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Incidence, Prevalence and Epidemiology of Herpes Simplex Virus-2 in HIV-1-positive and HIV-1-negative Adolescents

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Abstract

Background—Several studies have assessed risk factors associated with herpes simplex virus-2 (HSV-2) prevalence in adults; however, few have focused on HSV-2 incidence, particularly in adolescents. The objective of this study was to determine HSV-2 prevalence and incidence and associated risk factors in a HIV-1-positive and at risk HIV-1-negative adolescent population.

Methods—Sera were tested for HSV-2 antibodies in 518 adolescents in the Reaching for Excellence in Adolescent Care and Health (REACH) cohort at baseline and again at the final follow-up visit. Prevalence at baseline and incidence (per person years) of HSV-2 infection were calculated. Furthermore, among HIV-1-positive individuals, a subgroup analysis was performed to assess risk factors for HSV-2 infection. Conditional logistic regression was used to estimate odds ratios (OR) and p-values (p) for associations between CD4+ T-cell (CD4+) count, HIV-1 viral load (VL), and HSV-2 acquisition, adjusting for antiretroviral therapy use, other sexually transmitted infections, gender, race, and number of sexual partners.

Results—At baseline, 179 (35%) subjects were HSV-2 positive, with an additional 47 (16%) new cases being identified during a median follow-up time of 1.95 years and an incidence rate of 7.35 cases per 100 person years (py). Several risk factors were associated with HSV-2 prevalence (being female, non-Hispanic, uncertainty of sexual preference, and HIV-1 positive) and incidence (using drugs, alcohol, and number of new sexual partners). Among HIV-1 positives, an increase in CD4+ count by 50 cell/mm^3 (OR, 1.17; 95% CI 1.04–1.31, p=0.008) was associated with HSV-2 acquisition.

Conclusions—The high prevalence and incidence of HSV-2 infection among adolescents, compared to the general population at this age group suggests a critical need for screening and preventive programs among this targeted group.

Keywords

HIV-1; HSV-2; CD4+ count; adolescents

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Introduction

Herpes simplex virus type 2 (HSV-2) is one of the most prevalent sexually transmitted infections worldwide and is the cause of most genital herpes.[1] The NHANES III survey showed that 16.2% of individuals 14 years and older were HSV-2 seropositive.[2] The public-health significance of HSV-2 infection is tremendous, with an estimated annual direct medical cost of $984 million in the United States (U.S.).[3] In adults, HSV-2 prevalence is associated with lower socioeconomic status, multiple sex partners, younger age at first intercourse, previous history of sexually transmitted infections (STIs), geography, race, and gender;[4–6] however, few studies have examined factors associated with HSV-2 incidence specifically within adolescents.

Co-infections of HSV-2 and HIV-1 are common as the two infections share many of the same risk factors. Immunosuppressed patients infected with HSV-2 have more frequent, severe, and persistent recurrences.[4, 7] Among HIV-1 infected individuals in the U.S., 60–70% are estimated to be seropositive for HSV-2 in general, and the prevalence is even higher, up to 80–95%, among African Americans.[4]

A clear association has been established between HSV-2 and HIV-1.[8–12] However, most studies are cross-sectional and do not evaluate the temporal order of HSV-2 and HIV-1 infection. Longitudinal studies have shown that HSV-2 infection is associated with HIV-1 acquisition, but little is known about the acquisition of HSV-2 among HIV-1 infected individuals. Assessing this relationship is important because HIV infected persons with HSV-2 co-infections may be more likely to transmit HIV than those without co-infection. Therefore, in this study, we evaluated risk factors for prevalent and incident HSV-2 infections in both HIV-1-positive and HIV-1-negative adolescents.”

Methods

Study Population

Participants from the Reaching for Excellence in Adolescent Care and Health (REACH) cohort were included in this study.[13, 14] Between 1996 and 2000, adolescents who acquired HIV-1 through risk behaviors, mainly sexual activities (perinatal transmission or blood product contamination were excluded), and comparable seronegative adolescents (aged 12–19 years) were recruited into a longitudinal study at 15 clinical sites in the U.S. to investigate the natural history of HIV-1.[13] The study design and methods for quarterly follow up, HIV-1 testing and viral-load measurement, and immunophenotyping of CD4+ counts, along with demographics, risk behavior, and other clinical data, have been previously described in detail.[13, 14] Serum samples taken at baseline and at the end of follow up were tested for HSV-2 antibodies using a gG-based type-specific immunoblot assay. All tests were performed in the Central Laboratory at the Centers for Disease Control and Prevention in Atlanta.[15, 16] Other STIs, including gonorrhea, Chlamydia, HIV-1 and HPV were also tested at baseline and each semi-annual follow up visit.[17] At the time of the study visit, HAART was defined as a combination of two nucleoside reverse transcriptase inhibitors and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor, or a zidovudine/lamivudine combination regimen plus another antiretroviral drug.

Based on HSV-2 serology at baseline and final visit, subjects were defined as seroprevalent (HSV-2 positive at baseline), seroincident (HSV-2 negative at baseline but seroconverted during follow up), and seronegative (HSV-2 negative at baseline and throughout follow up) cases. HIV-1 serostatus was assessed at each semi-annual visit and there were no HIV-1 seroconverters included in this analysis.

Statistical Analysis

HSV-2 prevalence was calculated as the proportion of seroprevalent cases in the total population at baseline. HSV-2 incidence (100 py) was calculated using the number of seroincident cases divided by the total follow-up time for both seroincident and seronegative cases; baseline seroprevalent cases were excluded from this calculation. Assuming that all missing data were at random, Markov chain Monte Carlo (MCMC) methods were used to impute CD4+ count (1% missing), viral load (14%), sexual partners (2%), days since HIV-1 diagnosis (22%), and anal HPV (19%) using follow-up time, gender, age, race, and HSV-2 status to increase power. Co-linearity between variables was assessed with all variables in general using Pearson's and Spearman's rank tests as appropriate. The r^2 values were significant only for two variables: "ever taken ART medications prior to the study" and "currently taking ART medications" (r^2=0.72). The correlation between these variables is expected, and "currently taking ART medications" was used in the model since it better explains current CD4+ count and HIV-1 viral load.

For the first part of the primary analysis, demographic characteristics and baseline clinical parameters known to be associated with HSV-2 infection were compared between seroprevalent cases and HSV-2 negative individuals at baseline (which included both seronegative and seroincident cases at the end of the study). Then, in the second part, using the follow-up data, seroincident and seronegative cases were compared to evaluate selected risk associations between the seroprevalent and seroincident cases. Based on multiple follow-up–visit data and excluding the baseline visit, a cumulative variable "ever during follow-up" was created for gonorrhea, chlamydia, anal HPV, survival sex (traded sex for food housing or drugs), engaged in receptive anal sex, homeless, smoked cigarettes, had ever drank alcohol, and used drugs. Total new sexual partners during follow up were calculated, as well as median CD4+ count. HSV-2 seroprevalent and HSV-2 seronegative at baseline and HSV-2 seronegative and HSV-2 seroincident at end of follow up characteristics were compared using t-test, chi-square, or Fisher exact tests as appropriate. Risk factors that were significant ($p<0.10$) in the univariable analysis were included in the multivariable logistic regression.

Since the majority of the HSV-2 incident cases occurred in HIV-1-positive individuals, a subset analysis was performed on HIV-1-positive HSV-2-seroincident versus HIV-1-positive HSV-2-seronegative adolescents. For this analysis we used a matched case-control design wherein cases were defined as being seroincident for HSV-2, and controls were seronegative for HSV-2 at the end of follow up. Two controls were matched for each case based on follow-up time (± 90 days), which allowed the cases and the controls an equal amount of time to acquire HSV-2. Demographic characteristics and clinical parameters known to be associated with HSV-2 acquisition were compared between cases and controls, assessing potential differences through paired t-tests and McNemar's chi-square. Since the actual date of HSV-2 acquisition is unknown, baseline characteristics were used. Conditional logistic regression was used to estimate odds ratios (ORs) and associated 95% confidence intervals (95% CIs) for the association between CD4+ count (increment of 50 cells/mm^3), HIV-1 viral load (log transformed), and HSV-2 acquisition. Other potential risk factors, such as antiretroviral therapy (ART) use, HAART use, other STIs, gender, race, and number of sexual partners also were assessed and adjusted in the models.

Results

Five hundred and thirteen adolescents (386 females and 127 males) with baseline and end of follow up HSV-2 serology data were included in this study. Of the eligible participants, 343 were HIV-1 seropositive, and 170 were HIV-1 seronegative. At baseline, prevalent HSV-2 infection was present in 179 (35%), and 47 (16%) incident cases were identified during a

median follow-up period of 1.95 years, resulting in an incidence of 7.35 cases/100 py. Incidence rates tended to be higher among females (7.70 vs. 6.64/100 py), African Americans (7.62 vs. 6.89/100 py), and HIV-1-positive participants (8.50 vs. 5.58/100 py); however, none of these differences were statistically significant.

Persons with prevalent HSV-2 infection were more likely to be heterosexual (81% vs. 69%), female (91% vs. 67%), black non-Hispanic (78% vs. 64%), HIV-1 positive (82% vs. 59%), and co-infected with chlamydia (25% vs. 16%). Perhaps surprisingly, fewer HSV-2 infected participants reported smoking cigarettes (47% vs. 59%) than HSV-2-negative subjects; however, 58% of HSV-2 seronegativs at baseline who reported smoking became HSV-2 seropositive at the end of the study (Table 1). In the multivariable model, being female (OR, 7.46; 95% CI, 3.12–17.83), HIV-1 positive (OR, 2.94; 95% CI, 1.75–4.96), uncertainty of sexual preference (OR, 3.87; 95% CI 1.31–11.42), and being Hispanic (OR, 0.42; 95% CI, 0.21–0.84) ethnicity remained significantly different between seroprevalent and seronegative persons (Table 2).

Likewise, upon comparison of HSV-2 incident cases and HSV-2 seronegatives, the seroincident subjects were older (19.4 vs. 18.8 years), and during follow-up, were more likely to have been infected with gonorrhea (21% vs. 9%), had ever consumed alcohol (51% vs. 32%), used drugs (57% vs. 37%), or had a greater number of sexual partners (mean 6.57 vs. 3.44) than HSV-2-seronegative subjects (Table 1). In the multivariable model, only having used drugs during the follow-up time (OR, 2.31; 95% CI, 1.23–4.34)) remained significantly different between seroincident and seronegative persons (Table 2).

A total of 197 (57%) of HIV-1-positive adolescents (124 females and 73 males) had negative HSV-2 serology at the time the study was started and of these, 33 tested HSV-2 positive during follow up. For the case-control analysis, the 33 HIV-1 infected persons who acquired HSV-2 were matched to 63 of the HIV-1-positive/HSV-2-negative individuals who had been followed an average of 940.36 and 906.89 days, respectively. Baseline sociodemographic and clinical characteristics are shown in Table 3. Cases and controls did not differ by age, gender, race, or the presence of other STIs. In the univariable analysis, compared to the controls, cases were more likely to have engaged in survival sex (15.2% vs. 3.2%), had higher CD4+ counts (568.9 vs. 451.4 cells/mm^3), and had lower HIV-1 viral loads (3.5 vs. 3.9 Log VL) at baseline (Table 3). The controls tended to be more likely to be on HAART than cases, although the numbers are small. In the multivariable model, CD4+ count increase by 50 cell/mm^3 (OR, 1.17; 95% CI 1.04–1.31) remained significantly different between cases and controls.

Discussion

HSV-2 prevalence rates were higher in the REACH cohort (35%) compared to adolescents (1.6%) of similar age (14–19) from NHANES, during the study period.[18] Most factors associated with HSV-2 seroprevalence at study baseline are similar to those reported in previous studies. As in prior studies, the prevalence was relatively higher (39%) among black non-Hispanics than among Hispanics (21%). In the most recent data from NHANES III, overall HSV-2 seroprevalence was 39.2% in black non-Hispanics (48% in women vs. 29% in men) as compared to 12.3% (15.9% in women and 8.7% in men) in white non-Hispanics and 10.1% (13.2% in women and 7.5% in men) in Mexican Americans,[2] similar to rates in suburban primary care offices.[19] HSV-2-prevalent individuals were also more likely to be females (r^2, 0.53 with being heterosexual) and HIV-1 positive. The cohort is comprised of 76% females and a stratified analysis by gender could not be conducted due to limited power; however a sensitivity analysis among females showed similar results to those presented in this study (data not shown). Adolescents who reported to be unsure of their

sexual preference were also likely to be HSV-2 seroprevalent. These individuals were more likely to be HIV-positive, engage in anal sex, and be involved in survival sex and had a higher number of sex-partners which could indicate that they were engaging in sexual acts to help determine their sexuality (data not shown).

Despite the high initial prevalence of HSV-2 among participants, HSV-2 incidence rates were high in the REACH cohort (7.35 per 100 py) compared to the general U.S. population (0.18 per 100 py)[18]; however, it was at the lower end of what has been reported in some special populations. These estimates of HSV-2 incidence are conservative since HSV-2 was tested only at two visits, the first and last, and thus the actual date of seroconversion was likely sooner than the date of the final follow-up visit. Among HIV-1-negative individuals attending U.S. STD clinics (RESPECT cohort), an incidence of 11.7 per 100py was reported.[20] Likewise, studies among women attending STD clinics in the U.S. have reported incidence ranging from 5.7–20.5 per 100 woman years[21, 22] and similarly 4.9–14.2 per 100 person years in other populations.[6, 23, 24]

Factors associated with HSV-2 seroprevalence at baseline differed from factors associated with HSV-2 seroincidence. HSV-2-seroprevalent cases differed demographically, such as with race and gender, and risk behaviors such as sexual preferences, and HIV status from HSV-2-seronegative individuals at baseline. Persons who experienced HSV-2-seroincidence during follow up were more likely to report drug use and a higher numbers of new sexual partners when compared to individuals who remained HSV-2-seronegative. Seroincident cases were more likely to be HIV-1-seropositive, and the trend was similar for drug use and co-infection with gonorrhea as in seroprevalent individuals. Having only had such data at the time of initial evaluation and at the end of the follow-up period, we acknowledge the lack of precision in our evaluation of time-dependent factors. Here, we used the baseline measurements for the prevalence study; but for the seroincident study, we either could only ascertain variables such as drug and alcohol use cumulatively for all follow-up visits or used the data reported at the time of the last visit. Future studies should assess HSV-2 serology at each visit to correspond to the risk factor at respective visits.

In the subset analysis of HIV-1-positive individuals who acquired HSV-2 during follow-up, persons with higher CD4+ counts at baseline were more likely to acquire HSV-2 than those with lower CD4+ counts at baseline. Likewise, lower viral load was associated with HSV-2 acquisition, but only CD4+ was significant in the multivariable analysis. CD4+ count is a strong indicator of the disease state and health of HIV-1-positive patient. The relatively healthy adolescents in the REACH study, as indicated by higher CD4+ counts, might also be more physically active than the sicker ones and therefore more likely to engage in risk behaviors, making them susceptible to HSV-2, as seen in other STI studies.[25, 26]. These results are similar to a follow-up study done in San Francisco and elsewhere, showing that HIV-1-positive individuals on HAART were more likely to develop an STD compared to those not on HAART.[27,28]

The present study is a multicenter study and unlike other studies from specific clinics or sites, where data may disproportionately represent certain social and sexual networks, our estimates may be more representative for at-risk adolescents in the U.S., in general. Our results indicate that adolescents were engaging in activities that made them susceptible to HSV-2 infection even after being infected with HIV-1 and add to the recommendation for continuing risk reduction counseling for persons with HIV, i.e “prevention for positives”.

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Table 1

Differences between a) HSV-2 sero-prevalent and HSV-2 negative adolescents at baseline and b) HSV-2 sero-incident and HSV-2 negative adolescents at the end of follow-up.

	a) Baseline			b) End of follow-up		
	HSV-2 negative (n=334)	**HSV-2 positive (n= 179)**	**P**	**HSV-2 negative (n=287)**	**HSV-2 positive (n=47)**	**p**
Female	66.77 (223)	91.06 (163)	**<0.0001**	66.20 (190)	70.21 (33)	0.59
Age[#]	16.76 ± 1.17	16.86 ± 1.12	0.37	18.84±1.55	19.36±1.63	**0.04**
Race/Ethnicity			**0.0014**			0.89
Black	64.07 (214)	77.53 (138)		63.76 (183)	65.96 (31)	
White	5.69 (19)	2.25 (4)		5.92 (17)	4.26 (2)	
Hispanic	23.95 (80)	11.80 (21)		23.76 (68)	25.53 (12)	
Other	6.29 (21)	8.43 (15)		6.62 (19)	4.26 (2)	
Sexual Preference			**<0.0001**			0.47
Heterosexual	69.33 (226)	81.07 (137)		68.68(193)	73.33 (33)	
Bisexual	10.74 (35)	4.73 (8)		10.32 (29)	13.33 (6)	
Homosexual	16.56 (54)	4.73 (8)		17.08 (48)	13.33 (6)	
Not Sure	3.37 (11)	9.47 (16)		3.91 (11)	0	
HIV positive	58.98 (197)	81.56 (146)	**<0.0001**	57.14 (164)	70.21 (33)	0.09
Gonorrhea[*]	7.07 (21)	12.42 (19)	0.06	9.41 (27)	21.28 (10)	**0.02**
Chlamydia[*]	15.72 (47)	25.00 (39)	**0.02**	26.48 (76)	29.79 (14)	0.64
Anal HPV[*]	31.72 (85)	35.82 (48)	0.41	36.24 (104)	46.81 (22)	0.17
Survival Sex[*]	5.99 (20)	3.35 (6)	0.20	7.32 (21)	14.89 (7)	0.08
Number of Sexual Partners at baseline			0.57[†]			0.15[†]
median (IQR)	6 (3, 14)	7 (4, 14)		6 (3, 14)	8.5 (3, 21)	
mean (SD)	13.96 (24.55)	15.54 (30.94)		13.18 (24.32)	18.91 (25.73)	
Engaged in receptive anal sex[*]	36.39 (119)	28.24 (48)	0.07	17.41 (50)	25.53 (12)	0.19
Homeless[*]	23.35 (78)	26.40 (47)	0.44	21.60 (62)	34.04 (16)	0.06
Ever Smoked cigarettes[*]	59.33 (194)	47.06 (80)	**0.009**	80.49 (231)	85.11 (40)	0.45
Ever drank alcohol[*]	71.25 (233)	64.12 (109)	0.10	32.06 (92)	51.06 (24)	**0.01**
Ever used drugs[*]	86.93 (266)	80.26 (122)	0.06	36.93 (106)	57.45 (27)	**0.008**

	a) Baseline			b) End of follow-up		
	HSV-2 negative (n=334)	**HSV-2 positive (n= 179)**	**P**	**HSV-2 negative (n=287)**	**HSV-2 positive (n=47)**	**p**
New sexual partners during follow-up						**0.04**†
median (IQR)				2 (0, 4)	2 (0, 6)	
mean (SD)				3.44±7.98	6.57±15.84	

#Age at baseline and age at end of follow-up;

*ever positive during follow-up (excluding baseline);

† p-value based on median

Table 2

Associations between demographic or risk behavior characteristics and a) prevalence b) incidence of HSV-2 infection. Odds ratios (OR) and 95% CI are estimated.

	a) Baseline (Odds Ratio)				b) End of Follow-up (Odds Ratio)			
	Crude	**95% CI**	**Adjusted**	**95% CI**	**Crude**	**95% CI**	**Adjusted**	**95% CI**
Female	5.07	(2.89, 8.89)	**7.46**	**(3.12, 17.83)**				
Race Ethnicity								
Black	1.89	(1.25, 2.86)						
White	0.38	(0.13, 1.13)						
Hispanic	0.43	(0.25, 0.71)	**0.42**	**(0.21, 0.84)**				
Other	1.36	(0.68, 2.72)						
Sexual Preference								
Not Sure	2.88	(1.31, 6.35)	**3.87**	**(1.31, 11.42)**				
Bisexual	0.24	(0.11, 0.52)						
Homosexual	0.40	(0.18, 0.88)						
Heterosexual	1.56	(1.03, 2.36)						
HIV positive	3.20	(2.06, 4.96)	**2.94**	**(1.75, 4.96)**	1.77	(0.91, 3.45)		
Gonorrhea*	1.86	(0.97, 3.58)			2.60	(1.17, 5.81)		
Chlamydia*	1.79	(1.11, 2.88)						
Engaged in receptive anal sex*	0.69	(0.46, 1.03)						
Ever Smoked cigarettes*	0.61	(0.42, 0.89)						
Ever used drugs*	0.61	(0.36, 1.03)			2.31	(1.23, 4.31)	**2.31**	**(1.23, 4.34)**
Age at end of study					1.24	(1.01, 1.52)		
Survival sex*					2.22	(0.89, 5.55)		
Homeless*					1.87	(0.96, 3.64)		
Ever used Alcohol					2.21	(1.19, 4.13)		
Cumulative new partners					1.02	(0.99, 1.05)		

* ever positive during follow-up (excluding baseline)

Table 3

Differences in demographic and risk behavior characteristics between HIV-1 positive HSV-2 incident cases and HSV-2 negative controls

	Controls (n=63)	Cases (n=33)	p
Females	65.1 (41)	72.7 (24)	0.4652
Age	16.9 ± 0.9	16.8 ± 1.3	0.4280
Race			0.42
Black/non-Hispanic	58.73 (37)	66.67 (22)	
White/non-Hispanic	6.35 (4)	3.03 (1)	
Hispanic	26.98 (17)	27.27 (9)	
Other/Non-Hispanic	7.94 (5)	3.03 (1)	
Follow-up time (days)	906.9 ± 376.4	940.4 ± 405.4	0.9066
Anal HPV	33.3 (21)	34.3 (11)	1.00
Any STI (Chlamydia, Gonorrhea, HPV)	61.9 (39)	69.7 (23)	0.4652
Survival Sex	3.2 (2)	15.2 (5)	**0.0209**
Number of Sexual Partners			0.2556†
Median (IQR)	7 (3, 18)	10 (3, 22)	
Mean (SD)	14.6 ± 21.1	18.8 ± 23.3	
CD4 count cells/mm^3	451.4 ± 236.3	568.9 ± 247.9	**0.0077**
HIV-1 Log Viral Load	3.9 ± 1.0	3.5 ± 0.9	**0.0226**
On HAART	25.4 (16)	12.1 (4)	0.0736
Days since HIV diagnosis	340.5 ± 306.9	301.9 ± 375.7	0.4855
Ever Taken ART meds prior to study			0.0846
No ART was ever taken	41.3 (26)	57.6 (19)	
Mono therapy not a PI	6.4 (4)	9.1 (3)	
Combo therapy without PI	25.4 (16)	15.2 (5)	
Combo therapy with PI	26.9 (17)	18.2 (6)	
Currently taking ART meds			0.0627
No ART was taken	52.4 (33)	63.6 (21)	
Mono therapy not a PI	9.5 (6)	9.1 (3)	
Combo therapy without PI	12.7 (8)	21.2 (7)	
Combo therapy with PI	25.4 (16)	6.1 (2)	

assessed by paired t-test and McNemars' chi-square;

† p-value based on median