

HERPES SIMPLEX VIRUS TYPE II INFECTION IS A RISK FACTOR FOR HIV SEROCONVERSION

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Herpes simplex virus type II (HSV-2) is the most common cause of genital ulcer diseases worldwide,¹ and through disruption of the epithelial barrier and inflammation it may increase the risk of HIV-1 transmission.²

In sub-Saharan Africa, where HIV-1 is spread mainly by heterosexual transmission, other sexually transmitted infections (STIs), including HSV-2, are common.³ In South Africa 24.5% of women attending antenatal clinics in 2000 were infected with HIV-1.⁴ A recent study showed 50% of men attending sexually transmitted disease clinics were infected with HSV-2, which was the most common cause of genital ulcer disease.⁵

While it has been shown that herpes simplex virus type II (HSV-2) is a risk factor for HIV-1, few studies have investigated the relationship between HIV-1 and HSV-2 seroconversion and the associated risk factors.

The present study was undertaken to: (1) measure baseline HIV-1 and HSV-2 prevalence among a cohort of female sex workers participating in a vaginal microbicide clinical trial; (2) investigate risk factors associated with HIV-1 and HSV-2 at screening; and (3) study the effect of HSV-2 seroconversion on the incidence of HIV-1 among HIV-negative women in the trial and the relationship between the incidence of HSV-2 and HIV.

METHODS

Four hundred and sixteen sex workers from five truck stops along the route between the port city of Durban and the commercial centre of Johannesburg were invited to participate in a phase III clinical trial of a vaginal microbicide containing 52.5 mg nonoxynol-9 (N9), funded by UNAIDS. The participatory recruitment process is described elsewhere.⁶ The majority of the women's clients are truck drivers. On average the women had 5 sexual partners per day and 20 per week.

On recruitment and screening the women were educated in HIV-1 prevention and counselled on safe sex behaviour. Women were excluded from the study if they were HIV-1 positive, had less than 5 sexual partners per week, were allergic to latex, had genital abnormalities, were pregnant or wanting to have a baby. The women were counselled to use condoms for every sexual act and condoms were provided at each visit.

Of the 416 women screened, 198 were HIV-1 negative and were followed up monthly for a period of 3 years to determine HIV-1 and HSV-2 incidence. An ELISA was used to test for HIV-1 and HSV-2 antibodies.

RESULTS

On recruitment 50% of the women were HIV-1 positive while 84% were HSV-2 positive. The two infections were strongly associated ($P = 0.001$). As in other populations in South Africa, the prevalence of HIV-1 increased with age, peaked among women at the age of about 24 years and declined with age thereafter.⁷ The prevalence of HSV-2, on the other hand, increased very rapidly with age, reaching 60% at the age of 18 years, 90% at the age of 25 years and 100% by the age of 35 years (Fig. 1).

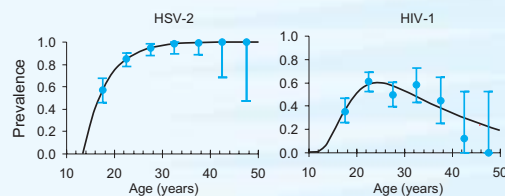


Figure 1. The age-specific prevalence of a) HSV-2 and b) HIV-1 infection. The HSV-2 data are fitted to an exponential curve, the HIV-1 data are fitted to a log-normal curve.

Of the women who seroconverted, all but 6 became HSV-2 positive *before* they became HIV positive. Hence we only determined HIV incidence among HSV-2 positive and HSV-2 negative women, and we did not calculate HSV-2 incidence among HIV-positive women.

On enrolment, HSV-2 was strongly associated with HIV-1 (OR = 4.6, $P = 0.001$). After seroconverting to HSV-2 the incidence of HIV-1 increased substantially (RR = 4.86, $P = 0.0024$), after allowing for potential confounding variables.

However, **those who were HSV-2 positive on admission had a lower incidence of HIV-1 (12% per year) than those who were HSV-2 negative on admission (22% per year) (RR = 0.531, $P = 0.048$). The median time to HIV-1 seroconversion among women who seroconverted for HSV-2 was 3.3 years compared to 5.6 years among women who were HSV-2 positive at enrolment.**

DISCUSSION

Incidence of HIV-1 was highest among women who had seroconverted to HSV-2 during the trial and lowest among women who were HSV-2 positive on enrolment. This paradoxical finding requires urgent investigation.

The high prevalences of HSV-2 and HIV-1 infections among sex workers are in keeping with those reported from Africa and elsewhere in high-risk groups.^{2,8,9} The odds ratio

for HIV-1 and HSV-2 found here (OR = 4.6; $P = 0.001$) confirms results of other studies^{10,11} which have shown a strong association between HIV-1 and HSV-2.

A recent study on the epidemiology of HSV-2 infection conducted in four African cities reported a strong and consistent association with HIV-1.¹² In that study, the adjusted odds ratio among women ranged from 4.0 to 5.5 in Kenya and Yaounde respectively, while age-specific prevalence data indicated that prevalence of HSV-2 was highest among young women aged 15-19 years.¹² Weiss *et al.*¹² found the highest prevalence of HSV-2 (60-90%) in the 18-25-year age group. In contrast, our study showed 100% prevalence among women of 30 years and older. Once infected with HSV-2 the patient remains infected for life, as is the case with other viral STIs including human papilloma virus and HIV-1.^{13,14}

The strength of the association between HSV-2 and HIV-1 and the high prevalence of HSV-2 in many developing countries may be important in explaining the very high rates of HIV in those settings. However, infections and clinical manifestations of HSV-2 are diverse - infected individuals are often asymptomatic or do not recognise the symptoms as being sufficiently severe to seek medical care.¹⁴ In addition, many clinics do not test for HSV-2 routinely, through lack of facilities or lack of recognition of the importance of the infection. Latent HSV-2 infections do reactivate and cause symptoms intermittently, rendering the carrier very contagious.¹⁵

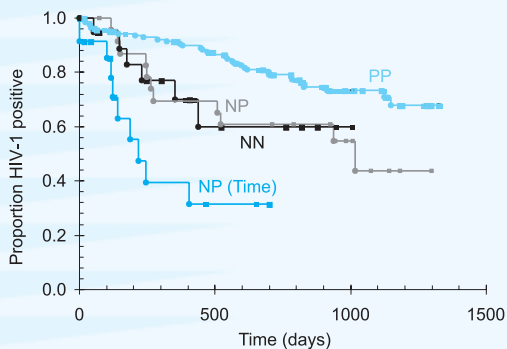


Figure 2. Kaplan-Meier curves for those who were HSV-2 positive on enrolment (PP); HSV-2 negative throughout (NN); seroconverted to HSV-2 during the course of the trial (NP); and with the starting time taken as the date of seroconversion to HSV-2 (NP time).

The present study is the first cohort study among women which demonstrates that HSV-2 seroconversion generally occurs before HIV-1 seroconversion (Fig. 2). HSV-2 seroconversion is a powerful predictor of HIV. A retrospective study by Holmberg *et al.*¹⁰ among men from whom three sequential samples were collected over a period of 12 months showed that prior infection with HSV-2 was a risk factor for HIV-1, even after controlling for factors influencing HIV-1 seroconversion. Another study among homosexual men established that HSV-2 was a risk factor for HIV-1; however, this relationship did not hold true after adjusting for confounders.¹⁶

Most strikingly, however, the present study shows that women who were HSV-2 positive on admission had a lower risk of HIV seroconversion than those who were HSV-2 negative on admission, after adjusting for confounding variables. The possibility that infection with a human herpes virus may slow HIV infection rates has recently been described in a study of the interaction between human herpes virus 6 (HHV-6) and HIV. In laboratory tests, it was shown that HHV-6 slowed reproduction of forms of HIV active in the early stages of HIV infection.¹⁷ A possible explanation of our finding is that women exposed to HSV-2 were protected from reinfection with the circulant HSV-2 during the study, thus reducing their risk of acquiring the HSV-2 infection and thus lesions which are a risk factor for HIV-1. New infection in the previously HSV-2 negative individuals would cause lesions and increase the risk of HIV-1 transmission.

Further, our findings may also explain the age-specific patterns of prevalence of HSV-2 and HIV-1 in our setting. The high-

est incidence of HIV-1 is among young women who also have a high incidence of HSV-2, suggesting that they are more likely to be exposed to the virus during their sexual debut. Since older men tend to seek young women for sexual favours, the risk of transmission and acquiring HSV-2 and HIV-1 is greater in the younger group.¹⁸ Conversely, older women who are chronic HSV-2 carriers have a lower risk of HIV-1 acquisition.

CONCLUSIONS AND RECOMMENDATIONS

Sex workers in our study were at greater risk of HIV infection if they had no evidence of past HSV-2 infection. However, HSV-2 infection during follow-up was associated with high risk of HIV infection. These paradoxical findings may be due to behavioural difference or some other type of interaction which needs further investigation.

These findings have enormous **public health implications** in South Africa and the developing world where infection with HIV-1 and HSV-2 coexist:

- There is an urgent need to recognise HSV-2 infection among populations at risk, especially the young, and to provide treatment and counselling of condom use. Results from a recent study have shown that condoms can effectively reduce HSV-2 transmission.¹⁹
- Identification of new HSV-2 infection in pregnancy may indirectly impact on mother-to-child transmission of HIV-1.
- While rapid tests for HIV-1 and syphilis are available, no such test is available for HSV-2 screening. Priority should be given to the development of rapid HSV-2-specific tests.
- There is a need to integrate HSV-2 and HIV-1 prevention efforts in all countries at risk of increasing HIV-1 infections.
- Intensive efforts and funding are currently invested in the development of an HIV-1 vaccine. This study has shown that equally, there is an urgent need to develop an HSV-2 vaccine in order to curb the spread of both HIV-1 and HSV-2.

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