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HERPES SIMPLEX VIRUS TYPE 2 IN THE UNITED STATES, 1976 TO 1994

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ABSTRACT

Background Herpes simplex virus type 2 (HSV-2) infection is usually transmitted sexually and can cause recurrent, painful genital ulcers. In neonates the infection is potentially lethal. We investigated the seroprevalence and correlates of HSV-2 infection in the United States and identified changes in HSV-2 seroprevalence since the late 1970s.

Methods Serum samples and questionnaire data were collected during the National Health and Nutrition Examination Surveys (NHANES) II (1976 to 1980) and III (1988 to 1994). HSV-2 antibody was assessed with an immunodot assay specific for glycoprotein gG-2 of HSV-2.

Results From 1988 to 1994, the seroprevalence of HSV-2 in persons 12 years of age or older in the United States was 21.9 percent (95 percent confidence interval, 20.2 to 23.6 percent), corresponding to 45 million infected people in the noninstitutionalized civilian population. The seroprevalence was higher among women (25.6 percent) than men (17.8 percent) and higher among blacks (45.9 percent) than whites (17.6 percent). Less than 10 percent of all those who were seropositive reported a history of genital herpes infection. In a multivariate model, the independent predictors of HSV-2 seropositivity were female sex, black race or Mexican-American ethnic background, older age, less education, poverty, cocaine use, and a greater lifetime number of sexual partners. As compared with the period from 1976 to 1980, the age-adjusted seroprevalence of HSV-2 rose 30 percent (95 percent confidence interval, 15.8 to 45.8 percent). The seroprevalence quintupled among white teenagers and doubled among whites in their twenties. Among blacks and older whites, the increases were smaller.

Conclusions Since the late 1970s, the prevalence of HSV-2 infection has increased by 30 percent, and HSV-2 is now detectable in roughly one of five persons 12 years of age or older nationwide. Improvements in the prevention of HSV-2 infection are needed, particularly since genital ulcers may facilitate the transmission of the human immunodeficiency virus. (N Engl J Med 1997;337:1105-11.)

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HERPES simplex virus type 2 (HSV-2) causes vesicular and ulcerative lesions in adults¹⁻³ and may cause severe systemic disease in neonates and immunosuppressed hosts.⁴⁻⁶ In addition, genital ulceration caused by HSV-2 may facilitate the transmission of the human immunodeficiency virus (HIV).⁷⁻¹² Infections with HSV-2 typically affect the genital area, and transmission is usually sexual.^{6,13,14} In contrast, herpes simplex virus type 1 (HSV-1) commonly causes oropharyngeal infection, and transmission is primarily by nongenital personal contact.^{2,15} However, both viruses are capable of causing either genital or oropharyngeal infection and can produce mucosal lesions that are clinically indistinguishable. After primary infection, herpes simplex viruses enter a latent state in the nerve ganglia and may emerge later to cause recurrent active infection.

Assessing the extent of HSV-2 infection nationwide is difficult, for several reasons. In most states, HSV-2 infection is not a reportable disease. Furthermore, most people with HSV-2 are unaware of the infection.^{5,14,16-20} And, although the number of initial visits to physicians' offices for genital HSV infection increased from about 75,000 per year in 1978 to more than 150,000 per year in the early 1990s,²¹ it is uncertain whether this increase was due to a real increase in incidence or to increased public awareness and improved diagnosis and treatment of genital herpes. For these reasons, serologic methods have

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been the best way to study the epidemiology of HSV-2. Comprehensive serologic data on HSV-2 in the United States were collected during the second National Health and Nutrition Examination Survey (NHANES II) between 1976 and 1980.²²

We report here the results of a nationally representative serologic survey of HSV-2 that was done as part of NHANES III from 1988 to 1994. NHANES III had a larger sample than NHANES II and included information on behavioral risk factors for HSV-2 infection. In addition, the new survey allows us to see changes in HSV-2 seroprevalence over the 13 years between the midpoints of the two surveys. During this period, public awareness of genital herpes and other sexually transmitted diseases increased, and national programs to prevent HIV infection were begun.

METHODS

Study Populations and Sample Design

The NHANES program comprises a series of cross-sectional national surveys conducted by the National Center for Health Statistics of the U.S. Centers for Disease Control and Prevention (CDC). Each survey had a complex, stratified, multistage, probability-cluster design for selecting a sample representative of the noninstitutionalized civilian population of the United States.^{23,24} The total sample was larger in NHANES III (40,000) than in NHANES II (28,000).

In NHANES III, children under 5 years of age, persons 60 years of age or older, Mexican Americans, and blacks were sampled at higher rates than other persons. Race or ethnic group was defined by self-report as non-Hispanic white or non-Hispanic black (referred to as "white" and "black" in this article), or as Mexican American. People who did not place themselves in any of these categories were classified as "other" and were included with the total population.

The poverty-index ratio in NHANES III was calculated by dividing the total family income by the poverty threshold, with adjustment for the family size in the year of the interview, as determined by the Bureau of the Census.²⁵ Residence in a county located in a metropolitan area was defined as urban residence. All other counties were defined as nonurban. Questions about the lifetime number of sexual partners, age at first intercourse, cocaine use, and history of genital herpes were asked of all study participants between 18 and 59 years old. Whether the participant had a history of genital herpes was addressed by the question, "Have you ever had genital herpes?"

In NHANES II, preschool children, older people, and people living below the poverty level were oversampled; the upper age limit was 74 years. Race was defined by self-report as "white," "black," or "other"; in that study, persons who gave their ancestry as "Hispanic" were classified as "other" so that the results could be compared with those of NHANES III.

Responses to the Surveys

Of the persons originally selected for NHANES III, 82.5 percent were interviewed, and HSV-2 test results were available for 60.2 percent. The reasons that results were unavailable included the inability to locate the selected subject, refusal by that person to be interviewed or to have blood drawn, unsuccessful venipuncture, the need to use serum for other tests, and the loss of serum samples during transportation, storage, or processing. The percentages of selected persons who agreed to be interviewed and the percentages of those for whom HSV-2 test results were available were similar among persons of different sex, race or ethnic

group, and age, except that HSV-2 test results were less likely to be available for persons 70 years old or older (51.9 percent).

The rates of college attendance, rates of use of cocaine, and lifetime numbers of sex partners were similar among interviewed persons for whom HSV-2 results were available and those for whom the results were unavailable. The results were more likely to be available for persons living below the poverty level (71.9 percent) than for those living at or above the poverty level (58.1 percent).

An analysis of survey nonresponse in NHANES II has been published elsewhere.²⁶ Nonresponse to the survey did not appear to introduce bias into the overall results.

Serologic Testing

Serum samples in both NHANES II and NHANES III were tested for antibodies to HSV-2 with the same type-specific immunodot test, performed in the same laboratory.^{22,27,28} The purified glycoprotein gG-2 of HSV-2, which is specific for HSV-2, served as antigen in the assay. The sensitivity of the immunodot test for recurrent, culture-proved genital HSV-2 infection is over 98 percent, and the specificity is over 99 percent.²⁷ The quality of the HSV-2 testing was confirmed during both surveys by testing, with each reaction plate, positive and negative controls derived from pools of reference serum.

In NHANES III, all the available serum samples from persons 12 years of age or older were tested for type-specific HSV-2 antibody. In NHANES II, a subgroup of serum samples was tested for HSV-2, as described previously.²² Subgroup sampling weights were calculated to account for the sampling design and for the unavailability of serum samples according to sex, race or ethnic group, and age group. The final weight for each person in the sample in NHANES II was calculated as the product of the overall survey weight and the subgroup sampling weight.

As previously described,²² in NHANES II serum samples were first screened with a non-type-specific enzyme-linked immunosorbent assay, which detected any antibodies to HSV-1 or HSV-2.^{27,28} Serum samples that were positive on the non-type-specific screening test were subsequently tested with the type-specific test. Serum samples that were negative on the screening test were then presumptively assigned a negative test result for the type-specific immunodot test, thus limiting the use of the scarce type-specific testing reagent. To ensure that the screening test had a negligible effect on the overall sensitivity or specificity of HSV-2 testing, 245 serum samples from a health maintenance organization that were negative on the screening test were tested with the type-specific test; no type-specific HSV-2 antibody was detected in any of the samples.²⁷

Statistical Analysis

For both surveys, the prevalence estimates were weighted to represent the total U.S. population and to account for oversampling and nonresponse to the household interview and physical examination. The weights were further ratio-adjusted according to age, sex, and race or ethnic group to estimates of the noninstitutionalized civilian U.S. population taken from the Current Population Survey, adjusted for undercounting.^{29,30} Standard errors were calculated with SUDAAN.³¹ The approximate standard errors of prevalence ratios were calculated by the delta method.³² For comparisons between NHANES II and III and across population subgroups of NHANES III, the data were age-adjusted to the 1980 U.S. population by the direct method,³³ and nonoverlapping 95 percent confidence intervals were taken to indicate statistically significant changes in seroprevalence.

Logistic regression was used to identify predictors of HSV-2 infection. The initial model included demographic and behavioral variables that had univariate odds ratios with 95 percent confidence intervals excluding 1.0. By using stepwise backward elimination, variables with P values greater than 0.05 were then removed from the model.

RESULTS

NHANES III (1988 to 1994)

The seroprevalence of HSV-2 among study participants 12 years of age or older was 21.9 percent (95 percent confidence interval, 20.2 to 23.6 percent) (Table 1). This prevalence corresponds to 45 million infected people in the noninstitutionalized civilian U.S. population. The seroprevalence was higher among women (25.6 percent) than among men (17.8 percent), yielding a female:male prevalence ratio of 1.4 (95 percent confidence interval, 1.2 to 1.7). The seroprevalence was 17.6 percent among whites, 45.9 percent among blacks, and 22.3 percent among Mexican Americans, yielding a black:white prevalence ratio of 2.6 (95 percent confidence interval, 2.3 to 2.9) and a Mexican-American:white prevalence ratio of 1.3 (95 percent confidence interval, 1.1 to 1.4). The female:male prevalence ratios were similar for each race or ethnic group. With increasing age, the overall HSV-2 seroprevalence rose rapidly in the younger age groups and then remained stable among people older than 30 years, in the range of 24 percent to 28 percent.

By univariate analysis, HSV-2 seroprevalence was associated with a number of variables (Table 2). HSV-2 seroprevalence was higher among persons who were divorced or separated and those who were widowed than among single or married people, those with less education, and those living below the poverty level. There was no statistically significant difference in HSV-2 seroprevalence between urban and nonurban areas, and only a slight variation among the four regions of the United States. As far as behavioral variables were concerned, HSV-2 seroprevalence was higher among those who had ever used cocaine, those who had first had intercourse at the age of 17 or younger, and those with a greater lifetime number of sexual partners.

With increasing lifetime numbers of sexual partners, HSV-2 seroprevalence initially rose more sharply for blacks than for whites, even after adjustment for age (Fig. 1). For example, the age-adjusted seroprevalence among blacks who reported having one partner over a lifetime was 4.4 times that among whites reporting one partner; this held true both for men and women. By contrast, with increasing lifetime numbers of sexual partners, the seroprevalence among blacks leveled off, whereas it increased sharply among whites.

Only 2.6 percent of adults report ever having had genital herpes. Persons with a history of genital herpes had an HSV-2 seroprevalence of 81.5 percent, whereas all other persons had a seroprevalence of 21.6 percent (Table 2). The sensitivity of a self-reported history of genital herpes for the presence of HSV-2 antibody was 9.2 percent overall and was similar for both sexes. In contrast, the sensitivity of a self-reported history of genital herpes for the presence of HSV-2 antibody differed markedly according to race or ethnic group; it was 12.2 percent for whites, 3.7 percent for blacks, and 3.8 percent for Mexican Americans.

In a multivariate model that examined the demographic and behavioral variables associated with HSV-2 status on univariate analysis, differences associated with marital status and age at first sexual intercourse were found not to be statistically significant ($P>0.05$) and were therefore dropped from the model. In the model, the multivariate independent

TABLE 1. HSV-2 SEROPREVALENCE IN NHANES III (1988 TO 1994) ACCORDING TO SEX, AGE, AND RACE OR ETHNIC GROUP.*

VARIABLE	OVERALL†		WHITES		BLACKS		MEXICAN AMERICANS	
	SAMPLE SIZE	PERCENT PREVALENCE (95% CI)	SAMPLE SIZE	PERCENT PREVALENCE (95% CI)	SAMPLE SIZE	PERCENT PREVALENCE (95% CI)	SAMPLE SIZE	PERCENT PREVALENCE (95% CI)
Sex								
Both sexes	13,094	21.9 (20.2–23.6)	4727	17.6 (15.7–19.8)	3884	45.9 (43.9–47.9)	3991	22.3 (21.2–23.5)
Male	6,407	17.8 (15.6–20.2)	2383	14.9 (12.3–18.1)	1798	34.7 (32.5–37.0)	1992	19.2 (17.9–20.6)
Female	6,687	25.6 (24.0–27.3)	2344	20.2 (18.3–22.2)	2086	55.1 (52.7–57.5)	1999	25.7 (24.2–27.2)
Age (yr)								
12–19	2,396	5.6 (4.3–7.2)	605	4.5 (3.0–6.8)	806	8.7 (6.4–11.9)	870	5.4 (4.0–7.3)
20–29	2,750	17.2 (15.0–19.7)	675	14.7 (12.0–18.1)	891	33.6 (30.3–37.2)	1072	14.8 (12.6–17.5)
30–39	2,567	27.8 (24.8–31.2)	792	21.9 (18.7–25.6)	884	54.4 (50.5–58.6)	793	28.7 (26.3–31.4)
40–49	2,061	26.6 (23.5–30.0)	724	19.9 (16.4–24.1)	634	58.9 (55.7–62.4)	612	33.0 (28.4–38.3)
50–59	884	25.1 (21.5–29.4)	456	19.4 (15.6–24.1)	211	62.7 (54.4–72.3)	185	42.5 (31.6–57.1)
60–69	1,069	24.3 (20.2–29.1)	480	18.2 (13.7–24.0)	258	76.8 (72.3–81.5)	310	38.7 (32.0–46.8)
≥70	1,367	27.7 (24.6–31.1)	995	23.3 (20.0–27.0)	200	74.3 (67.6–81.8)	149	44.6 (38.8–51.2)

*CI denotes confidence interval.

†Totals differ from the sums for whites, blacks, and Mexican Americans because other races and ethnic groups are included in the overall totals.

TABLE 2. HSV-2 SEROPREVALENCE IN NHANES III (1988 TO 1994) ACCORDING TO DEMOGRAPHIC AND BEHAVIORAL FACTORS AND HISTORY OF HERPES.*

VARIABLE	SAMPLE SIZE†	PERCENT PREVALENCE (95% CI)
Demographic factors		
Marital status		
Single	2793	17.1 (14.9–19.8)
Married	6732	21.5 (19.3–23.9)
Divorced or separated	1222	39.0 (34.9–43.7)
Widowed	813	35.0 (30.1–40.6)
Education (last year completed)		
Elementary	2194	35.2 (30.3–40.9)
High school	5775	24.2 (22.6–25.9)
Some college	3539	19.2 (16.8–22.0)
Poverty index		
Below poverty level	2848	33.5 (30.6–36.7)
At or above poverty level	8731	21.3 (19.3–23.4)
Residence		
Urban	9472	23.3 (21.3–25.5)
Nonurban	2107	21.0 (17.8–24.6)
Region		
Northeast	1488	21.7 (16.8–27.9)
Midwest	2070	18.4 (15.4–21.9)
South	5323	24.8 (22.4–27.5)
West	2698	26.4 (23.8–29.3)
Behavioral factors		
Ever used cocaine		
Yes	1011	33.9 (29.2–39.4)
No	7860	20.6 (18.9–22.4)
Age at first sexual intercourse (yr)		
≤17	5055	26.8 (24.7–29.1)
≥18	3437	18.9 (16.6–21.6)
Lifetime number of sexual partners		
0	361	3.0 (1.3–7.0)
1	1807	10.2 (8.2–12.7)
2–4	2633	20.7 (18.2–23.6)
5–9	1716	25.9 (22.7–29.5)
10–49	1830	30.9 (27.5–34.6)
≥50	346	46.1 (39.5–53.9)
Answer to question: "Have you ever had genital herpes?"		
Yes	167	81.5 (70.0–94.9)
No	8302	21.6 (19.8–23.5)

*The age ranges are ≥17 years for demographic variables and 18 to 59 for behavioral variables. CI denotes confidence interval.

†In some cases, data were not available for all subjects.

predictors of HSV-2 serologic status were female sex, black race or Mexican-American ethnic background, older age, less formal education, an income below the poverty level, a greater lifetime number of sexual partners, and having ever used cocaine. The strongest predictors (with odds ratios greater than 3.0) were sex, race or ethnic group, age, and the lifetime number of sexual partners.

Trends in HSV-2 Seroprevalence between NHANES II (1976 to 1980) and NHANES III (1988 to 1994)

The age-adjusted overall prevalence of HSV-2 antibody rose from 16.0 percent in NHANES II to 20.8 percent in NHANES III (Table 3), a relative increase of 30 percent (95 percent confidence interval, 15.8 to 45.8 percent). The relative increases

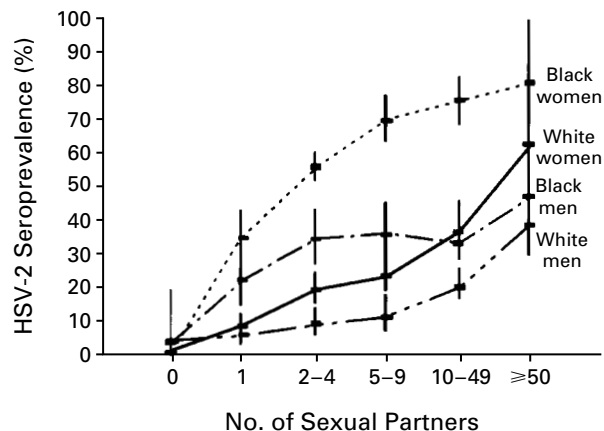


Figure 1. HSV-2 Seroprevalence According to the Lifetime Number of Sexual Partners, Adjusted for Age, for Black and White Men and Women in NHANES III (1988 to 1994).

Bars indicate 95 percent confidence intervals.

among men and women were similar. Among both whites and blacks there were similar absolute increases, but the relative increases were greater among whites because of the lower base-line prevalence among whites. The age-adjusted HSV-2 seroprevalence among whites increased from 12.7 percent in NHANES II to 16.5 percent in NHANES III, a relative increase of 30 percent (95 percent confidence interval, 9.9 to 54.3 percent). Among blacks, the age-adjusted seroprevalence increased from 43.6 to 47.6 percent, a relative increase of 9 percent (95 percent confidence interval, -1.2 to 20.4 percent).

The increases in HSV-2 seroprevalence between NHANES II and NHANES III were concentrated in the younger age groups. There were statistically significant increases overall in the three youngest age groups, encompassing subjects from 12 to 39 years of age (Fig. 2). Among whites, the seroprevalence increased from 0.96 to 4.5 percent (prevalence ratio, 4.7; 95 percent confidence interval, 1.4 to 16.0) among 12-to-19-year-olds, and from 7.7 to 14.7 percent (prevalence ratio, 1.9; 95 percent confidence interval, 1.3 to 2.8) among 20-to-29-year-olds. Among older whites and among blacks, the increases were smaller and did not reach statistical significance in any age group.

DISCUSSION

These findings document the increasing seroprevalence of HSV-2 in the United States during an era in which the acquired immunodeficiency syndrome (AIDS) became recognized and national prevention efforts were initiated. During the period covered by NHANES III (1988 to 1994), the overall seroprevalence of HSV-2 in the United States was 21.9 percent. From NHANES II (1976 to 1980) to NHANES III,

TABLE 3. CHANGES IN AGE-ADJUSTED HSV-2 SEROPREVALENCE BETWEEN NHANES II (1976 TO 1980) AND NHANES III (1988 TO 1994).*

CATEGORY OF SUBJECTS	NHANES II		NHANES III		PERCENT RELATIVE INCREASE
	AGE-ADJUSTED PERCENT		AGE-ADJUSTED PERCENT		
	SAMPLE SIZE	SEROPREVALENCE (95% CI)	SAMPLE SIZE	SEROPREVALENCE (95% CI)	
All races and ethnic groups†					
Both sexes	3597	16.0 (14.7–17.4)	13,094	20.8 (19.2–22.5)	30
Men	1681	13.4 (11.7–15.4)	6,407	17.1 (15.0–19.5)	27
Women	1916	18.4 (16.5–20.5)	6,687	24.2 (22.7–25.7)	32
Whites					
Both sexes	2153	12.7 (11.2–14.3)	4,727	16.5 (14.7–18.5)	30
Men	1021	10.7 (8.7–13.0)	2,383	14.1 (11.6–17.2)	32
Women	1132	14.5 (12.4–17.0)	2,344	18.7 (17.0–20.5)	29
Blacks					
Both sexes	1130	43.6 (40.0–47.6)	3,884	47.6 (45.4–49.9)	9
Men	495	34.1 (30.0–38.7)	1,798	37.5 (34.8–40.3)	10
Women	635	51.4 (47.6–55.6)	2,086	55.7 (53.3–58.2)	8

*Seroprevalence has been age-adjusted to the 1980 census. The age range is ≥12 years. CI denotes confidence interval.

†Totals differ from the numbers for whites and blacks because other races and ethnic groups are included in the category of all races and ethnic groups.

the age-adjusted seroprevalence increased by 30 percent, with the greatest relative increases among young whites.

Women were about 45 percent more likely than men to be infected with HSV-2 during both study periods. Potential explanations for this finding include the higher efficiency of HSV-2 transmission from men to women as compared with that from women to men¹⁴ and differences between women and men in sexual behavior.³⁴⁻³⁶ For example, women are more likely than men to choose sexual partners who are older than themselves³⁶ and who therefore have an increased risk of HSV-2 infection.

In both surveys, blacks were more likely than other racial or ethnic groups to be infected with HSV-2. The disparities may be due to a variety of factors, both current and historical, which include racial and ethnic differences in the prevalence of poverty and low socioeconomic status, access to health care, sexual behavior, health-related behavior, and illicit drug use, as well as the age and sex composition of the population.³⁷⁻³⁹

Of the other demographic and behavioral factors assessed in NHANES III, the most strongly predictive of HSV-2 infection was the lifetime number of sexual partners. However, this effect was not the same for both sexes or for all races or ethnic groups (Fig. 1). In fact, black men and women who reported having had only one sexual partner over their lifetimes were more than four times as likely to be infected with HSV-2 as white men and women with one sexual partner. This observation is consistent

with the idea that the pool of potential sexual partners is different for whites and blacks. Since white and black populations have different levels of HSV-2 prevalence and since sexual partnerships tend to form between members of the same race or ethnic group,^{36,40} whites and blacks will typically face different risks of exposure to HSV-2 with each sexual partner. A similar difference has been observed between white and black women with respect to the risk of pelvic inflammatory disease.⁴¹

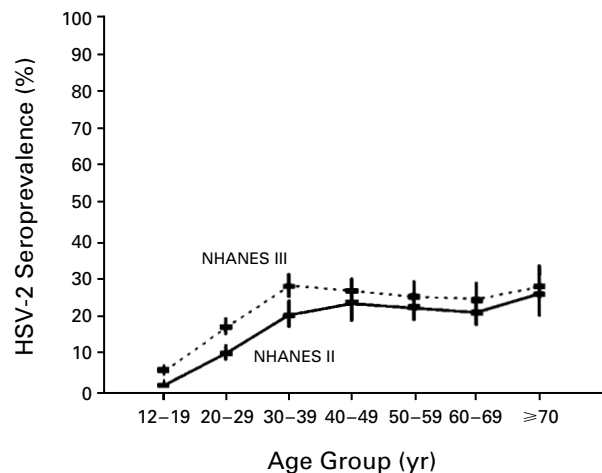


Figure 2. HSV-2 Seroprevalence According to Age in NHANES II (1976 to 1980) and NHANES III (1988 to 1994). Bars indicate 95 percent confidence intervals.

The great majority of people with serologic evidence of HSV-2 infection in the current study had no history of genital herpes. However, previous studies have demonstrated that many or most seropositive persons shed HSV-2 that is detectable by culture from the genital tract,^{5,17-19} and many have symptoms, such as itching and discharge, that are directly referable to HSV-2 detectable by culture. Such symptoms, however, are not often recognized as indicating an infection.^{16,19}

Could the increases in HSV-2 seroprevalence among young people in the 13 years between the two surveys be related to changes in sexual behavior? During these years, AIDS was recognized as a public health problem, and large-scale HIV prevention efforts were initiated that might conceivably also have contributed to a reduction in HSV-2 infection. For example, condom use by young men more than doubled between 1979 and 1988.⁴² Condoms are effective in preventing HIV transmission when they are properly used during every sexual encounter.⁴³ However, their effectiveness against HSV-2 transmission has been less well documented and may be more limited, because HSV-2 lesions can occur on areas of the body not covered by condoms.⁴³⁻⁴⁵ On the other hand, despite AIDS-prevention efforts, the prevalence of premarital sexual experience and multiple sexual partners increased among both young whites and young blacks.^{42,46-48} The increases in some types of risky behavior were more marked among whites.⁴⁶

These results highlight the ongoing need to prevent HSV-2 and other sexually transmitted infections. A concerted national effort is needed to overcome barriers to the adoption of healthful sexual behavior, as emphasized in a recent report on sexually transmitted diseases from the Institute of Medicine.⁴⁹ In addition, improvements in the diagnosis and treatment of established HSV-2 infection may have some effect on the transmission of HSV-2, since suppressive therapy with antiviral medications has been shown to decrease viral shedding.⁵⁰⁻⁵² Finally, new preventive techniques, such as the use of HSV-2 vaccines⁵³⁻⁵⁷ and topical microbicides⁵⁸ now under development, are urgently needed.

A primary goal of efforts to reduce HSV-2 infection should be the prevention of new HIV infections, since genital ulcers caused by HSV-2 may independently facilitate HIV transmission.⁷⁻¹² In the meantime, HSV-2 seroprevalence, as measured by NHANES, provides reliable data on the prevalence of this sexually transmitted disease in the United States. It may therefore be an important indicator to follow as we attempt to promote healthful sexual behavior and prevent sexually transmitted diseases, including HIV infection.

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