

Seroepidemiological study of herpes simplex virus type 2 infection in HIV positive patients, Delhi, India, 2007

Abstract

Background: Herpes simplex virus type 2 (HSV-2) infection is the primary cause of genital herpes worldwide and also has potential role in facilitating human immunodeficiency virus (HIV) transmission. **Materials and Methods:** In our analytical cross-sectional study we interviewed and collected serum samples from 91 HIV positive subjects coming to antiretroviral therapy center at a government hospital in Delhi, to determine the seroprevalence and relative prevalence of HSV-2 among subjects with specific risk attributes. The patients were interviewed using a structured questionnaire and their serum samples were tested for HSV-2 specific immunoglobulin G (IgG) antibodies. We compared prevalence of HSV-2 antibodies between exposed and unexposed; to demographic, socioeconomic, and behavioral variables. **Results:** Fifty-two (57.1%) male and 39 (42.9%) female HIV positive subjects participated in the study. Seroprevalence of HSV-2 was 48.4% (males: 51.9% and females: 43.6%). Only 4.5% had given current history of genital ulcer. Overall increasing number of lifetime sexual partners showed significant association with HSV-2 seropositivity (Chi-square for trend: 19.17; $P = 0.00001$). Among men sexual contact with commercial sex workers (prevalence ratio (PR) = 6.6; 95% confidence interval (CI) = 1.76-24.83; $P = 0.0002$) and age at first sexual intercourse < 19 years (PR = 2.3; 95% CI = 0.98-5.6; $P = 0.021$) were significantly associated with HSV-2 seropositivity. Use of condom during sexual intercourse among men, showed significant protective effect (PR = 0.57; 95% CI = 0.356-0.902; $P = 0.037$). Among women history of past genital ulcer was significantly associated (PR = 2.25; 95% CI = 1.14-4.45; $P = 0.026$) with HSV-2 seropositivity. **Conclusions:** The prevalence of HSV-2 is high in the study group with high proportions of undiagnosed HSV-2 infections. HSV type-specific serological testing in the HIV infected subpopulation should be used to diagnose HSV-2 infections and high risk groups should be targeted for interventions like behavioral intervention messages. Consistent condom use should be promoted.

Key words: Genital herpes, herpes simplex virus type 2, human immunodeficiency virus

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INTRODUCTION

The HIV/AIDS is now almost 30 years old and in these 30 years, millions of people have been infected by human immunodeficiency virus (HIV). Herpes simplex virus type 2 (HSV-2) infection is one of the many infections that is impacting this HIV/AIDS epidemic.

Herpes simplex virus type 2 (HSV-2) infection is the primary cause of genital herpes and its prevalence is increasing worldwide.^[1-3] There is currently very little data available on HSV2 prevalence in different parts of the world; including Asia, South America, and Africa. The HSV-2 incidence data are also scarce.^[4-6] The public health importance of HSV-2 relates to its potential role in facilitating HIV transmission. There is increasing evidence that HSV-2 facilitates HIV transmission.^[7] A prospective study among heterosexual HIV-1 discordant couples in Rakai, Uganda, found that genital ulcer disease in the HIV-1-infected partner, primarily resulting from HSV-2, was associated with a four-fold increase in the likelihood of HIV-1 transmission.^[8] Also in countries where coinfection with HIV and HSV-2 is common, the significance of HSV-2 as a cause of ulceration has probably been underestimated.^[9]

The HSV-2 ulceration that occurs in HIV infected individuals is frequently atypical, severe, and persistent.^[10]

Given this, an approach to impacting HIV/AIDS epidemic may be to consider HSV-2 serostatus among HIV positive subjects, for the implementation of available HSV-2 control methods and the development of vaccines for HSV-2.^[9,11,12]

Seroepidemiological studies are critical to understand the pattern and distribution of HSV-2 infection within populations^[9] and help generate evidence for target (focused prevention) efforts to lower HSV-2 risk factors.

The aim of the present study was to determine the seroprevalence of HSV-2 and its association with age, sex, as well as other demographic and behavioral factors among HIV-positive patients from antiretroviral therapy center of a government hospital in the city of New Delhi, India.

Objectives

1. To estimate the seroprevalence of HSV-2 antibodies among HIV positive patients attending an antiretroviral therapy (ART) center in Delhi, India, 2007.
2. To estimate the relative prevalence of HSV-2 infection among HIV positive patients with specific characteristics attending an ART center in Delhi, India, 2007.

MATERIALS AND METHODS

In our analytical cross-sectional study we interviewed and collected serum samples from 91 HIV positive subjects coming to ART center of a government hospital in Delhi, to determine the seroprevalence and relative prevalence of HSV-2 among subjects with specific risk attributes. The patients were interviewed using a structured questionnaire and their serum samples were tested for HSV-2 specific IgG antibodies. We compared prevalence of HSV-2 antibodies between exposed and unexposed; to demographic, socioeconomic, and behavioral variables.

RESULTS

During the study period we interviewed 98 HIV positive patients who attended the ART clinic and out of these 91 (92.9%) agreed to participate in the study. The overall prevalence of HSV-2 antibodies among these HIV positive subjects was 48.4% (95% confidence interval (CI): 37.7-59.1) [Table 1]. Seroprevalence was 51.9% (95% CI: 37.6-66.0) among men and 43.6% (95% CI: 27.8-60.4) among women [Table 2].

Lifetime duration of sexual activity, educational status, gender, income status, marital status, and occupation did not appear to be associated with HSV-2 serostatus [Table 3].

With regard to exposure category having past history of genital ulcer was significantly associated with HSV-2 seropositivity (prevalence ratio (PR): 2.25; 95% CI: 1.14-4.45; $P = 0.026$) among the male subjects. 4.5% of HSV-2 positive subjects had given current

Table 1: Prevalence of herpes simplex virus-2 (HSV-2) among HIV positive subjects

HSV-2 status	Frequency	Percentage	95% confidence limits
Positive	44	48.4	37.7-59.1
Negative	47	51.6	40.9-62.3
Total	91	100.0	

HSV=Herpes simplex virus, HIV=human immunodeficiency virus. Cross-sectional analytical study, Delhi, India, 2007

Table 2: Sociodemographic characteristics of study population

Variables	HSV-2 positive n (%)	HSV-2 negative n (%)	Total n (%)
Occupation			
Service	13 (29.5)	18 (38.3)	31 (34.1)
Labor	10 (22.7)	5 (10.6)	15 (16.5)
Others	21 (47.7)	24 (51.1)	45 (49.5)
Religion			
Hindu	43 (97.7)	43 (91.5)	86 (94.5)
Muslim	1 (2.3)	4 (8.5)	05 (5.5)
Education			
Illiterate	21 (47.7)	17 (36.2)	38 (41.8)
Primary school	7 (15.9)	10 (21.3)	17 (18.7)
High school	15 (34.1)	18 (38.3)	33 (36.3)
College	1 (2.3)	2 (4.3)	03 (3.3)
Marital status			
Married	42 (95.5)	45 (95.7)	87 (95.6)
Unmarried	1 (2.3)	0	01 (1.1)
Divorced	1 (2.3)	2 (4.3)	03 (3.3)
Sex			
Male	27 (61.4)	25 (53.2)	52 (57.1)
Female	17 (38.6)	22 (46.8)	39 (42.9)
Monthly family income			
<2,000	1 (2.3)	5 (10.6)	6 (6.6)
2,000-5,000	26 (59.1)	29 (61.7)	55 (60.4)
5,000-10,000	13 (29.5)	11 (23.4)	24 (26.4)
10,000-15,000	4 (9.1)	2 (4.3)	6 (6.6)
>15,000	0	0	0
Age group (years)			
0-14	0	0	0
15-24	2 (4.5)	0	2 (2.2)
25-34	36 (81.8)	40 (85.1)	76 (83.5)
35+	6 (13.6)	7 (14.9)	13 (14.3)

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history of genital ulcer, but was not significantly associated with the HSV-2 positivity ($P = 0.23$) [Table 4]. 59.1% of the HSV-2 positive subjects were those who gave no past history of genital ulcer [Table 4]. 84.1% of the HSV-2 positive subjects had first sexual intercourse before 19 years of age and was significantly associated with HSV-2 positivity (PR: 2.33; 95% CI: 0.98-5.6; $P = 0.021$) among men [Table 4].

The overall prevalence of condom use among males was 75%

Table 3: Sexual risk behavior of participants in the study

Variables n (%)	HSV-2 positive n (%)	HSV-2 negative n (%)	Total
History of genital ulcer in the past			
Yes	18 (40.9)	8 (17)	26 (28.6)
No	26 (59.1)	39 (83)	65 (71.4)
Currently suffering from any genital ulcer disease			
Yes	2 (4.5)	0	2 (2.2)
No	42 (95.5)	47 (100)	89 (97.8)
Age at first sexual intercourse			
<19	37 (84.1)	30 (63.8)	67 (73.6)
≥19	7 (15.9)	17 (36.2)	24 (26.4)
Use of condom during sexual intercourse (Male)			
Yes	17 (63)	22 (88)	39 (75)
No	10 (37)	3 (12)	13 (25)
Partner condom use (Female)			
Yes	8 (47.1)	16 (72.7)	24 (61.5)
No	9 (52.9)	6 (27.3)	15 (38.5)
Frequency of condom use (male+partner condom use female)			
Always/regular	12 (34.3)	17 (41.5)	29 (38.2)
Occasional	13 (37.1)	21 (51.2)	34 (44.7)
Never	10 (28.6)	3 (7.3)	13 (17.1)
Number of lifetime sexual partners			
≥3	28 (63.6)	11 (23.4)	39 (42.9)
<3	16 (36.4)	36 (76.6)	52 (57.1)
Life time duration of sexual activity			
>10	30 (68.2)	33 (70.2)	63 (69.2)
≤10	14 (31.8)	14 (29.8)	28 (30.8)
Sexual contact with commercial sex workers			
Yes	25 (56.8)	9 (19.1)	34 (37.4)
No	19 (43.2)	38 (80.9)	57 (62.6)
Men having Sex with men			
Yes	9 (33.3)	1 (4)	10 (19.2)
No	18 (66.7)	24 (96)	42 (81.8)

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and prevalence of condom use among HSV-2 positive males was 63%. Use of condom during sexual intercourse by male subjects showed significant protective effect (PR: 0.57; 95% CI: 0.356-0.902; $P = 0.037$) against HSV-2 infection [Table 4]. Use of condom by sexual partners of females showed a protective effect (PR: 0.56) against HSV-2 infection, but was not significantly associated ($P = 0.097$) [Table 4]. Always/regular use of condom was found to be protective as compared to occasional/never use of condom although the association was not statistically significant. (PR: 0.73; 95% CI: 0.45-1.19; $P = 0.17$) [Table 4]. In the present study 34.3% of the HSV-2 positive subjects or their partners always used condoms, 37.1% were those who used condoms occasionally, and 28.6% had never used [Table 3]. 63.6% of the HSV-2 positive subjects had ≥3 sexual partners in their lifetime and were having 2.3-fold higher risk for HSV-2

infection than those with <3 sexual partners in lifetime (PR: 2.3; 95% CI: 1.483-3.669; $P = 0.0001$). Lifetime number of sexual partners was also significantly associated with HSV-2 positivity on analysis for linear trend showing increasing prevalence ratio with increasing number of sexual partners. (Chi-square for trend: 19.17; $P = 0.00001$) [Table 5].

56.8% of the HSV-2 positive male subjects, have had sexual contact with commercial sex worker and were having 6.6 fold higher risk of acquiring HSV-2 infection than those who did not have sexual contact with commercial sex worker (PR: 6.6; 95% CI: 1.76-24.83; $P = 0.0002$) [Table 4].

DISCUSSION

The HSV-2 seroprevalence of 48.4% was observed in our study population, which is higher than that reported in antenatal clinic attendee's (7.9%; mean age: 24.9 years), and also higher than the crude prevalence rates observed among males (10.2%; mean age: 31.4 years) and females (14.6%; mean age: 30.9 years) in India,^[9] supporting the strong association between the two infections. World over the prevalence is higher in women compared with men, especially among the young.^[13] In our study Seroprevalence was slightly higher among men 51.9% than women 43.6% but was not significant ($p = 0.28$). HIV-HSV-2 coinfecting patients may be a common source of horizontal or vertical HSV-2 transmission. Moreover, these HIV-HSV-2 coinfecting individuals may constitute subpopulations at high risk for HIV transmission to HIV-negative exposed individuals for HSV-2 increases the risk of acquiring HIV by three times and of transmitting HIV.^[14]

HIV-1-infected persons have high rates of HSV-2 infection, ranging from 50 to 90% in studies of HIV-infected populations from different parts of the world.^[15]

The prevalence of HSV-2 antibody was 40.22% in 276 patients of genital ulcers in sexually-transmitted disease (STD) patients in Nagpur.^[16] There is wide variation seen among the prevalence rates among STD clinic attendee's in different parts of the country. The prevalence rate ranges from 20.5% in Chandigarh,^[17] 43% in Pune,^[18] to 85% in a hospital in south India.^[19]

There is very limited data on prevalence of HSV-2 among HIV patients in India. The prevalence of genital herpes among HIV patients was 28.8% in a study among STD clinic patients in JIPMER, Pondicherry.^[20] The prevalence was 20% among HIV/AIDS patients at STD Department, Government Mohan Kumar Mangalam Medical College Hospital, Salem.^[21] These rates are lower than that observed in our study.

World over the prevalence is higher in women compared with men, especially among the young.^[1,4,14] In our study seroprevalence was slightly higher among men (51.9%) than women (43.6%), but was not significant ($P = 0.28$). However, when man having sex with man (MSM) were excluded, the seroprevalence was 42.9%

Table 4: Prevalence of herpes simplex virus-2 among HIV positive subjects, according to selected characteristics

	Prevalence of HSV-2						Prevalence ratio	95% confidence interval (<i>P</i> -value from Fisher's exact test)
	Among exposed			Among unexposed				
	<i>n</i>	Total HIV +ve	Percentage	<i>n</i>	Total HIV +ve	Percentage		
History of genital ulcer in the past (yes or no)								
M	9	13	69.2	18	39	46.2	1.5	0.91-2.46 (0.13)
F	9	13	69.2	8	26	30.8	2.25	1.14-4.45 (0.026)
Currently suffering from genital ulcer disease (yes or no)	2	2	100	42	89	47.2	2.12	1.7-2.64 (0.23)
Age at first sexual intercourse (<19 or ≥19)								
M	23	37	62.2	4	15	26.7	2.33	0.98-5.6 (0.021)
F	14	30	46.7	3	9	33.3	1.4	0.51-3.81 (0.38)
Use of condom during sexual intercourse (male; yes or no)	17	39	43.6	10	13	76.9	0.57	0.36-0.902 (0.037)
Frequency of condom use (always/regular vs occasional/never)	22	53	41.5	13	23	56.5	0.73	0.45-1.19 (0.17)
Number of lifetime sexual partners (>3 or <3)								
M	21	30	70	6	22	27.3	2.57	1.25-5.28 (0.002)
F	7	9	77.8	10	30	33.3	2.33	1.26-4.32 (0.024)
Lifetime duration of sexual activity (>10 or <10 years)	30	63	47.6	14	28	50	0.95	0.61-1.5 (-0.506)
Sexual contact with commercial sex workers (males; yes or no)	25	34	73.5	2	18	11.1	6.6	1.76-24.83 (-0.0002)
Men having sex with men (yes or no)	9	10	90	18	42	42.9	2.1	1.4-3.15 (-0.008)

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Table 5: Increasing prevalence of herpes simplex virus-2 (HSV-2) antibodies among HIV positive subjects with the increase in total number of sexual partners in lifetime

Total no. of sexual partners in lifetime	HSV-2 status		Prevalence ratio
	Positive n (%)	Negative n (%)	
1	5 (11.4)	25 (53.2)	0.21
2	11 (25.0)	11 (23.4)	1.07
3	15 (34.1)	8 (17.0)	2.01
4	2 (4.5)	1 (2.1)	2.14
5	9 (20.5)	2 (4.3)	4.77
7	2 (4.5)	0 (0.0)	∞
Total	44 (100.0)	47 (100.0%)	
Chi-square for trend analysis	Probability		
19.17	0.00001		

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among men which was slightly lower than in women, but was not significantly associated (*P* = 0.56).

Infection has been associated with younger age at first sex,^[22] increased years of sexual activity,^[23] and increasing number of lifetime partners.^[1,4,14,22,24] In our study, increasing number of lifetime sexual partners was significantly associated with HSV-2 seropositive status (Chi-square for trend: 19.17; *P* = 0.00001) [Table 5]. 63.6% of

the HSV-2 positive subjects had ≥3 sexual partners in their lifetime and were having 2.30-fold higher risk for HSV-2 infection than those with <3 sexual partners in lifetime.

Also, among male participants younger age at first sex was significantly associated with HSV-2 positivity. In our study, there was no association between increasing years of sexual activity and HSV-2 positive status.

History of genital herpes was obtained from 40.9% of the HSV-2 positive subjects, which indicates that a major proportion of the patients were unaware of the HSV-2 infection, suggesting that although HSV-2 antibodies were quite frequent in the study population, clinical expression of the infection was rather uncommon.

This finding is in accordance with other reports,^[25] confirming that clinical information greatly underestimates the prevalence of HSV-2 disease and underscores the importance of teaching these patients how to identify the episodes of active genital herpes and counseling them to seek healthcare for genital signs and symptoms.

Condom use offers significant protection against HSV-2 infection in susceptible subjects^[26] and in our study use of condom during sexual intercourse by male subjects showed significant protective effect (PR: 0.57; 95% CI: 0.356-0.902; *P* = 0.037) against HSV-2 infection. The prevalence of condom use among HSV-2 positive males was 63% which was lower than overall rate of 75% among HIV subjects. Considering this, more efforts or interventions are

needed to promote higher usage of condoms.

Sexual contact with commercial sex workers (CSW) is a potential risk factor that influences HSV-2 transmission rates.^[27] In our study, we found strong association between HSV-2 positivity and sexual contact with CSW ($P = 0.0002$) HSV-2 positive male subjects who have had sexual contact with CSW were having 6.6-fold higher risk of acquiring HSV-2 infection than those who did not.

We recognized some limitations to our study. The results were based on cross-sectional data from HIV-positive patients representing the more severe forms of the clinical spectrum of the disease. Nevertheless, HSV infection is thought to precede and might increase the odds of HIV infection. As a result of the interaction of those infections, the frequency and severity of genital herpes and virus shedding may be modified.

In addition to that limitation, current data are based on HIV-positive patients selected from a public hospital and may not have been representative of the HIV-positive population of the Delhi. These selection factors limit the generalizability of the estimates of HSV 2 infection rates.

This was an exploratory study based on data available from a limited number of patients. Failure of patients to provide accurate information to questions related to sexual behavior may have biased our estimates as nondifferential misclassification is more likely.

However, our study has recorded very high rate of HSV-2 infection, which may affect the natural history of HIV/AIDS and enhance the transmissibility of both virus. Further studies should clarify the implications of the coinfection for HIV patients follow-up and prognosis.

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