MAJOR ARTICLE

Transmission of Herpes Simplex Virus Type 2 among Factory Workers in Ethiopia

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The herpes simplex virus type 2 (HSV-2) and human immunodeficiency virus (HIV) epidemics are believed to fuel each other, especially in sub-Saharan countries. In Ethiopia during 1997–2002, a retrospective study was conducted to examine risk factors for infection and transmission of HSV-2, in a cohort of 1612 factory workers. Prevalence of HSV-2 seropositivity at enrollment was 40.9%, and incidence of seroconversion was 1.8 seroconversions/100 person-years (PY), which decreased over time. Independent risk factors for seropositivity were having an HSV-2–seropositive partner, female sex, HIV antibodies, positive *Treponema pallidum* particle agglutination assay result, older age, low education level, and orthodox religion. These same factors were independent risk factors for HSV-2 seroconversion, with the exception of the latter 3. Most HSV-2–infected persons did not report symptoms. Among 41 monogamous HSV-2–serodiscordant heterosexual couples, incidence of HSV-2 seroconversion was 20.75 seroconversions/100 PY for women and 4.93 seroconversions/100 PY for men. The high burden of both HSV-2 and HIV infection in Ethiopia warrants stringent control measures.

The public health effect of genital herpes is increasingly recognized. Herpes simplex virus type 2 (HSV-2) infections are the most common cause of genital ulcerations worldwide [1]. In addition to genital herpes, infection with HSV-2 can result in neonatal herpes. It is believed that HSV-2 fuels the HIV epidemic, especially in many developing countries where the majority of transmissions of HIV in adults are heterosexual transmissions [2–9]. The management of HSV-2 is not only important for its potential effect on the HIV epidemic; it is needed to protect individuals, since infection can cause morbidity and since infection increases the risk for HIV infection. A meta-analysis of prospective studies demonstrated an odds ratio of 2.1 of acquiring an HIV infection when HSV-2 antibodies are present [10]. This association remains after adjusting for confounding factors, such as sexual risk behavior [11, 12].

In Ethiopia, as in other African countries, the prevalence of HSV-2 is high. A previous cross-sectional study among participants in a cohort in Akaki, Ethiopia, showed that half of the adult urban population had antibodies against HSV-2 [13]. Incidence and risk factors for seroconversion in Ethiopia are not known. The present study in this country was therefore conducted among factory workers to determine the incidence of HSV-2, to assess the risk factors for infection, and, especially, to examine the interaction between HSV-2 and HIV. Moreover, since a substantial number of couples were followed over time, the study provided a unique opportunity to investigate transmission of HSV-2 within monogamous HSV-2–serodiscordant couples.

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SUBJECTS AND METHODS

Study Population

The present study was conducted among factory workers participating in a open cohort set up in 1997 to study HIV infection and disease progression at Wonji and Akaki, 2 study sites near Addis Ababa. After signing an informed-consent form, cohort participants were seen every 6 months for collection of blood samples, counseling for HIV testing (optional), and sex-matched interviews on sociodemographic characteristics and sexual behaviors by use of a structured questionnaire [14]. By December 2002, 1874 persons had entered the cohort. From this population, all 1612 participants who had at least 1 follow-up visit were included in the present study. Among them were 133 heterosexual couples who were followed over time (a subgroup referred to as "couples").

HSV-2 Testing

Stored plasma samples from cohort participants obtained at enrollment between 1997 and December 2002 were tested for HSV-2 IgG. For participants who were HSV-2 negative at enrollment, the last follow-up sample was tested for HSV-2 IgG. When that sample was found to be positive for HSV-2 IgG, the sample obtained at enrollment was tested. In the case of a person who experienced seroconversion, samples obtained in between were tested to identify the last seronegative and the first seropositive visits. Of the persons who experienced seroconversion, 84.5% had a seroconversion interval of <1 year between the last negative and the first positive samples were obtained.

Testing for HSV-2 antibody was performed by use of recombinant IgG2 antigen in a commercially available ELISA kit (HerpeSelect 2 ELISA IgG; Focus Technologies). A cutoff value of 3.0 was used to determine seropositivity. Recently, this test kit was evaluated by use of serum samples from persons from different African countries, showing a sensitivity of 90.5% and a specificity of 97.8% at the cutoff value 3.0 [15]. In a large sample, the interassay agreement value (κ) between using serum or plasma samples was 98.9% [16]. We compared 40 paired samples of serum and plasma obtained approximately on the same date, for detection of HSV-2 antibodies, and found that the plasma test result is 88% sensitive and 100% specific, compared with serum test results, resulting in a κ of 86%.

HIV and Syphilis Testing

Plasma samples from the cohort participants were routinely tested for HIV-1 antibodies by use of HIVSPOT (Genelabs Diagnostics), Determine (Abbott Diagnostics), and ELISA (Vironostika HIV Uni-Form II Plus O; Organon Teknika). The samples producing a positive result in at least 1 test were confirmed by use of Western blot test (HIV Blot 2.2; Genelabs Diagnostics). At study entry, plasma samples were also screened for syphilis, by use of the rapid plasma reagin (RPR) test (RPR Nosticon II; Organon Teknika); samples producing a positive result were routinely confirmed by *Treponema pallidum* particle agglutination assay (TPPA) (Serodia-TP; Fujirebio).

Statistical Methods

The prevalence of HSV-2 infection was calculated, and risk factors for HSV-2 seropositivity at enrollment were examined by use of a generalized linear model for binomial data, using a log-link function [17]. Since men and women differ with respect to several sociodemographic and behavioral characteristics, all risk estimates were adjusted for sex. Whether risk estimates varied by sex was assessed by adding an interaction term between a risk factor and sex. To identify independent predictors, all variables found to be statistically significant ($P < .05$) by bivariate analysis were entered into a full model. By use of a stepwise backward procedure, those variables that remained significant were retained in the final model. In the final model, whether risk estimates differed by sex by adding interaction terms was also explored. An interaction term with $P \leqslant .10$ was retained in the model. The at-risk period is the time from the first through the last seronegative visit, for HSV-2–seronegative persons. For persons who experienced HSV-2 seroconversion, the at-risk period is the time from the first seronegative visit through the midpoint between the last HSV-2–seronegative visit and the first HSV-2–seropositive visit. Incidence of HSV-2 was calculated by dividing the number of seroconversions by the person-years (PY) at risk. Incidence and 95% confidence intervals (CIs) were assessed assuming a Poisson distribution. Risk factors for HSV-2 seroconversion were estimated by Poisson regression, in a similar fashion as described above in this section. Analyses were repeated with exclusion of persons who had a seroconversion interval of >1 year; similar incidence rate ratios (IRRs) were obtained by use of the complete and the restricted data sets.

Couples. Among the HSV-2–serodiscordant couples who claimed to be monogamous and for whom follow-up data were available for both partners, the incidence and risk factors for HSV-2 seroconversion were assessed. To explore possible underreporting of sexual relations outside the steady partnership or marriage, incidence of seroconversion was also calculated among seroconcordant HSV-2–seronegative couples who claimed to be monogamous.

Variables considered as risk factors for HSV-2 seropositivity or seroconversion are shown in tables 1 and 2. Risk factors related to seropositivity were measured at enrollment, and risk factors for seroconversion were time dependent (when applicable). In examination of risk factors for HSV-2 infection, special emphasis was placed on HIV infection. Moreover, HSV-2 infection was also evaluated as a risk factor for HIV seroconversion. To assess the independent association between HIV and HSV-2, analyses

Table 1. Prevalence and risk factors for seropositivity to herpes simplex virus type 2 (HSV-2)–specific antibodies among 1612 factory workers, at enrollment in a cohort study at Akaki and Wonji, Ethiopia, 1997–2002.

Characteristics	No. of HSV-2–seropositive persons/total no. of persons (%)[a]	Bivariate[b] PRR (95% CI)	Multivariate[c] PRR (95% CI)
Sex			
Male	417/1205 (34.6)	1	1
Female	242/407 (59.5)	1.73 (1.54–1.93)	1.52 (1.35–1.71)
Study site			
Wonji	304/868 (35.0)	1	
Akaki	355/744 (47.7)	1.09 (0.95–1.25)	
Age, years			
20–29	112/435 (25.7)	1	1
30–39	333/746 (44.6)	1.69 (1.42–2.02)	1.55 (1.31–1.85)
40–49	214/419 (49.9)	1.97 (1.65–2.37)	1.62 (1.35–1.82)
Education level[d]			
High	117/423 (27.7)	1	1
Low	542/1187 (45.7)	1.44 (1.22–1.72)	1.22 (1.15–1.46)
Religion			
Nonorthodox	120/404 (29.7)	1	1
Orthodox	539/1206 (44.7)	1.39 (1.19–1.64)	1.23 (1.05–1.46)
Lifetime no. of partners			
1	37/90 (41.1)	1	
2–5	534/1311 (40.7)	1.25 (1.06–1.47)	
>5	79/184 (42.9)	1.36 (1.10–1.66)	
Unknown	9/27 (33.3)		
Casual partners during last 12 months			
No	610/1493 (40.9)	1	
Yes	48/111 (43.2)	1.06 (0.83–1.30)	
Spouse/steady partner			
Women[e]			
No	40/57 (70.2)	1	
Yes	202/348 (58.0)	0.87 (0.73–1.08)	
Men[e]			
No	30/145 (20.7)	1	
Yes	387/1060 (36.5)	1.76 (1.30–2.51)	
HSV-2 serostatus of spouse/steady partner			
Women[f]			
No spouse/steady partner	40/57 (70.2)	1.95 (1.40–2.82)	
Partner's status unknown	143/230 (62.2)	1.73 (1.29–2.45)	
Partner's status negative	27/75 (36.0)	1	
Partner's status positive	32/43 (74.4)	2.07 (1.47–2.99)	
Men[f]			
No spouse/steady partner	30/145 (20.7)	0.77 (0.41–1.73)	
Partner's status unknown	361/1003 (36.0)	1.34 (0.98–2.87)	
Partner's status negative	7/26 (26.9)	1	
Partner's status positive	19/31 (61.3)	2.28 (1.22–5.06)	
Men and women combined			
No spouse/steady partner			1.51 (1.10–1.72)
Partner's status unknown			1.56 (1.19–1.90)
Partner's status negative			1
Partner's status positive			1.87 (1.42–2.54)
TPPA result			
Negative	396/1136 (34.9)	1	1
Positive	223/396 (56.3)	1.56 (1.40–1.74)	1.25 (1.12–1.41)
Unknown	40/80 (50.0)		
HIV status			
Negative	565/1468 (38.5)	1	1
Positive	94/144 (65.3)	1.51 (1.32–1.69)	1.25 (1.09–1.37)

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

[a] Totals do not always add up to 1612, because of missing data. When missing data exceed 10% of observations, prevalence is shown for the "unknown" data categories.

[b] PRR controlled for sex.

[c] PRR adjusted for the other variables in the column, modeled while taking account of unknown TPPA results.

[d] High, grade 12 and higher; low, less than grade 12.

[e] In bivariate analyses, interaction term between sex and having spouse/steady partner is $P < .001$.

[f] In bivariate analyses, interaction term between sex and serostatus of partner is $P = .007$. In multivariate analyses, interaction term is $P > .10$.

were controlled for sexual behavior (with reported casual partners and spouse/steady partner). Finally, incidence of reported symptoms was assessed among HSV-2–seronegative persons and persons who experienced seroconversion [18, 19].

RESULTS

Characteristics. During the period 1997–2002, a total of 1612 persons participated in the cohort study and had at least 1 follow-up visit. Half (53.8%) of the persons participated at the Wonji cohort site. There were 407 women (25.2%), of whom most (87%) were from Akaki. The median age for the men was 35 years (range, 19–62 years) and for the women was 33 years (range, 19–46 years). Only 6.9% of women and 32.9% of men had attained education of grade 12 and higher. At enrollment, 88.0% of men and 85.9% of women were married or had a steady partner; of these, 7.6% of men and 1.2% of women reported at least 1 casual partner during the last year. Of persons who neither were married nor had a steady partner, 18.2% of men and 0% of women reported having casual partners.

Prevalence of HSV-2 and risk factors for seropositivity at enrollment (table 1). At enrollment, the prevalence of HSV-2 infection was 40.9% (659/1612) and was higher for women than for men. Bivariate risk factors for HSV-2 seropositivity (controlling for sex) were older age, low education, orthodox religion, a higher lifetime number of partners, and TPPA or HIV positivity. These risks were similar in men and women. Risk factors for being HSV-2 seropositive were having an HSV-2–seropositive spouse/steady partner and, for men, being married or having a steady relationship in itself. Since having a spouse/steady partner and the serostatus of the partner are colinear variables, only the latter was included in the multivariate model. All bivariate risk factors remained independently related to HSV-2 seropositivity in multivariate analyses, except for the lifetime number of partners. The risk estimates were similar for men and for women. In the multivariate model, when the variable indicating the partner's serostatus was replaced by having a spouse/steady partner, this second variable was not statistically significant.

Incidence of HSV-2 and risk factors for seroconversion (table 2). Of all study participants, 953 (59.1%) were HSV-2 seronegative at enrollment and, thus, at risk for HSV-2 seroconversion; they were followed up for a total of 3225.5 PY. Of the 953 participants who were HSV-2 seronegative at enrollment, 58 experienced HSV-2 seroconversion, giving an incidence of 1.80 seroconversions/100 PY (95% CI, 1.39–2.33 seroconversions/100 PY). Incidence was higher for women than for men. Bivariate risk factors were having an HSV-2–seropositive partner, being TPPA positive, being HIV seropositive, and earlier calendar time; in the multivariate model, all risk factors remained independently related to HSV-2 seroconversion, along with female sex. In the multivariate model, risk estimates were similar for men and for women. Addition of the reported casual partners did not substantially alter the estimates of the independent predictors (data not shown).

Monogamous HSV-2–serodiscordant couples. Among the 1612 persons in the study, there were 133 heterosexual couples; most were married, and some were involved in a long-standing, steady relationship. Two persons in a couple were not necessarily recruited simultaneously. At the first visit at which both persons were participating in the cohort, there were 51 seroconcordant HSV-2–seronegative (38.3%), 41 seroconcordant HSV-2–seropositive (30.8%), and 41 serodiscordant (30.8%) couples. The median age of the 133 women was 30 years (range, 20–46 years) and of the men was 38 years (range, 32–42 years). Recent (during the last 6–12 months) casual partners were reported by 8.1% of the men and 0.8% of the women; most couples claimed to be monogamous. Tables 1 and 2 show that having an HSV-2–seropositive partner was strongly and independently associated with being HSV-2 seropositive at enrollment or acquiring HSV-2 infection during follow-up.

The 41 serodiscordant couples included 12 in which the man was seropositive and 29 in which the woman was seropositive. During follow-up, 8 persons experienced seroconversion (table 2, variable on positive serostatus of the partner). Excluding the visits at which casual partners were reported (1.8% of all visits), 7 seroconversion events remained. Among the 41 presumed-monogamous couples, the seroincidence of HSV-2 among women was 20.75 seroconversions/100 PY (95% CI, 7.79–55.29 seroconversions/100 PY), and, among men, it was 4.93 seroconversions/100 PY (95% CI, 1.59–15.29 seroconversions/100 PY). The risk of HSV-2 seroconversion in a serodiscordant relationship was higher for women than for men (IRR, 4.21; 95% CI, 0.93–18.98; $P = .061$). The incidence of HSV-2 seroconversion in 5 couples in which both partners were HIV seropositive was 20.32 seroconversions/100 PY (95% CI, 5.08–81.25 seroconversions/100 PY); it was 7.11 seroconversions/100 PY (95% CI, 2.96–17.09 seroconversions/100 PY) in 36 couples who were HIV seronegative. The risk of HSV-2 seroconversion was higher in HIV-positive couples than in HIV-negative couples (IRR, 7.01; 95% CI, 0.58-84.15; $P = .125$ when controlling for sex).

To investigate possible underreporting of sex partners outside of the steady partnership or marriage, the incidence of HSV-2 seroconversion was calculated among couples who reported no casual partners and who had an HSV-2–seronegative spouse/steady partner. There were 51 HSV-2–negative couples for whom follow-up data were available. At the visits at which no casual partners were reported, 2 of the women (incidence, 1.74 seroconversions/100 PY; 95% CI, 0.44–6.97 seroconversions/100 PY), and none of the men experienced seroconversion, in 114.70 PY of follow-up.

Incidence of HIV in relation to HSV-2 infection. During the period 1997–2002, a total of 21 HIV seroconversions occurred

in the cohort, during 5791.8 PY of observation, resulting in an incidence of 0.36 seroconversions/100 PY (95% CI, 0.24–5.56 seroconversions/100 PY). Of the 21 persons who experienced HIV seroconversion, 12 were HSV-2 seropositive at enrollment, and 2 experienced HSV-2 seroconversion during follow-up; these 2 persons had a wide HSV-2 seroconversion interval (>1 year), and the temporal relationship between HIV and HSV-2 seroconversion could not be established. Among the 12 who were HSV-2 seropositive at enrollment, the incidence of HIV was 0.46 seroconversions/100 PY (95% CI, 0.26–0.82 seroconversions/100 PY), and, among those who remained HSV-2 seronegative during follow-up, this was 0.22 seroconversions/100 PY (95% CI, 0.10–0.46 seroconversions/100 PY). The IRR between HSV-2 seropositivity and HIV seroconversion was 2.21 (95% CI, 0.90–5.47; $P = .085$), when controlling for being married/having a steady partner and for TPPA status. Controlling for casual partners was not possible, since no one experienced HIV seroconversion when reporting casual partners.

Reported symptoms in relation to HSV-2 infection. Among women who were HSV-2 seropositive at enrollment, 97.6% ($n = 407$) and 87.8% ($n = 366$) reported no episode of genital ulcers or genital discharge, respectively, in the 5 years preceding enrollment; these figures were 92.6% ($n = 224$) and 81.0% ($n = 196$) for men who were HSV-2 seropositive at enrollment. Of the 58 persons who experienced HSV-2 seroconversion during follow-up, none reported genital ulcer, and only 2 women and 1 man reported genital discharge in the 6 months preceding the first HSV-2–seropositive visit. For women, the incidence of genital discharge in this period of recent infection was 19.68 episodes/100 PY (95% CI, 4.92–78.64 episodes/100 PY), compared with 12.70 episodes/100 PY (95% CI, 9.94–16.22 episodes/100 PY) in the seronegative period; for men, incidence was 6.03 episodes/100 PY (95% CI, 0.85–42.77 episodes/100 PY) and 1.0 episode/100 PY (95% CI, 0.69–1.46 episodes/100 PY) in the 2 periods, respectively.

DISCUSSION

The present study followed a substantial number of persons at risk for HSV-2 infection and HSV-2–serodiscordant couples, over time, and provided a unique opportunity to investigate transmission of HSV-2 among heterosexual factory workers in Ethiopia. It showed a high burden of infection in Ethiopia, as is the case in other African countries [13, 20–26].

The observed rate of HSV-2 seroconversion of 6.2 seroconversions/100 PY in the first year of our cohort study was comparable to other findings on the African continent (i.e., 6.2 seroconversions/100 PY among male factory workers in Zimbabwe and 10.3 seroconversions/100 PY among adult men and 8.7 seroconversions/100 PY among adult women in Tanzania [22, 23]). In recent years of our cohort study, the incidence of HSV-2 was considerably lower. The decrease in incidence over time may be a result of changes in sexual behavior of cohort participants during follow-up. Serological results of HSV-2, especially the characterization of incident infections, is a useful marker for changes in sexual behavior in HIV-intervention studies. In our cohort, we also observed a decreasing incidence of sexual risk behavior, genital discharge, and HIV infections (from 0.63 HIV seroconversions/100 PY in 1997 to 0.25 seroconversions/100 PY in 2002), pointing to a positive effect of the behavioral intervention (voluntary counseling and testing plus condom-use education for HIV prevention) routinely offered to the cohort participants ([14] and data not shown).

In spite of certain successes accomplished in reducing sexually transmitted diseases (STDs) [27], there is a worldwide rapid increase in the proportion of herpetic ulcers, in both HIV-positive and HIV-negative persons [1]. With HSV-2 infection being the common cause for genital ulcers, it is notable that most HSV-2–infected women and men in our study did not report a history of these ulcers during their infection. It might be that symptoms were unnoticed and/or underreported by the participants. The extent of underreporting is unknown, since medical examination for genital herpes was not routinely conducted in our study. Large numbers of the HSV-2 infections are probably unnoticed [28]. This is a great concern, because infected participants may continue to engage in unprotected sexual activity, causing the widespread dissemination of HSV-2 infection. HSV-2 shedding may occur at asymptomatic periods, and most transmission events are not associated with a clinically recognized HSV-2 infection [1, 29]. The high rate of HSV-2 acquisition when the partner is HSV-2 seropositive suggests that persons are not aware of their own HSV-2 serostatus, let alone their partner's, and that no substantial precautions are taken to avoid HSV-2 infection. Moreover, in marriage, the opportunity for personal protection might be limited, especially for women [21]. Women have a higher risk of acquiring HSV-2 infection than men, as shown by the 41 HSV-2–serodiscordant couples in our study. The annual rate of infection from their partner was 21% for women and 5% for men, findings that concur with transmission rates of 19% and 5%, respectively, in the United States [30]. Factors that may facilitate transmission of HSV-2 from men to women include the greater and more vulnerable surface area of the female genital tract and a higher rate of recurrences among men [31]. The prevalence of HSV-2 of 43.4% among women in the youngest age group (20–30 years) is an important finding, urging that prevention of genital herpes should begin at early ages.

It was shown that, in addition to female sex, prior infection with HIV was a strong independent risk factor for acquisition of HSV-2. This latter risk was still present when controlling for markers for sexual behavior, such as reported (casual) sex partners, and for TPPA status. HSV-2 infection increases susceptibility and infectivity of HIV, and HIV infection is a risk factor

Table 2. Incidence and risk factors for seroconversion to herpes simplex virus type 2 (HSV-2)–specific antibodies among 953 factory workers at risk for infection, in a cohort study at Akaki and Wonji, Ethiopia, 1997–2002.

Characteristics	No. of HSV-2 seroconversions/ observed PY[a]	Incidence (95% CI)	Bivariate[b] IRR (95% CI)	Multivariate[c] IRR (95% CI)
Sex				
Male	39/2711.34	1.44 (1.05–1.97)	1	1
Female	19/514.16	3.70 (2.36–6.0)	2.57 (1.49–4.43)	2.43 (1.39–4.27)
Study site				
Wonji	22/1664.18	1.32 (0.87–2.01)	1	
Akaki	36/1561.33	2.31 (1.66–3.20)	1.25 (0.62–2.52)	
Age, years				
20–29	10/741.75	1.35 (0.73–2.51)	1	
30–39	26/1449.08	1.80 (1.22–2.64)	1.33 (0.64–2.75)	
40–49	22/1034.671	2.13 (1.40–3.23)	1.67 (0.80–3.50)	
Education level[d]				
High	9/987.38	0.91 (0.47–1.75)	1	
Low	49/2236.98	2.19 (1.66–2.90)	2.02 (0.96–4.26)	
Religion				
Nonorthodox	9/876.64	1.03 (0.53–1.97)	1	
Orthodox	48/2336.28	2.05 (1.55–2.73)	1.81 (0.88–3.71)	
Casual partners during last 12 months				
No	54/3090	1.75 (1.34–2.28)	1	
Yes	3/106.73	2.81 (0.90–8.72)	1.92 (0.60–6.18)	
Spouse/steady partner				
Women[e]				
No	4/51.62	7.75 (2.91–20.65)	1	
Yes	15/458.82	3.27 (1.97–5.42)	0.42 (0.14–1.27)	
Men[e]				
No	5/436.16	1.15 (0.48–2.75)	1	
Yes	34/2268.86	1.50 (1.07–2.10)	1.31 (0.51–3.34)	
HSV-2 serostatus of spouse/steady partner				
Women[f]				
No spouse/steady partner	4/51.62	7.75 (2.91–20.65)	3.93 (0.72–21.58)	
Partner's status unknown	8/336.99	2.37(1.19–4.75)	1.20 (0.26–5.67)	
Partner's status negative	2/101.47	1.97 (0.49–7.88)	1	
Partner's status positive	5/20.36	24.56 (10.22–59.01)	12.46 (2.37–65.54)	
Men[f]				
No spouse/steady partner	5/436.16	1.15 (0.48–2.75)	0.77 (0.30–1.97)	
Partner's status unknown	31/2074.41	1.49 (1.05–2.12)[g]	1	
Partner's status negative	0/129.36	0[g]	1.03 (0.32–3.37)	
Partner's status positive	3/65.09	4.61 (1.49–14.29)[h]		
Men and women combined				
No spouse/steady partner				6.09 (1.47–25.25)
Partner's status unknown				4.28 (1.19–15.38)
Partner's status negative				1
Partner's status positive				15.19 (3.30–69.91)
TPPA result[i]				
Negative	35/2570.27	1.36 (0.98–1.90)	1	1
Positive	19/630.55	3.01 (1.92–4.72)	2.30 (1.31–4.02)	1.76 (0.96–3.23)
Unknown	4/24.68	16.21 (6.08–43.19)		
HIV status[j]				
Negative	48/3044.28	1.58 (1.19–2.09)	1	1
Positive	8/175.93	4.55 (2.27–9.09)	2.79 (1.34–5.77)	2.80 (1.30–6.01)

(continued)

Table 2. ***(Continued.)***

Characteristics	No. of HSV-2 seroconversions/ observed PY[a]	Incidence (95% CI)	Bivariate[b] IRR (95% CI)	Multivariate[c] IRR (95% CI)
Year				
1997	6/96.28	6.23 (2.80–1.39)	0.81 (0.67–0.98)[k]	0.77 (0.63–0.93)[k]
1998	9/648.20	1.34 (0.56–3.21)		
1999	12/799.54	3.60 (2.33–5.59)		
2000	6/717.40	0.84 (0.38–1.86)		
2001	20/554.80	1.50 (0.85–2.64)		
2002	5/373.26	1.31 (0.68–2.52)		

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

[a] When missing data exceed 10% of observations, incidence is shown for the "unknown" data categories.

[b] IRR controlled for sex.

[c] Multivariate analysis, IRR adjusted for the other variables in the column, modeled while taking account of unknown TPPA results.

[d] High, grade 12 and higher; low: less than grade 12.

[e] In bivariate analyses, interaction term between sex and having spouse/steady partner is $P = .126$.

[f] In bivariate analyses, interaction term between sex and serostatus of partner is $P = .1035$. In multivariate analyses, interaction term is $P > .10$.

[g] The 2 categories are combined in the reference category.

[h] Difference in incidence between having a seropositive partner and having a seronegative partner is $P = .010$ (likelihood ratio test).

[i] Measured at enrollment.

[j] Exact recent exposure to HIV for 2 persons who experienced HSV-2 seroconversion was not known, since they had a long seroconversion interval, and the 2 were excluded.

[k] Yearly decrease.

for transmission of HSV-2 [8, 13, 22, 32, 33]. In the present study, only a few persons experienced HIV seroconversion, and, hence, it may be difficult to draw associations. Still a borderline significant association between presence of HSV-2 infection and acquisition of HIV infection was demonstrated.

The observed reciprocal association between HSV-2 and HIV agrees with the results of seroepidemiological studies on the African continent and elsewhere [11, 12, 26, 34]. This has led to the belief that the 2 epidemics fuel each other, especially in sub-Saharan countries, and put management of HSV-2 as a central issue on the HIV-control agenda. For the management of HSV-2, modification of the current syndromic-management approach to STDs, especially in areas of high prevalence of HIV, should be considered. In particular, the inclusion of HSV-2–suppressive therapy with generic acyclovir could limit the spread of HSV-2. This therapy is relatively inexpensive and safe and can reduce the frequency of both genital herpes episodes and asymptomatic shedding [35]. The most effective strategy for management of HSV-2 would be prophylaxis through vaccination against HSV-2 infection. As long as such tools are unavailable in many resource-poor countries, including Ethiopia, primary behavioral prevention remains crucial. Individuals should be counseled on recognition of lesions and using condoms or avoiding sex when lesions are present. The decreasing incidence of HSV-2 found in our cohort suggests that such behavioral interventions can be effective. Serological testing could serve to identify persons with unrecognized HSV-2 infection and could help to determine where to aim intervention programs [36]. However, this approach might be beyond the capacity of resource-poor countries.

The investigators of the Mwanza trial in Tanzania and of the Rakai and Masaka trials in Uganda learned that the success of an HIV intervention (i.e., improved STD case management) in limiting the spread of HIV is related to many factors. Such factors include the state of the HIV epidemic, the prevalence of sexual risk behavior, and the prevalence of treatable and untreatable STDs [27, 37–39]. Genital herpes was not targeted in these trials. Though the effect of management of HSV-2 on reducing the incidence of HIV in a population is yet unproven, it may well help to avert new HIV infections and is needed to protect the individual.

Two limitations of the present study deserve mention. First, one may question the validity of self-reported data on sexual behavior obtained by use of a structured questionnaire [40]. Women especially might tend to underreport sexual behaviors. However, the low rate of HSV-2 seroconversion among couples who claimed to be monogamous but were infected by extramarital relations shows that underreporting of sexual behavior does occur but seems to be minimal. Second, the low numbers of HSV-2 seroconversions noted among the HSV-2–serodiscordant couples warrants caution for interpreting risk-factor analyses.

In conclusion, the study has shown a high burden of HSV-2 infection among factory workers in Ethiopia. Most HSV-2 infections were unnoticed, and the HSV-2–infected spouse/steady partner who is unaware of infection is a substantial source for

new infections. In both sexes, HIV is an independent risk factor for current HSV-2 infection and future HSV-2 seroconversion. Since infection with HSV-2 can cause morbidity and since the HSV-2 and HIV epidemics fuel each other, the high burden of infection in Ethiopia warrants control. Prevention activities are urgently needed and should be started at early ages.

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