

Zoster Incidence in Human Immunodeficiency Virus–Infected Hemophiliacs and Homosexual Men, 1984–1997

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Zoster is an important clinical problem for human immunodeficiency virus type 1 (HIV)–infected patients. Risk factors for zoster and trends in incidence in HIV-infected hemophiliacs and homosexual men ($n = 1218$) were examined. From 1984 to 1997, 174 zoster cases were identified (average yearly incidence, 2.5%). Prior zoster episodes were associated with increased risk for a subsequent episode (relative risk [RR], 4.30; 95% confidence interval [CI], 3.11–5.95). Among hemophiliacs, children and adolescents had the highest zoster risk, and zoster risk declined with age (RR, 0.80 per decade; 95% CI, 0.68–0.93). These findings suggest that HIV-infected persons do not produce or maintain adequate booster responses after varicella zoster virus exposure. Zoster risk was relatively constant when CD4 cell counts >200 cells/mm³ but increased steeply below this level. During the 14 years of follow-up, zoster incidence declined 9% per year. This trend occurred despite decreasing CD4 cell counts and was unexplained by zidovudine or acyclovir use.

Zoster, a debilitating cutaneous eruption caused by varicella zoster virus, is common among persons infected with human immunodeficiency virus type 1 (HIV). More than 90% of HIV-infected adults are latently infected with varicella zoster virus [1], and immunosuppression during HIV disease is associated with varicella zoster virus reactivation and clinical zoster. Published estimates of zoster risk in HIV-infected persons vary from 3% to 5% per year [2–5], which is 10–20 times higher than among healthy middle-aged adults [3, 6]. Risk for zoster increases with declining CD4 cell counts [2], and HIV-infected persons with 1 episode of zoster may be at heightened risk for a subsequent episode [2, 7].

HIV-infected adults may develop complications from zoster [5]. These complications include prolonged postherpetic neuralgia [5], chronic skin lesions (some caused by acyclovir-resistant viral strains) [8, 9], and central nervous system and ocular disease [5]. Persons who develop zoster are also at high risk for AIDS or death [2, 10, 11], although this increased risk may be attributable to advanced immunosuppression.

We have followed HIV-infected subjects in cohort studies of

homosexual men and hemophiliacs since 1982 [12, 13]. We noticed an apparent decline in zoster incidence, which was unexpected, because our participants became progressively more immunocompromised over time. In the present study, we describe trends in zoster incidence in HIV-infected subjects in these cohorts and examine factors that might be related to zoster risk, including CD4 cell count, age, previous episodes of zoster, and use of antiviral agents.

Methods

Study subjects and data collection. We studied 2 prospective cohorts of HIV-infected persons who have been followed since the early 1980s: the Multicenter Hemophilia Cohort Study (MHCS), which includes hemophilia patients enrolled at 16 comprehensive treatment centers in the United States and Europe [13], and the District of Columbia Gay (DCG) cohort study, consisting of homosexual men recruited from primary care practices in Washington, DC, and New York City [12]. In both studies, subjects are seen at ~12-month intervals, when clinical events and current treatments are recorded and biologic specimens are obtained for laboratory testing.

In the present analysis, we included all subjects from each study for follow-up time when they were known to be HIV infected (1984–1997). Subjects were considered HIV infected when they had a positive EIA confirmed by either HIV Western blot or RIA [12, 13]. Follow-up time before subjects had a first documented CD4 cell count was excluded.

At each visit, study personnel noted the dates of preceding episodes of zoster, which was the end point for the present study. In the DCG study, subjects were asked “Have you been treated for shingles (zoster), consisting of painful skin lesions like chicken pox, usually in 1 segment or on 1 side of the body?” For MHCS subjects,

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This study was approved by institutional review committees at the National Cancer Institute and participating centers. Study subjects gave informed consent.

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Table 1. Unadjusted relative risk estimates for zoster.

Characteristic	Person-years of follow-up	Zoster incidence, % per year (95% CI)	Relative risk (95% CI)	P
Hemophiliacs (MHCS)	6165	2.1 (1.8–2.5)	1.00	<.0001
Homosexual men (DCG)	799	5.5 (4.1–7.4)	2.61 (1.86–3.68)	
No prior zoster	6335	1.9 (1.6–2.3)	1.00	<.0001
Prior zoster	628	8.3 (6.3–10.9)	4.30 (3.11–5.95)	
No prior AIDS	6352	2.4 (2.1–2.9)	1.00	.34
Prior AIDS	612	3.1 (2.0–4.9)	1.27 (0.79–2.05)	

NOTE. CI, confidence interval; MHCS, Multicenter Hemophilia Cohort Study; DCG, District of Columbia Gay cohort study.

a physical examination and review of clinic and hospital records at the hemophilia center were used to identify zoster cases.

We recorded each subject's age and most recent CD4 cell count (as of 1 January) for each calendar year. We also noted whether the subject had a diagnosis of AIDS based on the 1987 CDC definition [14].

Data analysis. We used Poisson regression to model the relationship between subject characteristics and zoster risk (measured as incidence) [15]. In univariate and multivariate analyses, variables examined for their effects on zoster incidence included calendar year, age, most recent CD4 cell count, prior zoster, and prior AIDS. We compared zoster incidence in the 2 cohorts (MHCS and DCG) and, in multivariate analyses, controlled for cohort to eliminate any confounding that might arise from combining the 2 groups. Regression models were compared by use of the differences in their log likelihoods. We fitted regression splines to check for and model nonlinearity of the effect of continuous variables on zoster risk [16]. We determined whether changes in treatment explained zoster trends by examining yearly data on medication use in the MHCS cohort (treatment data in DCG were not documented in detail). We used the Wilcoxon rank sum test for age comparisons between groups [17] and logistic regression to test for time trends in the proportion of subjects with AIDS at study entry [18]. A 5% level was used for statistical significance. Statistics were calculated with Matlab (version 5; Math Works, Natick, MA) and S-Plus (version 4.5; MathSoft, Seattle).

Results

Description of subjects. The present study included 1218 subjects, 1091 from MHCS and 127 from DCG. The median age at entry was 29 years. At entry, MHCS subjects were younger (median age, 27 years; interquartile range, 19–36) than those in DCG (median age, 35; interquartile range, 32–40; $P < .0001$). All but 9 subjects (women with bleeding disorders) were men.

New subjects entered the present study in each year from 1984 to 1997, but most entered in the early years of the study: 690 subjects (57%) entered in 1984–1988, 448 (37%) in 1989–1992, and 80 (7%) in 1993–1997. The median duration of follow-up was 5.5 years (interquartile range, 2.8–8.3).

At study entry, 61 subjects (5%) had an AIDS diagnosis. Of 690 subjects entering in 1984–1988, 18 (3%) entering in 1984–1988 had an AIDS diagnosis, compared with 31 (7%) of 448 entering in 1989–1992 and 12 (15%) of 80 entering in

1993–1997 ($P < .0001$). At study entry, the median CD4 cell count was 403 cells/mm³ (interquartile range, 237–596).

Because of advancing HIV disease, 354 subjects (29%) developed AIDS during follow-up. Similarly, CD4 cells declined as subjects were followed during successive calendar years. For example, the median CD4 cell count was 539 cells/mm³ in 1984, 340 cells/mm³ in 1990, and 258 cells/mm³ in 1997. At any point in follow-up, CD4 cell counts tended to be higher among homosexual men than hemophiliacs (median difference, 74 cells/mm³).

Factors related to zoster risk. There were 174 zoster cases during 6964 person-years of follow-up (average incidence, 2.5% per year). In all, 108 subjects (9%) had 1 zoster episode, 24 (2%) had 2 episodes, and 6 (0.5%) had 3 episodes. For those who had 2 or 3 episodes of zoster, the median time between zoster episodes was 1.7 years (interquartile range, 1.0–3.8). The minimum time between episodes was 0.3 years; the maximum interval was 7.7 years.

Several characteristics were associated with zoster incidence in univariate analyses (table 1). Homosexual men had higher zoster incidence than hemophiliacs (relative risk [RR], 2.61). Having had a prior episode of zoster was significantly associated with an elevated risk for subsequent zoster (RR, 4.30 vs. risk for first episode). Prior AIDS diagnosis was associated with a nonsignificantly increased zoster incidence (RR, 1.27).

The median CD4 cell count of subjects who developed zoster was 321 cells/mm³ (range, 0–1237). Zoster incidence was highest at very low CD4 cell counts (figure 1). Incidence was 2.1% per year for ≥ 500 CD4 cells/mm³, 2.2% per year for 200–499 cells/mm³, 2.5% per year for 100–199 cells/mm³, and 4.1% per year for < 100 cells/mm³. A 2-segment regression spline modeled the relatively flat relationship between CD4 cells and zoster incidence for ≥ 200 CD4 cells/mm³ and the steep increase in incidence below this level (figure 1; $P = .01$ for spline model).

Zoster incidence declined over calendar time (figure 2). Incidence was 7.1% per year in 1984, 3.1% per year in 1990, and 1.6% per year in 1997. This decline over time was linear (RR, 0.91/year; 95% confidence interval [CI], 0.87–0.96). The crude incidence rates suggested that incidence decreased abruptly in 1986 or 1987 (figure 2). To explore this possibility, we compared the linear model to spline models that could accommodate sudden changes in the incidence slope. None of the spline models

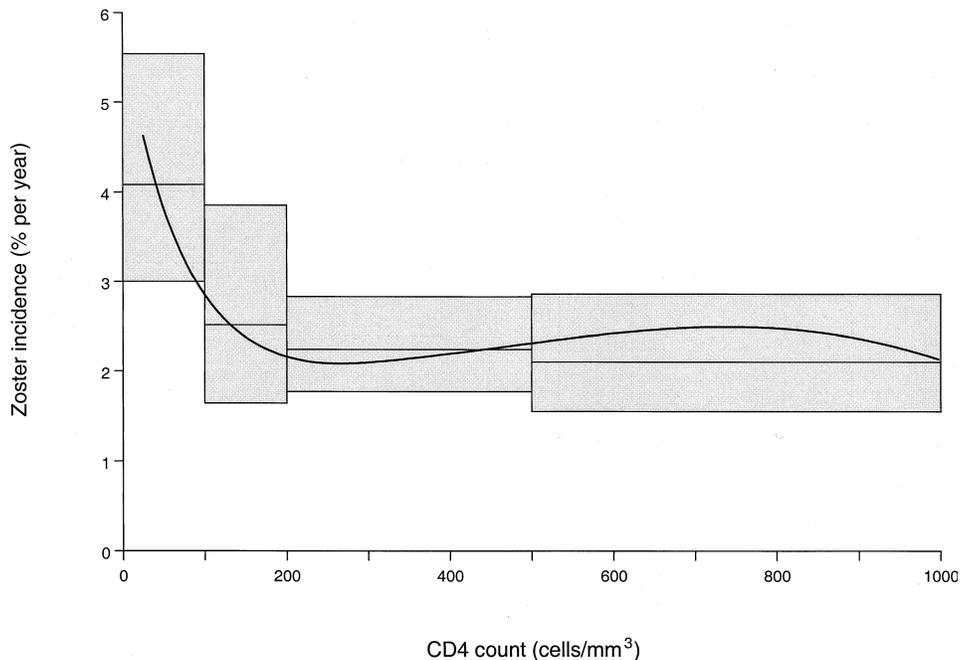


Figure 1. Zoster incidence estimates and 95% confidence intervals (gray boxes) for subjects with <100, 100–199, 200–499, or ≥ 500 CD4 cells/mm³. Also shown is zoster incidence predicted by a Poisson regression model that includes a two-segment cubic spline term for CD4 cell count. Confidence limits for spline (not shown) were similar in width to those for 4 separate CD4 cell count intervals.

fitted better than the linear model. All of the more flexible spline models confirmed that incidence was lower in the later years of follow-up.

Changes in therapy (in particular, acyclovir and antiretroviral therapies) did not account for the changes in zoster incidence over time. Prophylactic acyclovir was used by <5% of MHCS subjects during any of the years under study. Also, zoster incidence was already falling before zidovudine was introduced in 1987 (figure 2), and <25% of subjects in MHCS received this drug in 1987–1989. Use of HIV protease inhibitors among MHCS subjects increased from 1% in 1995 to 19% in 1996 and 40% in 1997; corresponding estimates for zoster incidence in MHCS were 1.6% for 1995, 1.1% for 1996, and 1.3% for 1997.

Finally, among all subjects together, age was not related to zoster incidence (table 2). However, differences in the age distribution in the 2 cohorts obscured the relationship between age and zoster incidence: DCG subjects were older and also had higher incidence. Within the MHCS, children and adolescents had particularly high zoster rates (table 2), and incidence decreased with age (RR, 0.80 per 10-year age increase; 95% CI, 0.68–0.93). Within the DCG cohort, which included only adults, there was no significant age trend in zoster incidence (RR, 1.07/10-year age increase; 95% CI, 0.71–1.60). The difference in these age effects between the 2 cohorts was not statistically significant ($P = .75$), although the relatively small number of events in DCG may have limited our ability to detect a difference.

Multivariate analysis. Table 3 shows variables indepen-

dently associated with zoster incidence in multivariate analysis. Independent predictors of zoster included acquisition of HIV infection through homosexual activity (RR, 2.16) and a previous episode of zoster (RR, 3.67). The fitted relationship between CD4 cell counts and zoster incidence was nonlinear: incidence was relatively flat at ≥ 200 CD4 cells/mm³ and increased below this level (table 3). Persons who were older had decreased zoster incidence (RR, 0.84/10 years of age). Finally, calendar time continued to be independently related to zoster incidence, so that incidence decreased 8% per calendar year (RR, 0.92/year; table 3). There were no significant interactions between these variables; in particular, there was no evidence that calendar or age trends differed between cohorts or that the effect of prior zoster on current zoster risk changed over time.

Discussion

For HIV-infected subjects in our cohort studies, the 9% per year decline (77% overall) in the crude incidence of zoster over this 14-year period represents an important decrease in morbidity. This decline was unexpected, because it occurred despite worsening in the immune status of study subjects, as manifested by decreasing CD4 cells and an increasing proportion of subjects with AIDS. Possible explanations for declining zoster incidence include reporting artifacts, improvements in clinical care, and loss of zoster-susceptible subjects from our study population.

Because zoster is an obvious clinical problem likely to be

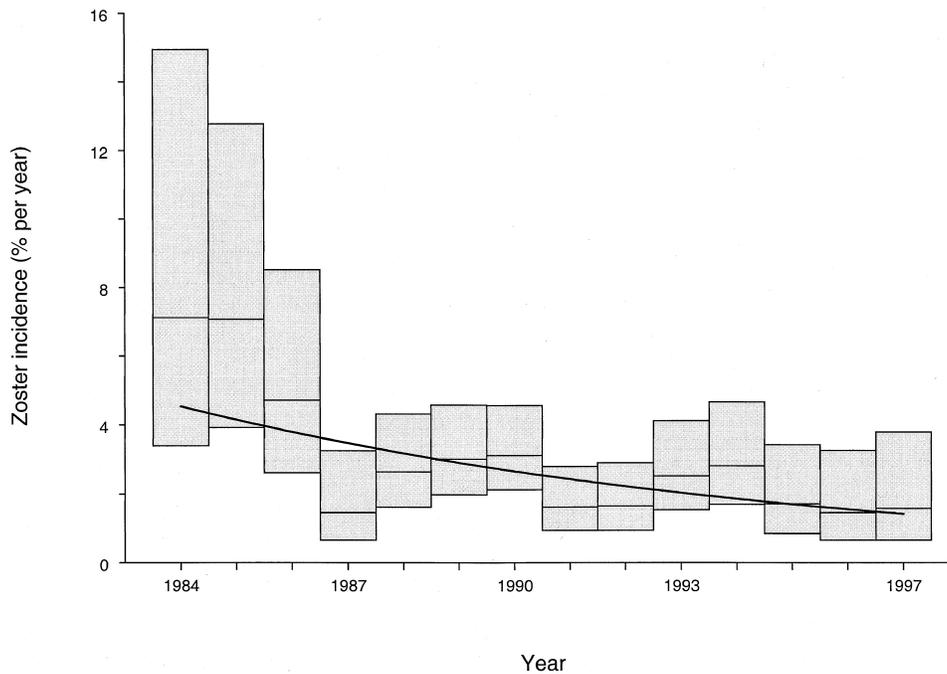


Figure 2. Zoster incidence estimates with 95% confidence intervals (gray boxes) for each year of follow-up. Also shown is incidence predicted by a Poisson regression model that includes a linear term for calendar year (this appears as curve, rather than as straight line, because the regression model is fitted on logarithmic scale).

noticed by study subjects, reporting artifacts are unlikely to explain the decreasing zoster risk. With advancing immunodeficiency, subjects received more intensive care and, if anything, this scrutiny would have led to increased zoster reporting over time. Although methods of ascertaining zoster in MHCS and DCG differed, we found no difference in time trends for these 2 groups.

Improvements in patient care could possibly have contributed to the decrease in zoster incidence. For example, decreasing zoster incidence may be partially due to increasing use of antiretroviral therapy. Although we documented declining CD4 cells over the study period, some of the clinical benefit of antiretroviral therapies occurs independently of changes in CD4 cell counts [19]. Nonetheless, zoster incidence was declining even before zidovudine, the first licensed antiretroviral drug, was used. Of interest, although combination therapy, particularly with protease inhibitors, has led to substantial declines in AIDS incidence since 1996 [20, 21], initial uncontrolled studies suggested that protease inhibitor therapy was associated with paradoxical increases in zoster risk [22, 23]. However, we did not observe a change in zoster incidence in 1996 or 1997, when use of protease inhibitors increased markedly. Finally, high-dose acyclovir decreases zoster risk [24], but very few subjects ever utilized this form of zoster prophylaxis. Therefore, we did not identify therapies responsible for the declining zoster incidence.

A third possible explanation for declining zoster incidence is that, over time, our cohorts became depleted of their most zoster-susceptible subjects. This situation could occur, for ex-

ample, if zoster-susceptible subjects (like those who actually develop zoster [2]) had a particularly high risk of death. This possibility is difficult to exclude in our study, because most subjects were infected with HIV by the early 1980s and relatively few new subjects entered in later years of follow-up. Examination of other cohorts that include persons who acquired HIV infection at diverse times will be necessary to determine whether the time trends we observed can be generalized to other groups of HIV-infected persons.

In HIV infection, zoster risk is related to the CD4 cell count [2]. In our cohorts, zoster incidence was fairly constant for ≥ 200 CD4 cells/mm³ and increased significantly when the number of CD4 cells fell below this level. Nonetheless, even subjects with relatively preserved CD4 cells (≥ 500 /mm³) had a zoster incidence that was 10-fold higher than comparably aged HIV-uninfected persons [6]. Thus, although the profound immunodeficiency of late-stage HIV infection is associated with the highest risk, zoster is not solely a late complication of HIV disease.

After reexposure to the varicella zoster virus, healthy varicella-immune adults develop a vigorous cell-mediated immune response [25, 26]. In contrast, we found evidence that HIV-infected persons fail to mount or maintain adequate immune responses after reexposure to varicella zoster virus. First, zoster incidence increased markedly after HIV-infected subjects had a first zoster episode (adjusted RR, 3.67). This situation differs from that in HIV-uninfected adults, who develop boosted cell-mediated immune responses after zoster [25] and are not later

Table 2. Zoster incidence by age and cohort.

Study group	Age group, years			
	≤12	13–18	19–35	≥36
All subjects				
Zoster incidence ^a (95% CI)	3.8 (2.1–6.8)	3.7 (2.6–5.3)	2.1 (1.7–2.7)	2.5 (2.0–3.2)
Person-years	293	789	3438	2444
Hemophiliacs (MHCS)				
Zoster incidence ^a (95% CI)	3.8 (2.1–6.8)	3.7 (2.6–5.3)	2.0 (1.5–2.5)	1.4 (1.0–2.1)
Person-years	293	789	3210	1873
Homosexual men (DCG)				
Zoster incidence ^a (95% CI)	— ^b	— ^b	4.4 (2.4–8.2)	6.0 (4.3–8.3)
Person-years	—	—	228	571

NOTE. CI, confidence interval; MHCS, Multicenter Hemophilia Cohort Study; DCG, District of Columbia Gay cohort study.

^a Incidence is % per year.

^b No subjects in DCG cohort study in youngest 2 age groups (≤12 and 13–18 years).

at increased zoster risk [27]. Second, within the MHCS cohort, zoster incidence was particularly high for children and adolescents. Similarly, Gershon et al. [28], in a study of children with perinatally acquired HIV infection, noted a high incidence of zoster following varicella, especially for children with low CD4 cell counts. Repeated exposures to varicella during healthy childhood may expand the repertoire of varicella zoster virus-directed T cell clones [26], which could be important for prolonged protection from viral reactivation as zoster. We therefore speculate that high zoster incidence in HIV-infected young persons might arise because they do not have the opportunity, before acquiring HIV infection, to develop a full complement of varicella zoster virus-specific T cell clones.

We noted an elevated zoster risk among homosexual men compared with hemophiliacs. This observation was not explained by differences in CD4 cells, because the homosexual men in our study actually had slightly more CD4 cells than hemophiliacs. There were differences in the methods for recording zoster events in MHCS and DCG subjects. However, others have also reported elevated zoster risk for persons who acquire HIV sexually, compared with those who acquire HIV parenterally (through drug use) [11]. The reasons for these differences in zoster risk are unknown, but we note that, among

HIV-infected persons, homosexuals also have higher AIDS risk than hemophiliacs [29].

Although it is encouraging that zoster incidence has apparently declined over the last decade and a half, zoster remains an important clinical problem among HIV-infected persons. Our results may have practical implications for zoster prevention. Young HIV-infected persons and those with prior zoster might be candidates for zoster prophylaxis, particularly if they have <200 CD4 cells/mm³. High-dose acyclovir prophylaxis reduces zoster incidence by ~70% [24]. Use of varicella zoster virus vaccine to boost immunity might also be an attractive zoster prevention strategy. However, a concern regarding the currently available vaccine is that it is a live vaccine, and there are no data on its safety in HIV-infected persons. In addition, our historical cohorts provide evidence that HIV-infected persons may not mount effective booster responses to varicella zoster virus. Thus, further studies are needed to assess the safety and efficacy of secondary vaccination in HIV-infected persons.

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Table 3. Multivariate model for zoster incidence.

Characteristic	Relative risk, adjusted (95% CI)	P
DCG vs. MHCS	2.16 (1.38–3.38)	.001
Prior zoster	3.67 (2.59–5.18)	<.0001
Age, per 10 years	0.84 (0.73–0.98)	.02
Calendar time, per year	0.92 (0.87–0.97)	.001
CD4 count, ^a cells/mm ³		.004
1000	1.00	
500	1.15 (0.58–2.29)	
200	1.30 (0.68–2.49)	
100	1.76 (0.93–3.30)	
50	2.29 (1.12–4.48)	

NOTE. CI, confidence interval; DCG, District of Columbia Gay cohort study; MHCS, Multicenter Hemophilia Cohort Study.

^a Relative risks are calculated from a two-segment spline for CD4 cell count.

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