

A PROSPECTIVE STUDY OF NEW INFECTIONS WITH HERPES SIMPLEX VIRUS TYPE 1 AND TYPE 2

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ABSTRACT

Background Herpes simplex virus (HSV) infections are endemic, but the clinical characteristics of newly acquired HSV type 1 (HSV-1) and HSV type 2 (HSV-2) infections in adults have not been rigorously defined.

Methods We monitored 2393 sexually active HSV-2-seronegative persons for clinical and serologic evidence of new HSV infection. Of the participants, 1508 were seropositive for HSV-1 and 885 were seronegative. Charts were reviewed in a blinded manner for classification of those with genitourinary or oropharyngeal symptoms. Charts were also reviewed for all 174 persons with HSV seroconversion.

Results The rates of new HSV-1 and HSV-2 infections were 1.6 and 5.1 cases per 100 person-years, respectively. Of the 155 new HSV-2 infections, 57 (37 percent) were symptomatic, 47 of which (82 percent) were correctly diagnosed at presentation. Among the 74 patients given a clinical diagnosis of genital HSV-2 infection during the study, 60 were given a correct diagnosis and 14 were given an incorrect diagnosis, for a ratio of true positive results to false positive results of 4:1. Among the 98 persons with asymptomatic HSV-2 seroconversion, 15 percent had genital lesions at some time during follow-up. Women were more likely than men to acquire HSV-2 ($P < 0.01$) and to have symptomatic infection. Previous HSV-1 infection did not reduce the rate of HSV-2 infection, but it did increase the likelihood of asymptomatic seroconversion, as compared with symptomatic seroconversion, by a factor of 2.6 ($P < 0.001$). Of the 19 new HSV-1 infections, 12 were symptomatic. The rates of symptomatic genital HSV-1 infection and oropharyngeal HSV-1 infection were the same (0.5 case per 100 person-years).

Conclusions Nearly 40 percent of newly acquired HSV-2 infections and nearly two thirds of new HSV-1 infections are symptomatic. Among sexually active adults, new genital HSV-1 infections are as common as new oropharyngeal HSV-1 infections. (N Engl J Med 1999;341:1432-8.)

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HERPES simplex virus (HSV) infections are endemic throughout the world.¹⁻³ In both point-prevalence and prospective studies, a large percentage of persons who are seropositive for HSV type 1 (HSV-1) or HSV type 2 (HSV-2) have no clinical manifestations of the disease.³⁻⁶ Many of the clinical characteristics of symptomatic genital HSV are similar to those of other conditions, such as nongonococcal urethritis in men,⁷⁻¹⁰ nonchlamydial urethritis¹¹ and recurrent vaginitis⁷ in women, and neurologic diseases, including aseptic meningitis.^{12,13} No studies have prospectively defined the relative frequency of symptomatic or asymptomatic HSV infection and the relative proportions of typical clinical manifestations of infection and atypical manifestations. In 1993 we initiated two parallel phase 3 trials of a glycoprotein-subunit vaccine against HSV-2 that was subsequently shown to be ineffective.¹⁴ These studies were conducted at 27 sites by clinicians experienced in the diagnosis and management of genital herpes.¹⁴ In this report we describe the clinical spectrum and course of the 155 new cases of HSV-2 infection and the 19 new cases of HSV-1 infection that occurred during these trials.

METHODS

Study Participants

Sexually active adults who were seronegative for both HSV-2 and the human immunodeficiency virus were recruited into two similarly designed trials to evaluate the effectiveness of a glycoprotein-subunit vaccine for the prevention of HSV-2 infection. One trial, conducted at 18 centers, enrolled 531 HSV-2-seronegative persons, each of whom reported that he or she had been in an exclusive sexual relationship with a partner infected with HSV-2 for a minimum of six months. The second trial involved 22 clinics for the treatment of sexually transmitted diseases and enrolled 1862 persons who reported having had four or more sexual partners in the year before enrollment or who reported having one or more of the following sexually transmitted diseases: pelvic inflammatory disease (in women), a first episode of nongonococcal urethritis (in men), gonorrhea, chlamydia, primary or secondary syphilis, or trichomoniasis. The protocol was approved by the institutional review board at each of the study sites, and the participants gave written informed consent.

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Study Design

The details of the study design and the overall outcomes of the trials have been reported elsewhere.¹⁴ In brief, the participants were randomly assigned to receive three immunizations with the recombinant glycoprotein-subunit gD2-gB2-MF59 HSV vaccine (Chiron, Emeryville, Calif.) or citrate buffer alone in MF59 adjuvant (placebo) and were followed at 11 routine visits at intervals of 2 weeks to 3 months during the 18-month study period.

All the participants received standardized counseling about the practice of safe sex at every scheduled study visit, including the recommendation to use condoms during each sexual exposure. The participants were instructed about the signs and symptoms of genital herpes and were requested to present to the study clinic for evaluation of all genitourinary and orolabial signs and symptoms during the course of the trial. At visits for symptoms, genital examination was performed to determine whether lesions were present and to record the number and location of lesions and the duration of symptoms. Specimens for culture for HSV were obtained from all symptomatic sites. All data from such visits were recorded on standardized case-report forms and entered in a centralized data base. In addition, the clinical diagnosis at each visit for the evaluation of genital symptoms was recorded. Blood was collected at every scheduled visit and at visits for the evaluation of genital symptoms.

The glycoprotein-subunit vaccine demonstrated no significant efficacy in either clinical trial (9 percent overall calculated efficacy; 95 percent confidence interval, -29 to 36 percent).¹⁴ In addition, detailed analyses identified no significant effect of vaccination on either the frequency of clinical signs and symptoms or the subsequent clinical course of genital herpes acquired during the trial. All cases of genital and orolabial herpes that were identified in either study are included in this report.

Definition of the Acquisition of HSV Infection

The acquisition of HSV infection was defined by the demonstration of HSV-1 or HSV-2 seroconversion, a positive culture for HSV, or both. Cultures for HSV were performed at all study sites with the use of standard techniques.¹⁵ Serum samples drawn at the time of trial entry and on the date of termination of the study were paired, and the latter samples were tested for the presence of new antibodies to HSV-specific proteins. We reassayed in parallel all serum samples from persons in whom differences from base line in the antibody profile were noted.¹⁶⁻¹⁸ The Western blot assay used for these procedures has a specificity of more than 99.5 percent for the detection of HSV-2 antibodies among persons with positive cultures^{15,17} and more than 96 percent for the detection of past HSV-1 infection among persons with positive cultures for HSV-1. It also is more sensitive than any other currently used assay for the detection of recent HSV-2 infection.¹⁷⁻²⁰ Of the 178 persons in whom HSV infection had been identified in the initial screening, 174 were confirmed to have seroconversion with respect to either HSV-1 or HSV-2 through the examination of sequential serum samples. These 174 persons constituted the group of patients with newly acquired HSV infection.^{17-19,21}

The date of the first positive culture was considered the date of acquisition of symptomatic infection unless there was an earlier date of seroconversion. For asymptomatic disease, the midpoint between the last negative assay and the first positive sample was used as the date of acquisition. Chart review was performed in a blinded manner for all persons reporting genitourinary or oropharyngeal symptoms and for all 174 persons with seroconversion at the conclusion of the trials.

Statistical Analysis

The log-rank test was used to compare the distribution of times to the acquisition of HSV-2 infection between men and women and between persons who were seropositive and those who were seronegative for HSV-1 at study entry. The Cox proportional-hazards regression model was used to compute the rel-

ative risk of acquiring HSV-1 or HSV-2 infection. Relative risk was estimated by the exponential function of λ , where λ was the coefficient from the Cox model, with sex (or HSV-1 serologic status at entry) as the only independent variable. The 95 percent confidence interval for the relative risk was calculated in a similar fashion, with the use of the upper and lower 95 percent confidence limits for λ . Statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.). All reported P values are two-sided.

RESULTS

Characteristics of the Study Participants

Of the 2393 persons enrolled, 1646 were men and 747 were women. At entry, 1508 persons had HSV-1 antibodies and 885 were seronegative for both HSV-1 and HSV-2. All but 2 of the 2393 persons had subsequent serum samples that could be evaluated by Western blot analysis. These two persons (both men) were initially seronegative for both HSV-1 and HSV-2. The remaining 2391 persons were followed prospectively for a total of 3016 person-years. The demographic characteristics of the participants who acquired HSV infection did not differ significantly from those of the participants who did not have seroconversion (Table 1).

Rates of Acquisition of HSV-1 and HSV-2 Infection

During the trials, 155 new cases of HSV-2 and 19 new HSV-1 infections were documented. The overall rate of HSV-2 infection averaged 5.1 cases per 100 person-years. The rate of acquisition of HSV-2 infection was significantly higher for women than for men (6.8 vs. 4.4 cases per 100 person-years; relative risk, 1.55; 95 percent confidence interval, 1.11

TABLE 1. DEMOGRAPHIC AND SEROLOGIC CHARACTERISTICS OF THE STUDY PARTICIPANTS WHO ACQUIRED NEW HERPES SIMPLEX VIRUS INFECTIONS.*

CHARACTERISTIC	HSV-1 POSITIVE (N=19)	HSV-2 POSITIVE (N=155)	No New INFECTION (N=2217)
Age — yr			
Mean \pm SD	29.8 \pm 10.8	28.0 \pm 7.8	30.3 \pm 9.4
Median	25.0	26.0	28.0
Range	18–52	18–69	17–79
Sex — no. (%)			
Male	15 (79)	92 (59)	1537 (69)
Female	4 (21)	63 (41)	680 (31)
Base-line serologic status — no. (%)			
HSV-1 positive	0	95 (61)	1413 (64)
HSV-1 negative	19 (100)	60 (39)	804 (36)
Race or ethnic group — no. (%)			
Asian	0	4 (3)	28 (1)
Black	2 (11)	61 (39)	542 (24)
White	17 (89)	82 (53)	1538 (69)
Hispanic	0	5 (3)	78 (4)
Other	0	3 (2)	31 (1)

*HSV-1 denotes herpes simplex virus type 1, and HSV-2 herpes simplex virus type 2.

TABLE 2. FREQUENCY AND RATE OF SYMPTOMATIC AND ASYMPTOMATIC HERPES SIMPLEX VIRUS INFECTION IN ADULTS.*

TYPE OF INFECTION	TOTAL PERSON-YEARS	rate per 100 person-yr (no. of cases)		TOTAL
		ASYMPTOMATIC	SYMPTOMATIC	
Total no. of new HSV-1 infections	1170	0.6 (7)	1.0 (12)	1.6 (19)
Men	786	0.8 (6)	1.1 (9)	1.9 (15)
Women	384	0.3 (1)	0.8 (3)	1.0 (4)
Total no. of new HSV-2 infections	3015	3.2 (98)†	1.9 (57)	5.1 (155)
Men	2086	3.0 (63)‡	1.4 (29)	4.4 (92)§
White, <30 yr	628	1.6 (10)	0.8 (5)	2.4 (15)
White, ≥30 yr	776	1.7 (13)	1.2 (9)	2.8 (22)
Nonwhite, <30 yr	410	6.6 (27)	3.2 (13)	9.8 (40)
Nonwhite, ≥30 yr	272	4.8 (13)	0.7 (2)	5.5 (15)
Women	929	3.8 (35)	3.0 (28)	6.8 (63)
White, <30 yr	458	2.8 (13)	3.7 (17)	6.6 (30)
White, ≥30 yr	310	2.3 (7)	2.6 (8)	4.8 (15)
Nonwhite, <30 yr	106	9.4 (10)	2.8 (3)	12.3 (13)
Nonwhite, ≥30 yr	55	9.1 (5)	0 (0)	9.1 (5)
HSV-1 positive at base line	1868	3.6 (68)¶	1.4 (27)	5.1 (95)
HSV-1 negative at base line	1147	2.6 (30)	2.6 (30)	5.2 (60)

*HSV-1 denotes herpes simplex virus type 1, and HSV-2 herpes simplex virus type 2.

† $P < 0.01$ for the comparison with symptomatic HSV-2 infection.

‡ $P < 0.001$ for the comparison with symptomatic infection in men.

§ $P < 0.01$ for the comparison of overall rates of HSV-2 infection between men and women.

¶ $P < 0.001$ for the comparison with symptomatic infection in HSV-1-positive persons.

to 2.11; $P < 0.01$) (Table 2). Among white women, the rate of HSV-2 infection was 5.8 cases per 100 person-years, as compared with 11.2 cases per 100 person-years among nonwhite women (relative risk, 0.52; 95 percent confidence interval, 0.34 to 0.94; $P = 0.03$). The comparable rates for white men and nonwhite men were 2.6 and 8.1 cases per 100 person-years, respectively (relative risk, 0.32; 95 percent confidence interval, 0.22 to 0.51; $P < 0.001$). The rates of acquisition were higher among men and women less than 30 years of age (5.3 and 7.6 cases per 100 person-years, respectively) than among those 30 and older (3.5 and 5.5 cases per 100 person-years, $P = 0.04$).

Asymptomatic HSV-2 infection was significantly more common than symptomatic HSV infection among men (3.0 vs. 1.4 cases per 100 person-years, $P < 0.001$), whereas among women the rates of asymptomatic infection and symptomatic infection were nearly equal (3.8 and 3.0 cases per 100 person-years, respectively). Persons who were seropositive for HSV-1 at study entry were almost as likely to acquire HSV-2 as those who were seronegative for HSV-1 (5.1 vs. 5.2 infections per 100 person-years; relative risk, 0.98; 95 percent confidence interval, 0.70 to 1.34); however, HSV-2 infections among the HSV-1-seropositive participants were more likely to be asymptomatic than symptomatic (3.6 vs. 1.4 cases per 100 person-years, $P < 0.001$). For HSV-1-seronegative subjects, both men and women, the frequency of asymptomatic HSV-2 infection was the same as that

of symptomatic HSV-2 infection (2.6 cases per 100 patient-years).

The rate of new HSV-1 infection averaged 1.6 cases per 100 patient-years and was similar for women and men (1.0 and 1.9 cases per 100 person-years, respectively; relative risk, 0.53; 95 percent confidence interval, 0.18 to 1.65).

Clinical Recognition of the New HSV-2 Infections

Among the 155 persons with HSV-2 seroconversion, 57 (37 percent) had genital lesions or other symptoms of infection between the time of screening and the time that HSV-2 seroconversion was confirmed, for a rate of acquisition of symptomatic HSV-2 infection of 1.9 cases per 100 person-years. The median time between the onset of these symptoms or lesions and seroconversion was 56 days (interquartile range, 16 to 121). Of these 57 persons with symptomatic infection, 54 presented to the clinic for medical evaluation (Fig. 1). All three persons who did not initially present with symptoms reported typical lesions at the time of seroconversion, and one of them subsequently presented with a recurrence confirmed by a positive culture.

Forty-seven (87 percent) of the 54 participants who presented for evaluation were given a diagnosis of genital HSV disease. Of these 47, 43 had typical signs and symptoms, including genital pain, papules, pustules, vesicles, ulcers, crusts, and fissures. The other four cases of genital herpes, involving two women

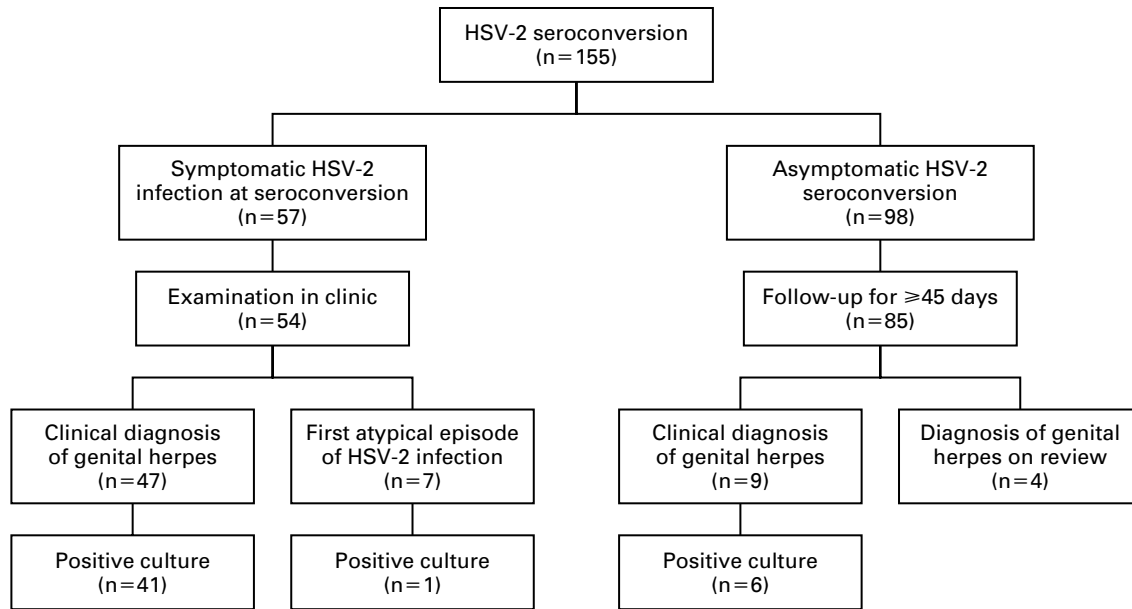


Figure 1. Serologically Documented Herpes Simplex Virus Type 2 (HSV-2) Infections.

Three patients with symptomatic HSV-2 infections reported genital symptoms and lesions that were consistent with a diagnosis of HSV; only one of these patients subsequently presented with recurrent symptoms. Atypical episodes of HSV-2 included aseptic meningitis, cystitis, dysuria, radicular pain, nonchlamydial nongonococcal urethritis, penile dermatitis, pubic folliculitis, fever, malaise, myalgia, and purulent vaginal discharge.

with genital pain only and two men with urethral discharge, were diagnosed clinically and were included as cases because the results of the screening cultures specified by the protocol were positive. HSV-2 was isolated from lesions in 41 (87 percent) of the 47 persons who presented with clinically recognized signs and symptoms of herpes (Fig. 1).

During follow-up, two of the six persons with clinically diagnosed genital herpes who initially had negative cultures subsequently had HSV-2 isolated from a recurrent genital lesion. In addition, one of seven persons who became positive for HSV-2 who were not considered to have herpes at the initial presentation (Fig. 1) subsequently had a culture-positive recurrence.

Thus, 41 of the 57 persons with symptomatic HSV-2 seroconversion had positive cultures at the time of their initial presentation to the clinic, and an additional 4 had positive cultures at the time of recurrence. Altogether, at some point during the study, 45 of the 57 persons (79 percent) who had genital symptoms and lesions in association with their seroconversion to HSV-2 had positive HSV-2 cultures.

Seven persons who became positive for HSV-2 presented with symptoms without external genital lesions. None of these seven were initially given a diagnosis of HSV-2, although one was subsequently given such a diagnosis at the time of the first recognized recurrence. One woman, hospitalized for aseptic meningitis and cystitis, had HSV-2 DNA detect-

ed in her cerebrospinal fluid by the polymerase chain reaction and had seroconversion by 111 days after the onset of symptoms. Another woman had 11 days of dysuria accompanied by radicular pain on the left side of vertebral bodies L2 and L3. She became positive for HSV-2 within 45 days after the onset of these symptoms. On follow-up, she reported recurrent episodes of genital pain and vaginal numbness during which HSV-2 was isolated. Four men were given a diagnosis of nonchlamydial, nongonococcal urethritis, of whom three were given concomitant diagnoses of penile dermatitis and pubic folliculitis. The seventh person, a woman, had fever, malaise, myalgias, and a purulent vaginal discharge without external genital lesions. These last five persons had had seroconversion by the time of the first available serum sample after the resolution of their symptoms (median, 36 days). The seven cases were classified as nonlesional HSV-2 infections, since urethritis, aseptic meningitis, and cervicitis are well-recognized complications of the first episodes of HSV infection.^{7,8}

Natural History of Asymptomatic HSV-2 Infection

Asymptomatic HSV-2 seroconversion was defined as the absence of any reported or clinically confirmed genital lesions between the time of screening and the time of seroconversion. Of the 155 persons who acquired HSV-2 infection, 98 had asymptomatic seroconversion (63 men and 35 women). The frequency

of asymptomatic seroconversion was 2.1 times as high as that of symptomatic seroconversion among men, and 2.6 times as high among HSV-1-seropositive persons (Table 2).

Eighty-five of the 98 persons with asymptomatic HSV-2 seroconversion were prospectively followed for at least 45 days after the date of their first HSV-2-positive serologic test (median number of days of follow-up, 351; interquartile range, 223 to 510). Of these 85 persons, 13 (15 percent) had genital lesions at some later time during follow-up (incidence, 17 per 100 person-years) (Fig. 1). Nine of these 13 episodes (69 percent) were clinically diagnosed as genital herpes. Diagnoses recorded for the other four episodes included molluscum contagiosum in a woman in whom ulcerative genital lesions were also found, perineal skin fissure in another woman, papular penile dermatitis in a man in whom ulcerative lesions were also found, and nongonococcal urethritis in another man.

The Predictive Value of a Clinical Diagnosis of Genital Herpes

Of the 155 persons who acquired HSV-2 infection, 58 (37 percent) received a clinical diagnosis of genital herpes during the course of the trial; 47 had contemporaneous seroconversion, 1 had a subsequent lesional recurrence, and in 10 infection was recognized at the first recurrence. Two additional persons had typical lesions for which they did not present for examination but which were classified by the investigator as consistent with herpes. Therefore, a total of 60 cases were considered to be true positives after clinical evaluation.

Fourteen persons were given an incorrect diagnosis of genital herpes — that is, they were given a clinical diagnosis of infection, but all had negative cultures for HSV and no evidence of HSV-2 or HSV-1 seroconversion, despite at least six months of follow-up. Among the 74 persons given a clinical diagnosis of genital HSV-2 during the study, therefore, 60 had true positive test results and 14 had false positive results (ratio of true positives to false positives, 4:1). Thus, 60 persons with symptomatic HSV-2 infection among a total of 155 persons with HSV-2 seroconversion were identified, yielding a sensitivity of 39 percent for the clinical diagnosis of HSV-2 infection and a specificity of 99 percent. The positive predictive value of a clinical diagnosis of genital herpes was 81 percent (60 of 74 symptomatic cases were correctly identified). Since the rate of acquisition of genital herpes was relatively low in this group of patients, the negative predictive value was quite high (96 percent; 2222 of 2317 persons who did not have symptoms were correctly identified).²⁰

Newly Acquired HSV-1 Infection Manifested as Genital Herpes

HSV-1 infection, defined as the isolation of HSV-1 from cultures of the genital tract or seroconversion

to HSV-1 between the time of study entry and the time the last follow-up serum sample was obtained, occurred in 19 of the 883 originally seronegative study participants for whom samples were available (2.2 percent). The overall rate of HSV-1 infection was 1.6 cases per 100 person-years. Four of the 19 persons were women and 15 were men (1.0 vs. 1.9 cases per 100 person-years, *P* not significant).

Of the 19 persons with primary HSV-1 infection, 6 (32 percent) had genital lesions associated with seroconversion. HSV-1 was isolated from the genital lesions of five of these six persons. The sixth person was given a diagnosis of penile fungal dermatitis, but he had seroconversion within 30 days after onset (he thus represented a false negative diagnosis of genital HSV-1). During a median of 266 days of follow-up, only one of the six persons with symptomatic genital HSV-1 infection reported a subsequent genital recurrence. An additional six persons with documented HSV-1 seroconversion reported either orolabial lesions or pharyngitis. Orolabial HSV-1 infection was clinically diagnosed in three persons; the other three had pharyngitis, including one who underwent a tonsillectomy. The remaining seven persons with HSV-1 seroconversion reported no signs or symptoms (i.e., they were asymptomatic). Thus, the rates of newly acquired genital and oropharyngeal HSV-1 infection were both 0.5 case per 100 person-years.

DISCUSSION

This prospective study defines the natural history of newly acquired symptomatic and asymptomatic HSV infection in sexually active adults. Of the 155 cases of newly acquired HSV-2 infection, 57 (37 percent) were associated with clinically symptomatic disease, which contrasts with the 9 percent in the second National Health and Nutrition Examination Survey and the 15 to 25 percent in other serologic studies.^{2,5} Over 75 percent of the incident cases of symptomatic HSV-2 were associated with lesions of the skin and mucous membranes of the genital tract. However, 13 percent of those who presented with symptomatic HSV-2 had conditions that were not immediately suggestive of herpes, such as cystitis, meningitis, urethritis, and cervicitis. Although this is a small proportion of the total number of cases, the large number of HSV-2 seroconversions that occur in the United States yearly (about 750,000) indicate that these “atypical” presentations will be seen in most clinical practices.

In addition, clinical disease subsequently developed in 15 percent of the persons with asymptomatic seroconversion on follow-up. This percentage represents the minimal number of cases, since it is likely that the percentage would increase with additional prospective follow-up. The observation that seroconversion can precede symptomatic disease is important for the management of genitourinary lesions.

Persons with newly recognized disease often assume that they acquired the infection very recently, not months or years earlier.^{22,23} These data confirm that the detection of HSV-2-specific antibodies at the time of the first presentation with genital lesions may be a useful way to distinguish between past and newly acquired HSV-2 infection.^{22,23}

We also documented a high frequency of genital HSV-1 infection among those with seroconversion to HSV-1. Several studies have described the increasing prevalence of genital HSV-1.²⁴⁻²⁶ Since the study participants were selected at least in part on the basis of their sexual activity, the frequency of genital HSV-1 infections in this group may differ from that in other populations. However, the equal incidence rates of symptomatic genital HSV-1 and oropharyngeal HSV-1 indicate that sexually active people need counseling about the risk of oral-genital contact, especially during pregnancy.^{27,28}

Our data have several implications for programs to prevent HSV infection. As was noted in previous seroepidemiologic studies, acquisition of HSV-2 was more frequent among women than among men and among nonwhites than among whites.² The background seroprevalence of HSV-2 of sexual partners may be one explanation for these differences. Sex and past HSV-1 infection had important effects on the presentation of HSV disease. Men were significantly more likely to acquire HSV-2 asymptotically than were women. Other studies have shown that nearly all asymptomatic HSV-2-seropositive persons, both men and women, shed virus in the genital region.^{9,29} The higher rate of asymptomatic infection in men may be a factor in the higher rate of male-to-female (as compared with female-to-male) transmission of HSV-2.^{9,30} Among HSV-seronegative persons, about half of new infections were symptomatic and half were asymptomatic. Previous HSV-1 infection did not reduce the frequency of acquisition of HSV-2 infection, but it did markedly increase the frequency of seroconversion to asymptomatic HSV-2. These data suggest that vaccination with heterotypic antigens might be expected to reduce the incidence of symptomatic HSV-2 disease but not the incidence of infection.

The results of our study also demonstrate the value of type-specific serologic testing for HSV in the diagnosis and clinical management of HSV infection. Even among experienced clinicians following patients in a clinical trial of herpes infection, genital herpes was both underdiagnosed and overdiagnosed. Although cell cultures were useful in identifying infection in persons with skin lesions, serologic assays provided the critical diagnostic confirmation of the "atypical" syndromes and identified the persons with initial asymptomatic seroconversion who had subsequent recurrences.

In summary, incident cases of HSV infection are

often symptomatic. Although sex, socioeconomic status, and access to health care professionals skilled in the diagnosis of genital herpes may influence the degree to which this infection is recognized clinically, the clinical spectrum of newly acquired HSV infections was similar in all the clinic populations we studied. Clinical presentation without lesions and acquisition of asymptomatic HSV, followed by clinical reactivation of the disease, were common. Among sexually active adults, new genital HSV-1 infections are as common as new oropharyngeal HSV-1 infections. Laboratory assays that define the type of HSV by viral isolation or serologic screening tests are often needed to ensure an accurate diagnosis.

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APPENDIX

Other members of the Chiron HSV Vaccine Study were as follows: J.M. Douglas, Jr., Denver Disease Control Service, Denver; H.H. Handsfield, Harborview Medical Center, Seattle; T. Warren and L. Marr, Westover Heights Clinic, Portland, Oreg.; S. Tyring, University of Texas Medical Branch, Galveston; R. DiCarlo and D. Martin, Louisiana State University, New Orleans; A. Rompalo and J. Zenilman, Johns Hopkins University, Baltimore; A.A. Adimora, University of North Carolina School of Medicine, Chapel Hill; P. Leone, Wake County Health Department, Raleigh, N.C.; A. Wald and L. Corey, University of Washington, Seattle; W. McCormack and M. Feminella, State University of New York Health Science Center, Brooklyn; R. Kee and J. Schwebke, Chicago Department of Health, Chicago; E. Sandstrom and H. Carlberg, Karolinska Institute, Stockholm, Sweden; K. Fife, University of Indiana, Indianapolis; E.W. Hook, University of Alabama, Birmingham; S. Sacks, Viridae Clinical Sciences, Vancouver, B.C., Canada; K. McKee, Fort Bragg, N.C.; P. Olson and S. Brodine, Naval Health Research Center, San Diego, Calif.; C. Miller and D. Campbell, Deaconess Health System, St. Louis; K. Workowski, Emory University, Atlanta; K. Beutner, Solano Dermatology Associates, Vallejo, Calif.; G. Mertz, University of New Mexico, Albuquerque; A. Mindel, Sydney Sexual Health Centre, Sydney, Australia; C. Prober and M.A. Carmark, Stanford University, Palo Alto, Calif.; J. Bingham and E. Fox, St. Thomas' Hospital, London; M. Reitano and J. Stern, Riverside Medical Associates, New York; R. Kost, P. Hohman, and S.E. Straus, National Institutes of Health, Bethesda, Md.; T. Rudolph, Detroit Department of Public Health, Detroit; and R. Murphy, Northwestern University, Chicago.

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