A Pooled Analysis of the Effect of Condoms in Preventing HSV-2 Acquisition

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Background: The degree of effectiveness of condom use in preventing the transmission of herpes simplex virus 2 (HSV-2) is uncertain. To address this issue, we performed a large pooled analysis.

Methods: We identified prospective studies with individual-level condom use data and laboratory-defined HSV-2 acquisition. Six studies were identified through a review of publications through 2007: 3 candidate HSV-2 vaccine studies, an HSV-2 drug study, an observational sexually transmitted infection (STI) incidence study, and a behavioral STI intervention study. Study investigators provided us individual-level data to perform a pooled analysis. Effect of condom use was modeled using a continuous percentage of sex acts during which a condom was used and, alternatively, using absolute numbers of unprotected sex acts.

Results: A total of 5384 HSV-2–negative people at baseline contributed 2 040 894 follow-up days; 415 persons acquired laboratory-documented HSV-2 during follow-up. Consistent condom users (used 100% of the time) had a 30% lower risk of HSV-2 acquisition compared with those who never used condoms (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.40-0.94) ($P=.01$). Risk for HSV-2 acquisition increased steadily and significantly with each unprotected sex act (HR, 1.16; 95% CI, 1.08-1.25) ($P<.001$). Condom effectiveness did not vary by gender.

Conclusions: To our knowledge, this is the largest analysis using prospective data to assess the effect of condom use in preventing HSV-2 acquisition. Although the magnitude of protection was not as large as has been observed with other STIs, we found that condoms offer moderate protection against HSV-2 acquisition in men and women.

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STUDIES THAT PROSPECTIVELY measure sexual activity, condom use, and sexually transmitted infection (STI) incidence are necessary to assess preventive effect of condom use on STI acquisition. In the absence of randomized controlled trials, the best evidence available on condom use and STI acquisition comes from prospective observational studies, or intervention trials conducted for other purposes in which the STI of interest was an end point. Compelling evidence from such studies indicates that consistent condom use reduces transmission of human immunodeficiency virus (HIV).[1] Additionally, increasingly strong data support condom effectiveness in preventing STIs that target urethral or cervical epithelia, such as chlamydia and gonorrhea.[2] However, the effectiveness of condoms in preventing the transmission of herpes simplex virus 2 (HSV-2) is less certain.[3-5] A 2001 panel convened by the National Institute of Allergy and Infectious Diseases concluded that the available evidence on condom effectiveness was insufficient to establish that condoms were protective against HSV-2 acquisition[6] because the research was derived from studies that used prevalent HSV-2 infection as the outcome and thus were unable to determine the temporal relationship between condom use and HSV-2 acquisition.[6,7] Since that time, 3 studies have been published that show moderate efficacy (approximately 50%) for condom use.[8-10] However, in these studies, measures of condom use and definitions of condom effectiveness differed. More precise measurement of condom efficacy, with attention to subgroups in which condom effectiveness may differ, is desirable.

In this study, we sought to increase the precision of the estimates of condom use on HSV-2 acquisition by pooling data from

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Table 1. Characteristics of Studies Included in the Pooled Analysis

Source	Population, Study Years, Location	Participants, No. (Planned Follow-up)	Condom Use Measurement	Objective	Main Finding
Kamb et al (Project RESPECT),[28] 1998	Individuals aged ≥14 y having heterosexual vaginal intercourse in the previous 3 mo, 1993-1996, United States	5758 (52 wk)	Percentage of vaginal or anal sex acts	Evaluation of a face-to-face prevention counseling program to reduce HIV and STI acquisition	20% Reduction in STI acquisition and increase in condom use as result of intervention
Corey et al (vaccine partners),[29] 1999	Monogamous, HIV$^-$, HSV-2$^-$ individuals aged ≥18 y with an HSV-2$^+$ partner, 1993-1995, United States	531 (72 wk)	Percentage of genital sex acts	Evaluation of a candidate subunit glycoprotein vaccine for prevention of HSV-2 acquisition	Vaccine was found not to prevent HSV-2 acquisition
Corey et al (vaccine STI clinic),[29] 1999	HIV$^-$, HSV-2$^-$ STI clinic attendees aged ≥18 y with STI diagnosis or ≥4 partners in previous year, 1993-1995, United States	1862 (72 wk)	Percentage of genital sex acts	Evaluation of a candidate subunit glycoprotein vaccine for prevention of HSV-2 acquisition	Vaccine was found not to prevent HSV-2 acquisition
Noell et al (adolescents),[30] 2001	Individuals aged ≤21 y, 1994-1997, United States	536 (24 wk)	Never, sometimes, about half, most times, or every time	Assessment of sexual behaviors and STI incidence of homeless adolescents	Incidence of HSV-2 and *Chlamydia trachomatis* was relatively high in female subjects; inconsistent condom use was the primary factor associated with increased risk
Stanberry et al (vaccine),[31] 2002	HSV-1$^-$, HSV-2$^-$, and HIV$^-$ individuals aged 19-45 y with a partner with a history of genital herpes, 1995-1997, North America, Europe, and Australia	847 (19 mo)	Never (0%), sometimes (<50%), usually (>50%), or always (100%)	Evaluation of a candidate subunit glycoprotein-D-adjuvant vaccine for prevention of HSV-2 acquisition	Vaccine efficacy only in women
Corey et al (valacyclovir),[32] 2004	Heterosexual, monogamous, immunocompetent individuals aged ≥18 y with an HSV-2$^+$ partner, 1998-2001, North America, Europe, Latin America, and Australia	741 (56 wk)	Never (0%), sometimes (1%-90%), or nearly always (91%-100%)	Evaluation of the effect of suppressive valacyclovir use in HSV-2$^+$ individuals in reducing HSV-2 acquisition in susceptible partners	HSV-2 acquisition was significantly reduced in susceptible participants

Abbreviations: HIV, human immunodeficiency virus; HSV, herpes simplex virus; STI, sexually transmitted infection; $^-$, negative; $^+$, positive.

all published studies that prospectively assessed condom use and HSV-2 incidence. We performed an individual-level pooled analysis that combined prospective data from such studies to assess the relationship between condom use and time to HSV-2 acquisition. In addition, we performed additional analyses to assess the relationship between the absolute number of unprotected sex acts per week and HSV-2 acquisition.

METHODS

DATA COLLECTION

We sought to identify all relevant studies for this analysis by conducting literature searches as well as discussions with other researchers in the field. First, we conducted a PubMed search of studies published through October 2004 using the terms "genital herpes AND condom" and "herpes AND condom." The initial search resulted in 147 articles that were reviewed for inclusion according to 3 predetermined eligibility criteria: (1) use of prospective cohort study design in which participants were tested with type-specific HSV-2 antibody tests at baseline and follow-up; (2) assessment of both condom use and frequency of sexual activity throughout the study; and (3) laboratory documentation (either culture analysis, polymerase chain reaction assay, or type-specific serologic analysis) of HSV-2 acquisition. From this review, we identified 21 studies as potentially eligible, 17 of which did not meet the inclusion criteria.[11-27] Six studies documented in 5 reports met our predetermined criteria (**Table 1**),[28-32] including 4 identified through the literature review process[28-30] and 2 identified through asking researchers in the field about their knowledge of studies meeting the eligibility criteria.[31,32] We included 2 HSV-2 vaccine studies from 1 report,[29] 1 HSV-2 drug study (placebo arm only),[32] 1 HSV-2 vaccine study (placebo arm only),[31] 1 observational STI incidence study,[30] and 1 HIV behavioral intervention study (Table 1).[28] All studies incorporated safer sex counseling as part of their routine follow-up.

Next, we asked the investigators to provide individual-level data from the eligible studies. We were provided data for all participants in 4 studies (3 reports)[28-30] and for the placebo arm par-

ticipants in 1 drug study (valacyclovir[32]) and 1 vaccine study (glycoprotein-D-adjuvant vaccine[31]). After completing the preliminary analyses, we performed a second literature review of published articles since 2004 and identified 9 additional studies,[33-41] none of which met the criteria for inclusion.

STATISTICAL METHODS

Information on participant characteristics, sexual behaviors, and HSV-2 acquisition was standardized across each data set. The frequency of genital or anal sex acts and the proportion of condom use for sex acts were available in each study. For studies that reported categories of condom use (such as "never," "sometimes," or "always"), the corresponding ranges of percentage condom use for each category were obtained from the study questionnaire. The numeric value at the midpoint of each response category's range was used in analyses that included condom use as a continuous variable. We included only participants who were known to be HSV-2 negative at baseline (based on laboratory determination). We also excluded data from participants who during the follow-up period reported no sexual activity, had no laboratory tests performed, or who were not interviewed about condom use. At each assessment time, HSV-2 status was compared with sexual risk behavior and other potential risk factors (age, race, sexual practices, STI history, and other risk factors) that were available across studies over the preceding time period. Race data were obtained from the original studies and categorized by using indicator variables for "African American" and "other," with "white" used as the reference group. This variable was included because of the higher incidence of HSV-2 in African Americans.[42] When values for potential risk factors were missing, data from previous visits up to 6 months before the time of the missing data were carried forward. Date of HSV-2 acquisition were set at the midpoint between the date of the most recent negative test result and the date of the first positive test result. Annualized incidence of HSV-2 acquisition was calculated by study and gender. Continuous measures taken repeatedly on individuals were summarized by first averaging over all time points and then by computing study-specific and overall means or medians of these values.

A univariate Cox regression model stratified by study was generated for each potential risk factor and tested using a likelihood ratio test at a significance level of .05. Stratified Cox models were used throughout the analysis to allow for differing baseline hazards between studies, possibly due to any effects of study-specific interventions, that might not satisfy the proportional hazards assumption. The proportional hazards assumption was examined using plots of scaled Schoenfeld residuals for univariate and multivariate models, and no violations were found. Graphical analysis was also used to assess parameterization of continuous variables and to select cut points or categories. Number of genital or anal sex acts per week was included in the models as a categorical variable (0-1, 2, 3-5, 6-10, >10). Age was grouped into tertiles (≤23, 24-31, >31 years) and included as a grouped linear variable. Gender, STI history (ever or never), baseline HSV-1 status, sexual orientation during the study (heterosexual or other), and monogamy (only 1 sex partner) during the study were included as binary variables. The effect of having only 1 partner vs multiple partners in a measurement period on time until HSV-2 acquisition was hypothesized to differ based on whether the subject participated in a study that recruited monogamous couples. Therefore, an interaction was tested between number of partners and participation in a couples study because some persons reported having multiple partners despite their participation in a couples study.

The association between condom use and the risk of HSV-2 acquisition was initially evaluated with a Cox regression model stratified by study and controlling for categorical number of sex acts by week. Condom use was included in the model as a continuous variable (percentage of sex acts during which a condom was used). Coefficients were multiplied by 25 to ascertain the aggregate effect of condoms for every 25% increase in use. We examined whether the effect of condom use differed by gender using an interaction term for condom use by gender.

Adjusted models for the effect of condom use on the risk of HSV-2 acquisition were generated with the Hosmer and Lemeshow stepwise method.[43] An adjusted model was generated for the effect of percentage condom use stratified on study and adjusted for number of sex acts per week and other significant covariates by this method. Two-way interaction terms for condom use by gender and by study were also evaluated in this model.

The frequency of unprotected sex acts was determined by multiplying the number of total sex acts per week by the percentage condom use for each time interval and subtracting this from the total sex acts per week. Frequency of unprotected sex acts per week was included in a secondary model as a categorical variable with categories for values 0, 1, 2, 3, and 4 or more. The effect of an increasing number of unprotected sex acts on risk of HSV-2 acquisition was estimated using a Cox regression model stratified on study. An adjusted model for the effect of unprotected sex acts included interaction terms for frequency of unprotected sex acts by study and by gender.

All reported *P* values are 2 sided. All statistical analyses were performed with STATA 8.0 software (StataCorp, College Station, Texas).

RESULTS

The 6 studies yielded a total of 5384 subjects whose baseline HSV-2 test results were negative and who were included in this pooled analysis. Four-hundred seventy-five subjects were excluded because they reported no sexual activity or underwent no laboratory tests or had no interview on condom use during the follow-up period: 10 from Corey et al (vaccine partners),[29] 118 from Corey et al (vaccine STI clinic),[29] 40 from Corey et al (valacyclovir),[32] 38 from Kamb et al (Project RESPECT),[28] 260 from Noell et al (adolescents),[30] and 9 from Stanberry et al (vaccine).[31] Overall, subjects had a mean age of 29 years; 66.2% were male; 60.4% were white; 94.1% were heterosexual; and most reported no prior STIs (**Table 2**). Sixty percent of the subjects were HSV-1 seropositive at study entry. The 5384 subjects contributed 2 040 894 follow-up days, with a median follow-up of 374 days (range, 4-987 days).

Overall, 415 persons acquired laboratory-documented HSV-2 during follow-up. The overall incidence was 7.4 per 100 person years (95% confidence interval [CI], 6.7-8.2), but varied among studies (**Table 3**). Incidence was consistently higher for women than for men, though the differences between genders varied greatly (Table 3). The study-specific median frequency of sex acts averaged 1.4 per week (range, 0.6-1.9). The median number of partners reported during the study was 1 (interquartile range, 1-1.74) in the pooled data set and matched the study-specific median values except for the adolescent STI incidence study[30] (median, 2) and the vaccine STI clinic study[29] (median, 1.4). The median percentage condom use during follow-up was lower in the studies

Table 2. Characteristics of Subjects Included in the Pooled Analysis

Characteristic	Corey et al (Vaccine Partners),[29] 1999 (n=521)	Corey et al (Vaccine STI Clinic),[29] 1999 (n=1744)	Corey et al (Valacyclovir),[32] 2004 (n=701)	Noell et al (Adolescents),[30] 2001 (n=277)	Kamb et al (Project RESPECT),[28] 1998 (n=1728)	Stanberry et al (Vaccine),[31] 2002 (n=413)	Pooled Data Set (n=5384)
Continuous Variables							
Duration of follow-up, median (range), d	561 (18-706)	553 (17-819)	242 (14-337)	182 (46-255)	365 (4-542)	546 (14-987)	374 (4-987)
Age, mean (range), y[a]	36.0 (18-62)	29.0 (17-64)	35.9 (18-76)	18.1 (13-22)	25.9 (14-60)	32.1 (18-46)	29.2 (13-76)
Categorical Variables, No. (%)							
Gender							
Male	255 (49.0)	1296 (74.3)	470 (67.1)	167 (60.3)	1095 (63.4)	283 (68.5)	3566 (66.2)
Female	266 (51.1)	448 (25.7)	231 (33.0)	110 (39.7)	633 (36.6)	130 (31.5)	1818 (33.8)
Race[b]							
White	483 (92.7)	1093 (62.7)	636 (90.7)	213 (78.0)	431 (24.9)	395 (95.6)	3251 (60.4)
Black	14 (2.7)	536 (30.7)	18 (2.6)	6 (2.2)	893 (51.7)	6 (1.5)	1473 (27.4)
Other	24 (4.6)	115 (6.6)	47 (6.7)	54 (19.8)	404 (23.4)	12 (2.9)	656 (12.2)
Sexual orientation[c]							
Heterosexual	507 (97.5)	1523 (87.3)	701 (100)	204 (73.7)	1728 (100)	401 (97.3)	5064 (94.1)
Other	13 (2.6)	221 (12.7)	0	73 (26.3)	0	11 (2.7)	318 (5.9)
HSV-1$^+$ at baseline[d]	309 (59.3)	1111 (63.7)	487 (69.5)	135 (49.8)	1183 (68.5)	0	3225 (60.0)
Past STI diagnosis[e]	16 (3.1)	704 (40.4)	155 (22.1)	95 (34.3)	963 (56.0)	NA	NA

Abbreviations: HIV, human immunodeficiency virus; HSV, herpes simplex virus; NA, not applicable; STI, sexually transmitted infection; $^+$, positive.
[a] Data for age missing for 8 study subjects.
[b] Data for race missing for 4 study subjects.
[c] Data for sexual orientation missing for 1 study subject.
[d] Data for baseline HSV-1 missing for 8 study subjects.
[e] Data for past STI diagnosis missing for 9 study subjects.

Table 3. Incidence of HSV-2 per 100 Person-Years[a]

Study Subjects	Corey et al (Vaccine Partners),[29] 1999	Corey et al (Vaccine STI Clinic),[29] 1999	Corey et al (Valacyclovir),[32] 2004	Noell et al (Adolescents),[30] 2001	Kamb et al (Project RESPECT),[28] 1998	Stanberry et al (Vaccine),[31] 2002	Overall
Women	8.7 (6.1-12.5)	5.4 (3.8-7.7)	11.5 (7.1-18.8)	21.8 (12.1-39.4)	15.5 (12.6-19.2)	15.0 (9.9-22.8)	10.8 (9.4-12.5)
Men	1.9 (0.9-3.9)	5.1 (4.1-6.3)	3.2 (1.7-6.2)	12.3 (6.4-23.6)	9.5 (7.8-11.6)	3.0 (1.7-5.4)	5.8 (5.1-6.6)
All subjects	5.1 (3.7-7.1)	5.1 (4.3-6.2)	6.0 (4.1-8.9)	16.2 (10.4-25.0)	11.7 (10.1-13.5)	6.6 (4.8-9.3)	7.4 (6.7-8.2)

Abbreviations: HSV, herpes simplex virus; STI, sexually transmitted infection.
[a] Data are reported as incidences (95% confidence intervals).

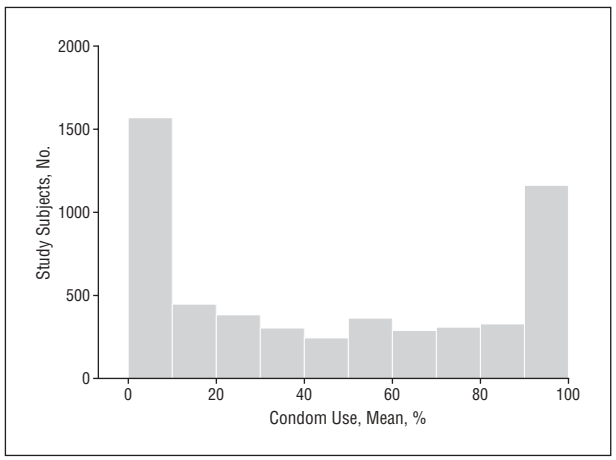

Figure 1. Distribution of average percentage condom use during study follow-up.

that recruited discordant couples (7%, 14%, and 18% in the Corey et al[29] vaccine partners, Stanberry et al[31] vaccine, and Corey et al[32] valacyclovir studies, respectively) compared with other studies (from 46% to 53%). In the pooled data, the median percentage of condom use was 39%, and the subject averages over study follow-up had a U-shaped distribution (**Figure 1**).[44]

Variables univariately associated with HSV-2 acquisition included female gender, younger age, nonwhite race, and history of STIs (**Table 4**).

The association between a 25% increase in condom use and HSV-2 acquisition, adjusted for number of sex acts and stratified by study, indicated a weak protective effect that was not statistically significant (hazard ratio [HR], 0.95 [95% CI, 0.88-1.00]) (P=.09). This effect did not significantly differ by gender (P=.22 for interaction).

In a multivariate model (**Table 5**), a 25% increase in condom use significantly decreased the risk of HSV-2 acquisition (HR, 0.93 [95% CI, 0.85-0.99]) (P=.01). Similarly, the aggregate hazard ratio for 100% condom use compared with 0% use was 0.70 (95% CI, 0.40-0.94) (P=.01). No evidence of heterogeneity was found by study (P=.24) or gender (P=.22) in the adjusted model. In sepa-

rate analyses for each study, increasing condom use was found to decrease the adjusted risk of HSV-2 acquisition; however, these estimates were only statistically significant for 1 study (**Figure 2**). Baseline HSV-1 status, STI history, sexual orientation during the study, and monogamy during the study did not significantly predict HSV-2 acquisition during model selection and were not included in the final multivariate model.

In a univariate model stratified by study, the risk of HSV-2 acquisition increased significantly with increasing unprotected sex acts per week (0, 1, 2, 3, and ≥4) (HR, 1.10 [95% CI, 1.02-1.19]) (P=.01). After adjustment for age, race, and gender, the estimate showed an increased risk of HSV-2 acquisition with increasing numbers of unprotected sex acts per week (HR, 1.16 [95% CI, 1.08-1.25]) (P<.001) (**Table 6**). We found no evidence for significant variation of this effect by gender (P=.41). Overall estimates of the impact of the number of unprotected sex acts were also relatively consistent between study subgroups, except smaller effect was observed in the Project RESPECT[28] and Stanberry et al[31] vaccine subgroups (Figure 2). However, an interaction between study and frequency of unprotected sex acts was not significant (P=.41).

COMMENT

In our pooled analysis of data from all studies to date that have prospectively assessed condom use and HSV-2 incidence, we found that condom use moderately, albeit significantly, protected against HSV-2 acquisition. Persons who always used condoms had a 30% decreased risk of acquiring HSV-2 compared with persons who reported no condom use. Risk of HSV-2 acquisition decreased by 7% for every additional 25% of the time that condoms were used during anal or vaginal sex. Risk of HSV-2 acquisition also rose steadily and significantly with increasing frequency of unprotected sex acts, and our findings were consistent throughout multiple analysis strategies. Our method of pooled analysis circumvented the obstacles and expense of recruiting and following a large cohort of individuals, and the use of individual-level data in the pooled analysis allowed for uniform coding of the relevant variables and assessment of relationships that might not have been explored as part of the original results.[45] Since we did not find strong evidence of heterogeneity between studies for the effectiveness of condoms, we believe that this was a valid approach.

In some cases our pooled estimates of condom effects on HSV-2 acquisition varied from earlier published reports on those studies. For example, previously published analyses of the Project RESPECT[28] study data found that subjects who used condoms less than 50% of the time with occasional partners had twice the risk of acquiring HSV-2 as those with 100% condom use or no occasional partners (HR, 2.0 [95% CI, 1.2-3.3]).[8] We found a lower estimate in this analysis that is likely due to the inclusion of condom use between self-reported monogamous partners; level of condom use with main partners was not associated with reduced HSV-2 acquisition in the previous analysis. Also, in an analysis of the partners study,[29] Wald et al[10] reported an adjusted HR of 0.085 for women (95% CI, 0.01-0.67) using condoms more than 25% of the time, but this protection was not observed in

Table 4. Univariate Associations With HSV-2 Acquisition in the Pooled Analysis[a]

Covariate	Univariate Hazard Ratio (95% CI)	*P* Value
Frequency of sexual activity per week		.08
0-1	1 [Reference]	
2	0.92 (0.70-1.20)	
3-5	1.07 (0.83-1.36)	
6-10	1.32 (0.89-1.95)	
>10	2.21 (1.08-4.49)	
Race		<.001
White	1 [Reference]	
African American	2.46 (1.90-3.21)	
Other	1.48 (1.07-2.09)	
Women	1.79 (1.45-2.17)	<.001
HSV-1$^+$ at baseline	1.21 (0.97-1.50)	.09
Had an STI prior to study[b]	1.73 (1.39-2.16)	<.001
Homosexual or bisexual MSM	1.08 (0.70-1.68)	.73
Study		<.001
Corey et al (vaccine partners),[29] 1999	1 [Reference]	
Corey et al (vaccine STI clinic),[29] 1999	0.98 (0.68-1.42)	
Corey et al (valacyclovir),[32] 2004	0.87 (0.52-1.45)	
Kamb et al (Project RESPECT),[28] 1998	1.88 (1.31-2.69)	
Noell et al (adolescents),[30] 2001	2.06 (1.18-3.58)	
Stanberry et al (vaccine),[31] 2002	1.20 (0.75-1.93)	
Multiple partners vs 1 partner	1.02 (0.81-1.29)	.88
Age[c]	0.83 (0.75-0.92)	.001
Condom use (per every 25% increase)[d]	0.95 (0.88-1.00)	.09

Abbreviations: CI, confidence interval; HSV, herpes simplex virus; MSM, man who has sex with men; STI, sexually transmitted infection; $^+$, positive.
[a] All covariate results except for study are from a univariate model stratified by study.
[b] Does not include data from Stanberry et al.[31]
[c] For increasing categories of age (≤23, 24-31, and >31).
[d] Adjusted for weekly frequency of sex acts.

Table 5. Multivariate Model of Risk of HSV-2 Acquisition, Including Condom Effect, and Stratified by Study

Covariate	Adjusted Hazard Ratio (95% CI)	*P* Value
Age, y[a]	0.86 (0.75-0.99)	.04
Women	2.00 (1.64-2.50)	<.001
Race		<.001
White	1 [Reference]	
African American	2.60 (1.99-3.42)	
Other	1.29 (0.90-1.83)	
Sex acts, No./wk		.07
0-1	1 [Reference]	
2	0.96 (0.73-1.27)	
3-5	1.12 (0.87-1.45)	
6-10	1.44 (0.97-2.15)	
>10	2.57 (1.25-5.27)	
Condom use (per every 25% increase)	0.93 (0.85-0.99)	.01

Abbreviations: CI, confidence interval; HSV, herpes simplex virus; STI, sexually transmitted infection.
[a] For increasing categories of age (≤23, 24-31, and >31).

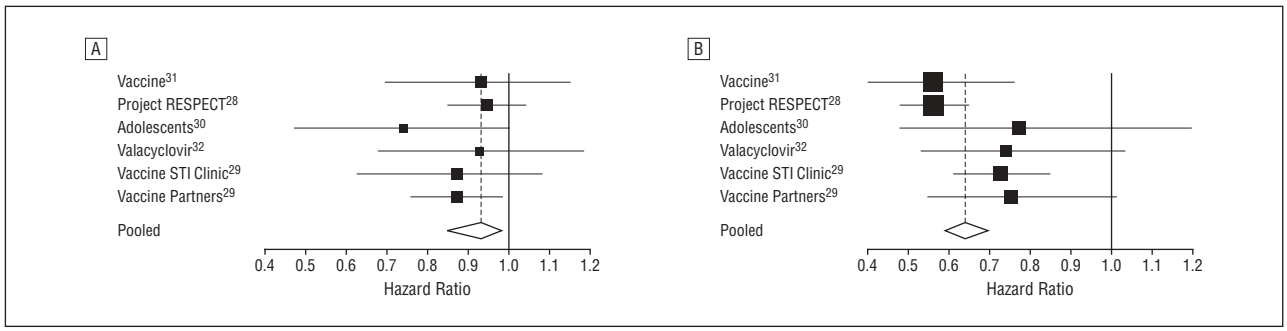

Figure 2. Study-specific hazard ratios. The effects of a 25% increase in condom use (A) and increasing number of unprotected sex acts (B) on herpes simplex virus 2 (HSV-2) acquisition. The sizes of the dark squares are proportional to the inverse variance of the estimate and centered on the hazard ratio. Horizontal lines indicate the 95% confidence intervals for effect on time until HSV-2 acquisition. Diamonds are centered on the pooled hazard ratio estimate (dashed vertical line), and width indicates the 95% confidence interval.

Table 6. Multivariate Model of Risk of HSV-2 Acquisition, Including Unprotected Sex Act Effect and Stratified by Study

Covariate	Adjusted Hazard Ratio (95% CI)	*P* Value
Age, y[a]	0.87 (0.75-1.00)	.05
Female	2.00 (1.64-2.50)	<.001
Race		<.001
White	1 [Reference]	
African American	2.62 (2.00-3.43)	
Other	1.31 (0.92-1.86)	
Unprotected sex acts, No./wk[b]	1.16 (1.08-1.25)	<.001

Abbreviations: CI, confidence interval; HSV, herpes simplex virus; STI, sexually transmitted infection.
[a] For increasing categories of age (≤23, 24-31, and >31).
[b] For increasing categories of frequency of unprotected sex acts (0, 1, 2, 3, and ≥4).

men. We did not find any significant differences in condom effectiveness between men and women, despite a higher incidence of HSV-2 acquisition in women (Table 3).The lack of effect reported in the earlier publication may have been related to few cases of HSV-2 acquisition in men; the large sample size in our pooled analysis allowed a more robust estimate.

The limitations of our study include the availability of only those covariates for the adjusted analyses that were collected in a consistent way across every study. For example, we were unable to adjust for some known risk factors for HSV-2 acquisition, such as the number of new sexual partners and the HSV status of each partner, which may have led to uncontrolled confounding.[46] Warner et al[47] have described unmeasured confounding in a similar cohort analysis of condom effectiveness as differences between consistent and inconsistent condom users related to unmeasured factors that led to an underestimate of the magnitude of the protective effect of condoms on STI acquisition. Condom use may have been inaccurately reported[48] owing to social desirability bias or incorrect usage,[49] or it may have been affected by recent HSV-2 acquisition. Condom use and HSV-2 acquisition were ascertained after various follow-up intervals, and it is possible that a primary HSV-2 episode in some cases could lead to increased condom use within the same measurement interval. These misclassifications attenuate the observed estimate toward the null and are present in other studies of condom effectiveness. Additionally, we identified studies to include in this analysis through a literature search, which may have led to publication bias. We believe, but cannot be certain, that our solicitations among other investigators identified most relevant studies.

This analysis adds to the growing number of condom analyses that use an absolute number of unprotected sex acts for exposure as opposed to the more traditional measure of percentage condom use.[47,50-52] Analyses of these 2 outcomes gave roughly the same conclusion. The unprotected sex act models may be more appropriate as they do not require the impact of percentage condom use to be consistent across varying numbers of sex acts, emphasizing that one's risk of acquiring HSV-2 is specific to each unprotected sex act.

The 30% reduction in HSV-2 acquisition observed in this pooled analysis was less than the reported 87% reduction associated with condom use on HIV acquisition.[3] This difference likely reflects different transmission mechanisms. While HIV is transmitted via contact with bodily fluids, HSV-2 is primarily transmitted through direct skin-to-skin or skin-to-mucosa contact. Therefore, some HSV-2 transmission can occur despite condom use when viral shedding is present in areas not covered by the condom. Nonetheless, based on findings of this large analysis using all available prospective data, condom use should continue to be recommended to both men and women for reducing risk of HSV-2 acquisition. Although the magnitude of the protective effect was not as large as has been observed with other STIs, a 30% reduction in HSV-2 incidence can have a substantial benefit for individuals as well as a public health impact at the population level.

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Author Contributions: Dr Wald had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Martin, Kamb, and Wald. *Acquisition of data:* Martin, Krantz, Gottlieb, Langenberg, Stanberry, Kamb, and Wald. *Analysis and interpretation of data:* Martin, Krantz, Magaret, and Wald. *Drafting of the manuscript:* Martin and Wald. *Critical revision of the manuscript for important intellectual content:* Martin, Krantz, Gottlieb, Magaret, Langenberg, Stanberry, Kamb, and Wald. *Statistical analysis:* Martin, Krantz, Magaret, and Wald. *Obtained funding:* Stanberry and Wald. *Administrative, technical, and material support:* Martin, Kamb, and Wald. *Study supervision:* Wald.

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Correction

Incorrect x-Axis Distribution. All data in Figure 2B of "A Pooled Analysis of the Effect of Condoms in Preventing HSV-2 Acquisition" published in the July 13, 2009, issue of the *Archives of Internal Medicine* (2009;169[13]:1233-1240) were incorrectly distributed across the x-axis. The corrected Figure 2B with the original figure legend appears here.

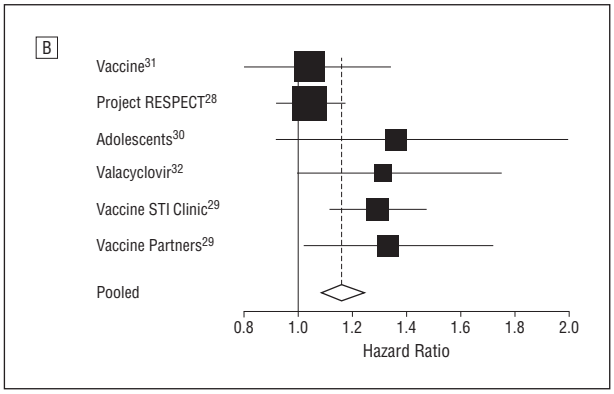

Figure 2. Study-specific hazard ratios. The effects of a 25% increase in condom use (A) and increasing number of unprotected sex acts (B) on herpes simplex virus 2 (HSV-2) acquisition. The sizes of the dark squares are proportional to the inverse variance of the estimate and centered on the hazard ratio. Horizontal lines indicate the 95% confidence intervals for effect on time until HSV-2 acquisition. Diamonds are centered on the pooled hazard ratio estimate (dashed vertical line), and width indicates the 95% confidence interval.