Clinical Reactivation of Genital Herpes Simplex Virus Infection Decreases in Frequency over Time

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Background: Visits to physicians for genital herpes simplex virus (HSV) infection continue to increase. Most patients with symptomatic infections have recurrences, but no studies of the long-term clinical course of genital herpes are available.

Objective: To determine whether the frequency of HSV recurrences decreases over time.

Design: Observational cohort study.

Setting: University-based research clinic.

Patients: 664 persons with genital herpes followed for at least 14 months.

Measurements: Patients were classified as having initial or recurrent HSV-1 or HSV-2 infection. Patient-reported recurrences and observed recurrences were recorded in a database; more than 12 000 recurrences were analyzed.

Results: Median recurrence rates in the first year of follow-up were one and five per year in patients with newly acquired HSV-1 and HSV-2 infection, respectively; second-year rates were significantly lower in both groups. Patients presenting with recurrent HSV-2 infection had higher rates of recurrence in the first and second years and no significant decrease; significant decreases were detected with longer follow-up. One third of all patients experienced a decrease of two or more recurrences per year between years 1 and 2. Patients infected with HSV-2 who were followed for more than 4 years had a median decrease of two recurrences between years 1 and 5. However, 25% of these patients had an increase of at least one recurrence in year 5, illustrating the variability among HSV-infected persons. Decreases over time among patients who never received suppressive therapy were similar to decreases during untreated periods in patients who received suppressive therapy.

Conclusions: Herpes simplex virus type 2 infection continues to be a chronic remitting illness. Over time, however, clinically significant reductions occur in a majority of patients. Physicians may wish to periodically assess the need for continued treatment with daily suppressive antiviral chemotherapy.

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Genital herpes continues to be epidemic throughout the world (1–7). A recent population-based survey in the United States showed a 31% increase in herpes simplex virus (HSV) type 2 seropositivity during the past decade (6). The seroprevalence of HSV-2 infection ranges from 30% to 50% in most sexually transmitted disease clinics and from 20% to 30% in most family practice, obstetric, and general medicine clinics (5, 7–9). The seroprevalence of genital HSV-1 infection is also being reported with increasing frequency (10).

Previous studies of persons with initial episodes of genital herpes have shown that more than 90% of persons infected with HSV-2 have a recurrence during the first year of follow-up (11, 12). However, little is known about the subsequent course of infection. Anecdotal reports have suggested that recurrences of HSV decrease over time (13, 14). However, in a study of the frequency of genital herpes recurrences among 22 women followed for two consecutive pregnancies, Harger and colleagues (15) were unable to detect any appreciable difference in recurrence rates between the first and second pregnancies. Fife and coworkers (16) investigated a group of patients enrolled in a long-term study of continuous daily acyclovir therapy. On discontinuation of therapy, most patients subsequently had a recurrence, although the rate was lower than that reported before treatment. The authors could not determine whether the lower rates were related to antiviral therapy or reflected the long-term natural history of the infection.

Studies of objectively defined observations on the long-term clinical course of recurrent genital herpes are not available. Because decisions to use long-term suppressive therapy or episodic therapy are based on frequency of reactivation, knowledge of the infection's natural history directly benefits clinical management (17). We report on the long-term history of recurrence rates among persons enrolled at a research clinic that studied the clinical course and pathogenesis of genital HSV infection.

Methods

Patients

In 1974, a research clinic dedicated to the study of symptomatic genital herpes infection was estab-

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lished at the Harborview Medical Center in Seattle, Washington (18–21). From 1974 to 1991, we recruited 664 patients with HSV infection documented by serologic studies or culture. These patients were enrolled in a prospective observational study of the frequency of genital HSV reactivation and were followed for at least 14 months. Testing for HIV infection was not part of the study protocol; however, none of these patients demonstrated clinical immunosuppression at study entry or during follow-up. All patients gave informed consent, and institutional review board approval was obtained throughout observation.

Using history, serologic studies, and viral isolation, we classified patients who presented to the clinic as having new or previous acquisition of genital herpes (12, 18–21). Patients with newly acquired HSV infection lack serum antibodies to the acquired HSV type, whereas patients with recurrent infection have these antibodies. From 1983 to 1991, the serologic status of all patients was determined by using Western blot assay, which accurately distinguishes antibodies to HSV-1 from antibodies to HSV-2 (22, 23).

Between 1974 and 1983, all serum samples obtained at entry were screened by microneutralization assay (18). All serum samples that demonstrated neutralizing activity were retrospectively analyzed by Western blot assay. Patients who had only antibodies to HSV-1 and whose HSV-2 infection was documented by culture or subsequent seroconversion to HSV-2 were included in this report as having nonprimary initial HSV-2 infection. Patients who had antibodies to HSV-2 at enrollment were included as having recurrent HSV-2 infection. Because neutralization and Western blot assays have equal sensitivity for detecting antibodies to HSV, all patients with entry serum samples that lacked neutralization were classified as having primary HSV infection (23). A viral isolate for genital herpes was used to classify these patients as having primary HSV-1 or primary HSV-2 infection.

Data Collection

Patients presenting at the clinic with a symptomatic recurrence were followed every 2 to 3 days until their lesions healed. Patients were instructed to return to the clinic during each subsequent recurrence and for routine visits every 2 to 3 months; they were also asked to return to the clinic for assessment of all genital symptoms until they were able to accurately recognize signs and symptoms of genital herpes recurrence (11, 12). At this time, routine clinic visits were changed from 2-month intervals to 4- to 6-month intervals to enhance long-term compliance with the protocol. Patients were asked to keep a record of onset and resolution dates for all recurrences so that we could document the time of onset of recurrences not observed by clinic personnel. Diary cards were collected and reviewed with clinic staff at each clinic visit. Data were coded on a standardized coding sheet and entered into a centralized database. Anatomic site of recurrence, date of onset, duration, and therapy were recorded for all genital lesions.

A recurrence was defined as the presence of vesicles, ulcers, or crusts. Anatomic sites categorized as genital recurrences were the mons, vulva, or perineum in women; the periurethral area, penis, and scrotum in men; and the perianal area and buttocks in both sexes. If new lesions appeared before other lesions completely healed, all lesions were considered part of the same recurrence.

Statistical Analysis

Annual recurrence rates for each patient were estimated by dividing the number of recorded recurrences in a specified period by the number of years in that period (12, 20). For example, the second-year recurrence rate for a patient followed the entire year is the number of recurrences in the second year. For a patient followed for only the first 2 months of the second year, the denominator is 2 divided by 12 (0.167). Comparisons of patient groups with respect to recurrence rates were made by using the Wilcoxon rank-sum test. Recurrence rates between years 1 and 2 were compared by using the Wilcoxon signed-rank test.

Exploratory data analyses (24) were used to investigate patterns over time in patients followed for more than 2 years. Two-way tables of recurrence rates with a row for each patient and a column for each year of data were created for subsets of patients with varying lengths of follow-up. Two methods were used to estimate an overall effect and patient and year effects: the least-squares fit (the method used in a two-way analysis of variance when no values are missing) and the median polish fit (a method that is resistant to outliers). Outliers in estimated recurrence rates occurred when persons were followed for a short period; that coincided with an unusually high number of recurrences.

Examination of year effects suggested that it was reasonable to hypothesize a linear time trend in recurrence rates. We therefore used a random-effects model (25) to assess the changes in recurrence rates over time. The slope coefficient in this model represents the average annual change in the recurrence rate (a positive slope if the recurrence rate increased and a negative slope if the recurrence rate decreased); the intercept represents the average rate in the first year of follow-up. A plot of mean annual recurrence rates by year provided a visual description of the fitted models. We used a

Table 1. Characteristics of Study Sample*

Variable	Primary HSV-1 Infection	Primary HSV-2 Infection	Nonprimary Initial HSV-2 Infection	Recurrent HSV-2 Infection	Total
Patients, *n*	60	205	41	358	664
Men, *n (%)*	22 (37)	56 (27)	12 (29)	187 (52)	277 (42)
Median age (range), *y*	23 (16–46)	26 (17–51)	25 (17–41)	29 (18–71)	27 (16–71)
Ever received suppressive acyclovir therapy, *n (%)*	0	32 (16)	6 (15)	156 (44)	194 (29)
Median follow-up (range), *mo*	35 (15–166)	36 (14–209)	30 (15–153)	38 (14–223)	36 (14–223)
Anatomic site of recurrences, *n*					
Genital	172	3110	562	8123	11 967
Oral	46	16	21	117	200
Other	6	58	2	168	234

* HSV = herpes simplex virus.

model that allowed the slope and intercept to vary from patient to patient. A consequence of this variability is correlation among the observations from a given patient. This is taken into account in the estimation procedure. We computed approximate 95% CIs, assuming that the estimated slopes and intercepts were normally distributed. Whether such a normal distribution existed for all data on recurrence rates for all subsets of patients is unclear. Therefore, the reported CIs should be interpreted descriptively.

When computing recurrence rates for individual patients, we excluded data from any time at which suppressive antiviral therapy was used. Some analyses were restricted to patients who never received suppressive therapy. Because antiviral treatment of symptomatic episodes has not been shown to affect recurrence rates (26–28), such treatment was not considered in these analyses.

All analyses were done by using S-Plus, version 3.1 (Statistical Sciences, Inc., Seattle, Washington). The function *twoway* was used for two-way table analyses, and the function *varcomp* was used for fitting random-effects models.

Role of the Funding Source

The agency had no role in the collection, analysis, or interpretation of the data or in the decision to submit this paper for publication.

Results

Of the 664 patients, 306 had newly acquired (first-episode) genital herpes. Sixty had primary HSV-1 infection, 205 had primary HSV-2 infection, and 41 had nonprimary initial HSV-2 infection (that is, HSV-2 infection after previous HSV-1 infection). Previously acquired (recurrent) HSV-2 infection was present at enrollment in the other 358 patients (**Table 1**). Our study included 277 men and 387 women. Demographic, socioeconomic, and sexual histories of our patients were similar to those of patients in previous reports (12, 18–21). Of the 664 patients, 412 were followed for more than 2 years, 277 were followed for more than 3 years, 117 were followed for more than 6 years, and 52 were followed for more than 9 years.

One hundred ninety-four patients received suppressive therapy at some time during follow-up, including 38 of the patients who presented with first-episode infection. Among these patients, the median duration of suppressive therapy was 10 months; the median follow-up time while patients were not receiving therapy was 35 months.

During follow-up, patients had 11 967 genital recurrences, 200 oral recurrences, and 234 recurrences at other sites (for example, leg, shoulder, arm, or finger) (**Table 1**). Patients who presented with primary genital HSV-1 infection had a lower percentage of genital recurrences (77%) and a higher percentage of oral recurrences (21%) than patients in the other groups (97% genital recurrences and 1% oral recurrences) (11, 12).

Recurrence Rates during Years 1 and 2 of Observation

Median first-year and second-year recurrence rates and the differences between them are presented in **Table 2** for 605 patients for whom these rates could be estimated. (We omitted from analysis the 59 patients who had no data in one of the first 2 years of follow-up because they were receiving suppressive antiviral therapy.) Recurrence rates in the first year of follow-up differed by viral type and by whether the patient had first or recurrent HSV infection. Patients with newly acquired HSV-1 infection had the lowest recurrence rates; patients who had previously acquired HSV-2 infection had the highest recurrence rates. The 316 patients with clinical and serologic evidence of previously acquired HSV-2 infection at the time of enrollment had a median of six recurrences in the first year. In comparison, the 230 patients who were followed after first-episode HSV-2 infection had a median of five recurrences in the first year.

The median recurrence rates decreased significantly between years 1 and 2 for patients who en-

Table 2. Recurrence Rates in the First 2 Years of Observation or Follow-up*

Variable	Primary HSV-1 Infection	Primary HSV-2 Infection	Nonprimary Initial HSV-2 Infection	Recurrent HSV-2 Infection	Total
Patients with available data in both first and second years, *n*†	59	191	39	316	605
Annual recurrence rates, *n*					
First-year median	1.0	5.0	5.0	6.0	5.0
Second-year median	0.0	4.0	4.0	6.0	5.0
Median difference	0.0	0.3	1.0	0.2	0.3
P value for difference‡	0.009	0.048	0.080	0.100	0.001

* HSV = herpes simplex virus.
† Patients were followed for at least 2 months and did not receive suppressive acyclovir therapy in either of the first 2 years.
‡ Determined by using the paired Wilcoxon rank-sum test.

tered the study with primary HSV-1 infection and those who had primary HSV-2 infection at entry. Decreases also occurred in the other patient groups, leading to a highly significant overall decrease between years 1 and 2. However, the median decrease was only 0.3 recurrences per year. Only one third of the patients experienced a clinically meaningful decrease during the first 2 years of follow-up (at least two fewer recurrences in year 2 than in year 1), and more than one third had more recurrences in the second year than in the first year (data not shown).

Among patients with newly acquired genital herpes, those who had antibodies to HSV-1 before acquiring HSV-2 infection and those who had primary HSV-2 infection had similar rates of recurrence during and similar reductions between the first and second years of follow-up. Even after using a linear model to adjust for sex, age, and duration of the acquisition episode of genital herpes, we could not detect differences in recurrence rates between these two groups of patients. This finding indicates that previous acquisition of HSV-1 infection seems to offer no measurable benefit in reducing the subsequent frequency of HSV-2 infection over time. In subsequent analyses, therefore, we combined all of the patients who entered the study with recently acquired HSV-2 infection (primary and nonprimary).

The linear model indicated that among patients with first-episode HSV-2 infection (primary and nonprimary), young age and longer duration of primary infection were predictive of higher first-year recurrence rates; this finding is similar to that in our previously published report (12). However, neither of these variables influenced the difference between first-year and second-year recurrence rates. Of interest, women tended to have lower second-year rates than first-year rates; men, however, did not. In subsequent analyses, the effect of sex was not significant in patients with primary HSV-1 infection or recurrent HSV-2 infection. As in our previous report (12), we found that subsequent recurrence rates were not affected by receipt of antiviral therapy for the first episode of infection. First-year recurrence rates were almost identical in patients who received antiviral therapy for primary episodes and those who did not (median, 4 recurrences; $P > 0.2$).

Recurrence Rates during 3 or More Years of Follow-up

Using a random-effects model, we investigated trends in recurrence rates for patients who were followed for more than 2 years. **Table 3** presents the estimated recurrence rate in the first year (the intercept from the model) and the magnitude of the slope estimating the annual change in rates in the next 2 years. In all patient groups, the slopes were negative, indicating a decrease in the recurrence rates during the 3-year follow-up. The decrease was smallest in the patients with HSV-1 infection, who have fewer recurrences than patients with HSV-2 infection and in whom recurrence rates are thus

Table 3. Trends in Genital Herpes Recurrences per Year over a 3-Year Period*

Group	Patients	First-Year Annual Recurrence Rate	Decrease per Year in Annual Recurrence Rate (95% CI)	*P* Value
	n			
Patients with primary HSV-1 infection	38	1.7	0.5 (0.1–0.8)	0.004
Patients with a first episode of HSV-2 infection	155	6.3	0.8 (0.4–1.2)	<0.001
Never received acyclovir therapy	126	5.4	0.6 (0.2–1.0)	0.003
Received some acyclovir therapy	29	10.3	1.8 (0.7–2.9)	0.002
Patients with recurrent HSV-2 infection	219	8.5	0.7 (0.3–1.0)	<0.001
Never received acyclovir therapy	99	6.2	0.8 (0.4–1.2)	<0.001
Received some acyclovir therapy	120	10.4	0.6 (0.0–1.1)	0.036

* HSV = herpes simplex virus.

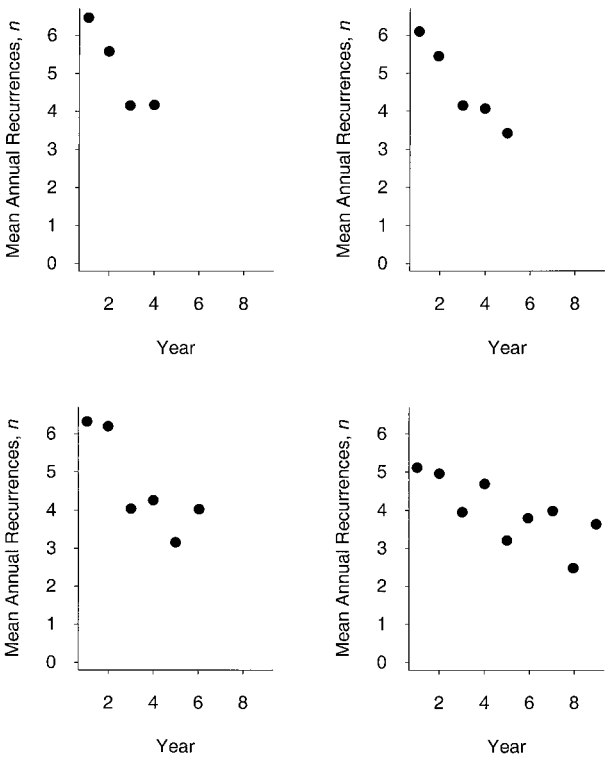

Figure. Mean annual recurrence rate in each year of follow-up among patients who presented with newly acquired herpes simplex virus type-2 infection. Top left. Mean values for all 103 patients followed for more than 3 years. **Top right.** Mean values for 64 patients followed for more than 4 years. **Bottom left.** Mean values for 39 patients followed for more than 5 years. **Bottom right.** Mean values for 19 patients followed for more than 8 years.

expected to decrease more slowly, if at all (estimated decrease of one fewer recurrence in year 3 than in year 1). Estimated decreases were greater in all groups of patients infected with HSV-2, but the decreases were modest (one to two fewer recurrences in year 3 than in year 1).

No patient with newly acquired HSV-1 infection received suppressive acyclovir therapy during follow-up. **Table 3** shows separate and combined results from patients with HSV-2 infection who did and did not receive suppressive acyclovir therapy during follow-up. When calculating recurrence rates, we always omitted the duration of suppressive therapy. First-year rates of recurrence for patients who were not receiving acyclovir were higher in those who ever received suppressive therapy than in those who never received suppressive therapy. This is not surprising because patients with higher recurrence rates would be more likely to receive suppressive therapy. Both groups of patients had significant decreases in recurrences per year during the 3-year period. Therefore, the downward trend in both groups seems to be a uniform phenomenon unrelated to the use of antiviral therapy. In subsequent analyses, we included all patients regardless of whether they received suppressive therapy at some point during follow-up.

To explore the long-term clinical course of genital herpes, we subdivided our analyses on the basis of duration of follow-up and estimated the decrease per year in annual recurrence rates. The **Figure** illustrates these results by displaying recurrences per year for patients with first episodes of HSV-2 infection who were followed for more than 3 years after acquiring the infection; an overall decrease in recurrence rates is indicated. The subsets include the same groups of patients in increasingly smaller numbers; therefore, these analyses are not independent and are presented for descriptive purposes. The data are useful from an illustrative point of view because in all instances, the random-effects model fitted to them indicates a decrease in recurrence rates over time (results not shown). Of interest, the decrease seems to become smaller as the follow-up times for patients become longer (for example, a decrease of 0.2 recurrences per year in patients who were followed for >8 years compared with a decrease of 0.8 recurrences per year in patients who were followed for ≤ 4 years).

The magnitude of the reduction in recurrence rates during long-term follow-up is clinically significant. Among the patients infected with HSV-2 who were followed for more than 4 years after presenting with their first episode of infection, the median decrease in the number of recurrences between the year 1 rate and the year 5 rate was two recurrences; this represents a 50% decrease from the median of four recurrences seen in year 1. For patients who presented with recurrent genital herpes at enrollment, the corresponding decrease was three recurrences per year between the rates in years 1 and 5. Most patients experienced a decrease of more than one recurrence per year between years 1 and 5. However, almost 25% of these patients (17% of those with initial infection and 28% of those with recurrent infection) had at least one more recurrence in year 5 than in year 1 (data not shown).

Discussion

Our study indicates that although genital herpes is a chronic infection, the frequency of symptomatic genital herpes reactivation decreases over time in a majority of patients. However, the magnitude of the annual decrease is small and highly variable. One third of patients experienced a clinically meaningful decrease in the number of recurrences between years 1 and 2. Among patients followed for at least 5 years, more than 50% had at least two fewer recurrences in year 5 than in year 1; however, approximately 25% had more recurrences in year 5 than in year 1.

We consistently observed decreases over time by

using various statistical techniques, only a few of which are presented here. The consistent decrease in recurrence rates did not depend on sex, serologic status, treatment for initial infection, or treatment for suppression of recurrences. Of note, women tended to have a lower second-year recurrence rate than first-year recurrence rate; men, in contrast, did not. This finding may be due to a greater tendency for women to continue follow-up after primary infection, even if their recurrence rates are decreasing.

In a long-term study of suppressive acyclovir therapy, Fife and colleagues (16) noted that after years of treatment, 75% of patients who were followed after discontinuation of therapy had lower recurrence rates than they had reported before enrolling in the trial. The authors noted that it was unclear whether these results were due to therapy or the natural course of the disease. In our experience, an additional limitation is that reported recurrence rates have historically been overestimated, resulting in an inflated estimate of the difference between pre- and post-treatment recurrence rates. Therefore, it is interesting that the results of our study, which is based on prospectively obtained information about recurrence, support the observation of decreased recurrence rates. The decreases in our study, however, are of smaller magnitude than those described by Fife and coworkers (16). A similar decrease in reactivation rates has also been seen with subclinical shedding of HSV-2 (21); that study, however, had considerably fewer patients and a shorter duration of follow-up than our study.

Our cohort included patients who were recruited at the onset of their primary episode of genital herpes and patients who had previously been infected and sought medical attention for symptomatic recurrences. As such, our cohort represented patients who had severe genital herpes infection. Duration of follow-up varied widely among our patients; patient dropout may be related to recurrence patterns and may have led to bias in our estimates. For example, a patient whose recurrence rates decreased might have been less likely to remain in intensive follow-up; thus, his or her low recurrence rates would not be included in our data. Conversely, a patient whose condition never improved (or even worsened) might have felt frustrated and declined to participate further.

The problems caused by the self-selected nature of the patient sample and the potential biases in follow-up compliance patterns are inherent in observational studies, particularly those of a chronic episodic disease (such as genital herpes). Caution must be used in attempting to generalize these conclusions to all patients with genital herpes. Nonetheless, our study represents the largest series of patients with genital herpes that includes a substantial number of persons who were followed for long periods and never received suppressive antiviral therapy. In addition, the recurrence rates among our patients are similar to those reported in other studies of genital herpes (29–33).

Our data provide important guidance for the clinical management of patients with symptomatic genital herpes. The observed decrease in most patients during a 5-year period suggests that medical management with daily suppressive antiviral chemotherapy should be reassessed periodically and may no longer be needed in some persons after 3 to 5 years of follow-up. Some patients may subsequently be managed best with episodic treatment, as clinically indicated. However, in a substantial number of patients (more than one third in our cohort), rates of symptomatic reactivation do not decrease during a 5-year period. This finding indicates that such a clinical course is not uncommon and does not warrant an extensive work-up for an immunologic deficiency.

Our data illustrate both the relapsing chronicity of recurrent genital herpes infection and the fact that the frequency of reactivation changes over time. It is intriguing to speculate why recurrence rates decrease over time in some patients. Is it related to a maturation in the control of the host response to HSV-2? The lack of substantial improvement over time in some patients may indicate the existence of a potential "set point" or stabilization for clinical reactivation that is unique to each person. Studies to define virologic differences and host differences in patients with differing recurrence patterns may be useful in understanding the pathogenesis of HSV infection.

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