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Case-crossover analysis of condom use and HSV-2 acquisition

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Abstract

Background—While growing evidence suggests that condoms offer moderate protection against herpes simplex virus type 2 (HSV-2), inability to control for unknown or unmeasured confounders associated with sexual activity may reduce the accuracy of the estimates. The case-crossover design offers increased control of individual-level confounders, and was thus used with the aim of producing a more accurate estimate of the effect of condom use on HSV-2 acquisition.

Methods—Data were pooled from six prospective studies that measured HSV-2 status at enrollment and over follow-up, and included periodic self-reported condom use and sexual activity. Sexual activity contemporaneous with acquisition was assigned to a case period; earlier sexual activity was assigned to a control period. Conditional logistic regression was used to assess differences in behavior during the case and control periods.

Results—One hundred ninety-one eligible participants acquired HSV-2 during follow-up. This approach detected a 3.6% increase in the odds of HSV-2 acquisition with each unprotected act (odds ratio (OR)=1.036; 95% confidence interval (CI): 1.021, 1.052), but no increase in the odds of acquisition associated with protected acts (OR=1.008; 95% CI: 0.987, 1.030).

Conclusions—This analysis suggests that condoms offer significant protection against HSV-2 transmission.

Keywords

HSV-2; herpes genitalis; herpes simplex; condoms; case-crossover; unprotected sex acts

INTRODUCTION

Despite evidence of the protective effect of condoms for human immunodeficiency virus (HIV) and several sexually transmitted infections (STI),¹ the effectiveness of condoms in

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preventing the transmission of herpes simplex virus type 2 (HSV-2) has been less well established.^{2, 3} Most studies of the protective effect of condoms against HSV-2 transmission have been limited by sample size,^{4, 5} or the use of retrospectively gathered self-reported condom use data among persons with prevalent HSV-2 infections.^{6–9} Nevertheless, most larger prospective studies suggest condoms to be moderately efficacious in preventing HSV-2 transmission.^{10–14} While these studies have benefited from larger samples and prospective data, they have been limited by their inability to control for individual-level characteristics that may be associated with sexual risk behavior.^{2, 11} For example, if participants who consistently use condoms are also more likely to engage in sex with riskier partners, measures of condom effectiveness would be attenuated.¹⁵ The case-crossover design is a method for dealing with unmeasured and unknown confounders: since each case-control set comes from the same person, pairs are perfectly matched on time-invariant factors (e.g., sex, birth year), and closely matched on factors that are likely to vary only slightly (if at all) during the study period (e.g., education, risk tolerance).¹⁶

The case-crossover design is generally applicable to events with short-term risk factors and, as such, case-crossover methodology has been applied to triggers of myocardial infarction, injuries, automobile collisions, and pollution effects.^{17, 18} In the field of sexual behavior, Warner and colleagues estimated the effect of condom use on gonorrhea and chlamydia acquisition, and found a stronger protective effect with case-crossover than with the cohort analysis, suggesting unmeasured confounding when comparing behavior between people.¹⁹

To investigate the effect of condom use on HSV-2 transmission, we applied the case-crossover design to prospective data pooled from several studies measuring both condom use and HSV-2 acquisition.^{20–24} These data were previously pooled and examined using a cohort design comparing condom use in those who acquired HSV-2 versus those who did not.¹¹ Our primary aim was to evaluate the effect of condom use on HSV-2 acquisition risk using a case-crossover analysis and to, secondarily, compare case-crossover and cohort analyses of condom use and HSV-2 acquisition.

MATERIALS AND METHODS

The data for this study were pooled by Martin et al¹¹ from six earlier prospective studies that documented HSV-2 acquisition: Corey et al (Recombinant Vaccine (Partners)),²⁰ Corey et al (Recombinant Vaccine (STI Clinic)),²⁰ Stanberry et al (Glycoprotein-D Vaccine),²⁴ Corey et al (Valacyclovir),²¹ Kamb et al and Gottlieb et al (Project RESPECT),^{10, 22} and Noell et al (Homeless Adolescents).²³ Selection methods have been previously described in full.¹¹ Briefly, studies were eligible for inclusion if they employed a prospective design, measured HSV-2 status at enrollment and over follow-up using serologic, culture or polymerase chain reaction (PCR) testing, and included repeated self-reporting of condom use and sexual activity by either interview^{10, 22, 23} or diaries^{20, 21, 24}.

The case-crossover design required all participants to have at least one control visit during which they remained HSV-2 negative, and a case visit during which they were documented to have acquired HSV-2. This design compares multiple periods of sexual behavior within the same individual, rather than comparing different persons to one another. Thus, participants who did not acquire HSV-2 during follow-up, and those who acquired between their baseline and first follow-up visit were excluded from the analysis. The few study visits in which participants reported more than 7 sexual acts per week were also excluded as, in an analysis involving precise numbers of acts, these persons might be overly influential. We compared characteristics between cases who were included versus excluded using the chi-squared and Wilcoxon rank-sum tests.

We established a range of days during which acquisitions were expected to have occurred based on expected delays between infection and diagnosis, and the time course of conversion:^{25, 26} this period of likely acquisition was assumed to be between 14 and 90 days prior to detection for those whose infections were detected by serology, and between 0 and 60 days prior to detection for those detected by culture. All study visits and their associated sexual behavior were then classified as belonging to either the case period (if sufficient overlap) or control period (all other visits). Models using this classification scheme are labeled “all-visits” models.

We described condom use during case and control periods by 1) using the estimated number of protected and unprotected sexual acts during each period and 2) classifying the period as involving condoms “never”, “sometimes” or “always”. For studies in which condom use was only recorded categorically,^{21, 23, 24} numbers of protected and unprotected acts were estimated based on the midpoint of each condom use category as previously described.¹¹ Classifying periods based on categories of condom use allowed for a sensitivity analysis of the effect of the aforementioned estimation of numbers of protected and unprotected acts.

Conditional logistic regression was used to assess the association between condom use and infection with HSV-2. The primary model included the number of protected acts and the number of unprotected acts as exposure variables. To determine if the effect of condoms differed between men and women, or between members of known HSV-2 discordant couples and those not known to be members of discordant couples (“singles”), we repeated this analysis separately, stratifying by gender and discordant couple status. Regression models yielded ORs for the odds of acquisition for each act of a given type (i.e., protected acts and unprotected acts) and Wald tests were used to test for differences in the ORs for acts of different types.

We tested the sensitivity of the findings to the varying intervals between study visits. In this secondary exposure duration-matched model, rather than including sexual behavior reported at each study visit, we included only behavior occurring within periods of pre-determined length, estimating the number of acts in these periods by interpolation (Figure 1). Case and control periods were determined precisely: 14 to 90 days prior to detection for *case periods* if HSV-2 infection was ultimately detected by serology and 0 to 60 days for those detected by culture. *Control periods* spanned an equal number of earlier days: the first 76 days of follow-up (i.e. 90 minus 14) if detected by serology, or the first 60 days if detected by culture.

For comparison, a cohort analysis was performed on the full sample with logistic regression using generalized estimating equations (GEE). All study participants and all follow-up were included, both cases and controls. Martin performed a similar analysis¹¹, but measured exposure differently. All analyses were performed using Stata 11.1 (StataCorp, College Station, TX).

RESULTS

The original studies included 5,384 participants, of whom 419 (7.8%) acquired HSV-2. Of these 419 cases, 188 (44.9%) were excluded because they acquired the infection during their first visit and therefore had no control period data. Thirty additional participants were excluded as either the date of HSV-2 detection ($n=4$), or sexual behavior over the risk period ($n=26$) was unknown. 10 more participants were excluded due to consistent reports of more than 7 sexual acts per week. Thus, 191 participants (45.6% of those who acquired) were included in our case-crossover analysis. The median age, gender, STI history, and method of HSV-2 detection were similar among included and excluded participants;

however, race, sexual orientation (for men) and source study differed between the two groups (Table 1).

Participants were 14 to 53 years of age (median: 25.0; interquartile range (IQR): 21.0, 32.6); 54.5% were men. 51.3% were white, 40.8% black, 4.7% Hispanic, and 3.1% were of other races or ethnicities. 86.5% of the men were heterosexual; 13.5% were men who have sex with men (MSM). 56.5% of participants were HSV-1 seropositive at baseline and 46.1% reported having ever had a sexually transmitted infection (STI). 94.8% of HSV-2 infections were detected using serologic assays and the remainder by viral culture (Table 1).

Per-person follow-up time ranged from 97 to 748 days (median: 299; IQR: 184, 382) for a total of 57,966 person-days of follow-up. The number of study visits per person ranged from 2 to 13 (median: 4; IQR: 3, 7). The median time between visits was 56 days (IQR: 32, 77). A total of 952 study visits were included, with 264 visits (27.7%) contributing to the case periods, and 688 visits (72.3%) contributing to control periods.

Participants reported from 0 to 80 sexual partners during follow-up, with 43.5% ($n=73$) reporting only one partner during follow-up, 1.8% ($n=3$) reporting no partners, 14.9% ($n=25$) reporting two partners and 39.9% ($n=67$) reporting 3 or more partners during follow-up; data on number of partners were missing for 23 (12.0%) subjects. Most (56.0%) participants reported no new partners; while 13.1%, 6.8% and 24.1% reported one, two, and three or more new partners, respectively, during follow-up.

11,742 sexual acts were reported: 4,380 during case periods and 7,362 during control periods. The median number of acts reported per study visit was 7 (IQR: 2, 16), with 10 acts per visit during case periods (IQR: 3, 21) and 6 acts per visit during control periods (IQR: 2, 14). The median rate of sexual activity was 1.5 acts per week (IQR: 0.6, 2.8), with 1.7 acts per week during case periods (IQR: 0.7, 3.0) and 1.5 acts per week during control periods (IQR: 0.5, 2.7).

Condoms were used in an estimated 29.3% of sexual acts, including 24.3% of case acts and 32.3% of control acts. Summarizing a person's condom use over all case periods and over all control periods separately, we compared each individual's category of condom use in the case and control periods. Of the 181 participants who reported at least one sexual act in both the case and control periods, 104 (57.5%) remained in the same category of condom use during both the case and control periods; 19 (10.5%) were in a category of more frequent condom use during the case period, relative to the control period; and 58 (32.0%) were in a category of less frequent condom use during the case period (Stuart-Maxwell test of marginal homogeneity $P<0.001$) (Table 2).

We found a 3.6% increase in the odds of HSV-2 acquisition with each unprotected act (OR=1.036; 95% CI: 1.021, 1.052). No significant increase in the odds of acquisition was detected for protected acts (OR=1.008; 95% CI: 0.987, 1.030). Thus, the estimated odds of acquiring HSV-2 were significantly lower with a protected act than with an unprotected act (Wald test $P=0.029$) (Table 3a). Similarly, the model based on the categorized condom use estimated a 3.6% increase in the odds of HSV-2 acquisition with every act when condoms were never used (OR=1.036; 95% CI: 1.021, 1.052), a 2.7% increase in the odds of acquisition with each act when condoms were sometimes used (OR=1.027; 95% CI: 1.010, 1.044), and no significant increase in risk when condoms were always used (OR=0.989; 95% CI: 0.957, 1.023) (Table 3b). Neither HSV-1 status, nor the number of partners, nor the number of new partners were explanatory or altered other associations in multivariate analyses.

Gender did not significantly modify the effect on HSV-2 acquisition of either the number of protected acts ($P=0.34$) or the number of unprotected acts ($P=0.48$). However, a difference was noted by discordant couple status (Table 3a). While neither subgroup demonstrated any change in odds of acquisition with protected acts ($P=0.49$), the effect of unprotected acts on acquisition was lower in discordant couples (OR=0.992) relative to the rest of the cohort (OR=1.050; $P=0.004$ for the interaction).

To ascertain that our results were not influenced by the varying duration of case and control periods, we repeated the analysis using the expected number of sexual acts based on exposure duration matching. Results were similar when case and control periods of equal duration were established, with a 2.2% increase in the odds of HSV-2 acquisition associated with each unprotected act (OR=1.022; 95% CI: 1.003, 1.042) and no significant increase in risk detected for protected acts (OR=0.987; 95% CI: 0.954, 1.020); the odds of acquisition were significantly lower with protected than unprotected acts ($P=0.043$). The results of these subgroup analyses and the results of the all-visits and exposure duration-matched models are summarized in Figure 2.

Next, we performed an analysis of the full cohort, including 5,324 participants who did and did not acquire HSV-2 during the follow up. 39 participants (0.7%) were excluded due to reports of more than 7 sexual acts per week, and 21 (0.4%) were excluded due to missing data. We found a 1.3% increase in the odds of HSV-2 acquisition with each unprotected act (OR=1.013, 95% CI: 1.008, 1.018), and no significant change in the odds of acquisition with protected acts (OR=0.998; 95% CI: 0.988, 1.008)(Table 3a). Thus, with each unprotected act the odds of acquisition were observed to increase 1.3% in the cohort analysis; a fraction of the 3.6% increase detected by the case-crossover analysis.

DISCUSSION

Our analysis provides evidence that condoms offer significant protection against HSV-2 acquisition, as the odds of HSV-2 acquisition were significantly lower with protected than unprotected sexual acts. We found a 3.6% increase in the odds of acquisition associated with unprotected acts, and failed to detect a significant increase in the odds of acquisition with protected acts. The similar results obtained with the continuous and categorical measures of condom use suggest that, despite its being sometimes approximated, our continuous measure of condom use can be interpreted with confidence. With the categorical measure of condom use, the odds of acquisition associated with sometimes using condoms fell between the odds associated with never and always using condoms; this dose-response relationship further supports the validity of our findings.

Exposure duration-matched models, used to test the sensitivity of our results to differences in time between study visits, yielded similar results to the models based on all visits. This suggests that our results were not driven by, or sensitive to, differences in the lengths of case and control periods. The stability of the results between the all-visits and exposure duration-matched analyses suggests that changes in risk between control and case periods resulted from changes in sexual risk behavior, rather than differences in exposure periods.

Effects were similar by gender, but not by partnership status: no protective effect of condom use was detected among participants from discordant couple studies. Possible explanations include 1) fewer discordant-couple participants (55 versus 136) may have reduced the precision of estimates, 2) more awareness of outbreaks within discordant couples may have resulted in decreased sexual activity or greater condom use during periods when transmission risk was greatest, 3) social desirability bias may have resulted in exaggerated reports of condom use among participants known to be at risk, and 4) the per act risk of transmission may be lower among stable couples regardless of condom use.²⁷

We evaluated condom use in terms of protected and unprotected acts, rather than proportional condom use (condoms during 100% of sexual acts relative to 0% of acts, for example), as analyses of proportional use assign the same effectiveness to condom use regardless of the number of sex acts. Evaluating condom use in terms of the absolute number of protected and unprotected acts is increasingly seen as offering more meaningful results,²⁸ and the absolute number of unprotected acts has been shown to be a better indicator of STI risk than is condom use proportion.²⁹

The case-crossover design is a strength of our study. Relative to the full cohort analysis, the case-crossover design yielded larger odds ratios for the effect of unprotected acts on acquisition risk (3.6% versus 1.3% increase per unprotected act). In either analytical approach, the confidence interval surrounding the OR for the risk of acquisition with protected acts included 1.0; as an OR of 1.0 corresponds to 100% efficacy, these findings are consistent with but do not demonstrate complete protection. Other strengths of our study include the use of laboratory confirmation of acquisitions, prospective data collection, and the large number of acquisitions observed.

Five factors may have attenuated the observed associations: differences between the timing of detection and the timing of acquisition, reliance on self-report, incomplete knowledge of the HSV-2 status of partners, incorrect condom use and the potential for greater condom use with high risk partners. Uncertainty about the timing of HSV-2 acquisition, relative to the timing of detection, was handled by using windows of time to seroconversion, or time to culture positivity. Uncertainty was also introduced by the infrequent testing schedule. The reliance on self-reported sexual activity and condom use introduces the possibility of measurement error from social desirability bias and poor recall.²⁸ Rose et al,³⁰ for example, reported significant discordance between self-reported condom use and biochemical markers of sperm exposure among female teens and young adults. Since we did not have access to the HSV-2 status of participants' sexual partners, all sexual acts were unrealistically assumed to involve possible HSV-2 exposure. Further, since condoms were probably not always used correctly, our estimate for the protective effect of condoms may be an underestimate. These misclassifications are present in other studies of condom effectiveness, and have the effect of attenuating the observed estimate of condom effectiveness toward the null.^{11, 19} Finally, more frequent use of condoms during high-risk sexual encounters than during low-risk encounters would have inflated the observed risk of acquisition associated with protected acts.

Other limitations of our analyses include having data originally collected for other purposes, the inability to include all observed cases, and the necessity for control periods to precede case periods. As data were pooled from multiple studies, condom use measurements and HSV-2 diagnostic methods were not consistent. We believe that we minimized the effects of these inter-study inconsistencies by applying different acquisition time frames to cases diagnosed by culture and serology, and by using multiple measures of condom use. More than half of all participants who were observed to acquire HSV-2 had no control period and were excluded. Though characteristics of included and excluded participants were similar, the differences in race, sexual orientation (among men) and source study that were noted between those who were included and excluded, and the large number of exclusions could limit the generalizability of our results. Finally, control periods necessarily preceded case periods. This ordering could induce bias if systematic changes in reporting of sexual behavior occurred over study participation. However, we have no evidence to suggest that such systematic changes occurred.

Our results add to the growing body of evidence supporting a protective effect of condoms against HSV-2 infection. This study suggests that there has likely been unmeasured

confounding in other assessments of condom effectiveness against HSV-2. Our study strengthens previous findings and confirms the appropriateness of recommending consistent condom use for HSV-2 prevention.

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SUMMARY

A case-crossover analysis using data pooled from six prospective studies found a significantly lower risk of HSV-2 acquisition with protected than unprotected sexual acts.

Figure 1.

Exposure duration-matched model. When acquisition was detected by serology, the case period was fixed as the window between 14 and 90 days before diagnosis (Dx); the control period was fixed as the window between the first day in the study and the 76th day in the study. In this example, all of the sexual behavior reported at visit (a) and a portion of visit (b) contribute to the control period, while all of visit (d) and portions of visits (c) and (e) contribute to the case period.

Figure 2.

Forest plot summarizing odds ratios and 95% confidence intervals for change in odds of herpes simplex virus type 2 (HSV-2) acquisition associated with each type of act. The height of each box is proportional to the number of participants included in that analysis.

Table 1

Baseline Characteristics of Those Who Acquired HSV-2 During Follow-Up, by Inclusion or Exclusion in the Case-Crossover Analysis

Variable	Included (n=191)		Excluded (n=228)		P-value
	Median/N	IQR (%)	Median/N	IQR (%)	
Age (years)	25.0	(21.0–32.6)	25.0	(20.1–32.0)	0.42
Gender					0.36
Female	87	(45.5%)	114	(50.0%)	
Male	104	(54.5%)	114	(50.0%)	
Race					0.004
White	98	(51.3%)	83	(36.4%)	
Black	78	(40.8%)	107	(46.9%)	
Hispanic	9	(4.7%)	18	(7.9%)	
Other	6	(3.1%)	20	(8.8%)	
Sexual orientation (males only)					
Heterosexual	90	(86.5%)	110	(96.5%)	0.008
MSM	14	(13.5%)	4	(3.5%)	
Baseline HSV-1 status					0.009
Negative	83	(43.5%)	71	(31.1%)	
Positive	108	(56.5%)	157	(68.9%)	
Ever had an STI					0.66
No	80	(47.6%)	98	(45.4%)	
Yes	88	(52.4%)	118	(54.6%)	
Method of HSV-2 detection					0.53
Culture	10	(5.2%)	9	(3.9%)	
Serology	181	(94.8%)	219	(96.1%)	
Trial					<0.001
Valacyclovir ³¹	10	(5.2%)	17	(7.5%)	
Glycoprotein-D Vaccine ³⁴	23	(12.0%)	11	(4.8%)	
Project RESPECT ^{15, 32}	50	(26.2%)	133	(58.3%)	
Homeless Adolescents ³³	6	(3.1%)	14	(6.1%)	
Recombinant Vaccine (Partners) ³⁰	22	(11.5%)	15	(6.6%)	

Abbreviations: HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; IQR, interquartile range; MSM, men who have sex with men; N, number; STI, sexually transmitted infection

Variable	Included (n=191)		Excluded (n=228)		P-value
	Median/N	(IQR/%)	Median/N	(IQR/%)	
Recombinant Vaccine (STI Clinic) ³⁰	80	(41.9%)	38	(16.7%)	

Table 2

Frequency of Condom Use During the Case and Control Periods for the 181 Participants Who Reported at Least One Sexual Act During Follow-Up

Control Periods	Case periods		
	Never	Sometimes	Always
Never	36 (19.9%)	7 (3.9%)	0 (0.0%)
Sometimes	43 (23.8%)	48 (26.5%)	12 (6.6%)
Always	1 (0.6%)	14 (7.7%)	20 (11.0%)

Stuart-Maxwell test of marginal homogeneity $P<0.001$

Table 3a

Odds Ratios Reflecting the Change in Odds of HSV-2 Acquisition With Each Unprotected Act and Protected Act as Estimated by the All-Visits, Stratified All-Visits, Exposure Duration-Matched, and GEE Models

	<u>Protected acts</u>		<u>Unprotected acts</u>	
	OR	95% CI	OR	95% CI
All-visits model	1.008	0.987, 1.030	1.036	1.021, 1.052
All-visits model stratified by gender:				
Men ($n=104$)	0.995	0.959, 1.031	1.041	1.019, 1.064
Women ($n=87$)	1.017	0.989, 1.047	1.030	1.010, 1.051
All-visits model stratified by discordant couple status:				
Discordant couples ($n=55$)	1.042	0.950, 1.142	0.992	0.959, 1.027
Singles ($n=136$)	1.007	0.985, 1.030	1.050	1.031, 1.070
Exposure duration-matched model	0.987	0.954, 1.020	1.022	1.003, 1.042
GEE model (full cohort)	0.998	0.988, 1.008	1.013	1.008, 1.018

Abbreviations: CI, confidence interval; HSV-2, herpes simplex virus type 2; OR, odds ratio

Table 3b

Odds Ratios Reflecting the Change in Odds of HSV-2 Acquisition With Each Act During Periods in Which Condoms Were Never Used (Never-Period Acts), Sometimes Used (Sometimes-Period Acts), or Always Used (Always-Period Acts), as Estimated by the All-Visit and Exposure Duration-Matched Models

	<u>All-visits</u>		<u>Exposure duration-matched</u>	
	OR	95% CI	OR	95% CI
Never-period acts	1.036	1.021, 1.052	1.040	1.014, 1.067
Sometimes-period acts	1.027	1.010, 1.044	1.010	0.990, 1.030
Always-period acts	0.989	0.957, 1.023	1.013	0.972, 1.056

Abbreviations: CI, confidence interval; HSV-2, herpes simplex virus type 2; OR, odds ratio