1.64	0.29 (0.07–1.18)		…	…
No preference	0/25.5	0.00	0.00 (0.00–2.64)		…	…
Wash genitals after sexual intercourse				.205		
No	28/641.25	4.37	1.00 (referent)		…	…
Yes	222/4006.5	5.54	1.29 (0.87–1.91)		…	…
Circumcised				.028		.007
No	168/3050	5.51	1.00 (referent)		1.00 (referent)	
Yes	116/2743.75	4.23	0.77 (0.60–0.98)		0.70 (0.55–0.91)	
Enrollment syphilis status				.815		
Negative	279/5677.25	4.91	1.00 (referent)		…	…
RPR and TPPA positive	5/116.5	4.29	0.87 (0.28–2.06)		…	…
Enrollment HIV status				.628		
Negative	275/5653.75	4.86	1.00 (referent)		…	…
Indeterminate	0/6	0.00	0.00 (0.00–12.72)		…	…
Positive	9/134	6.72	1.38 (0.71–2.69)		…	…

Category, parameter	Seroconverters/PY	Incident HSV-2 infections/100 PY	Unadjusted analysis		Adjusted analysis[b]	
			IRR (95% CI)	P[a]	IRR (95% CI)	P[a]

NOTE. CI, confidence interval; IRR, incidence rate ratio; PY, person-years; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination assay.

[a] Overall *P* value for risk factor category.

[b] Only sexually active individuals were included in the adjusted analysis.