Decreasing Incidence of Herpes Zoster in the Highly Active Antiretroviral Therapy Era

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We evaluated the effect of highly active antiretroviral therapy (HAART) on the incidence of herpes zoster (HZ) in human immunodeficiency virus (HIV)–infected subjects. The annual incidence of HZ per 100 person-years decreased significantly from 6.3 episodes in 1987 to 1.0 episode in 2011, probably reflecting improved immune function.

Keywords. HIV infection; herpes zoster; zoster vaccine; HAART era; pre-HAART era.

The incidence of herpes zoster (HZ) is 10–20 times higher in patients infected with human immunodeficiency virus (HIV) than in age-matched HIV-negative subjects [1, 2]. In the 1980s, HZ predicted the development of AIDS in a group of men who had sex with men (MSM), with half of the AIDS cases arising within 4 years of zoster [3]. In the pre–highly active antiretroviral therapy (HAART) era, several studies demonstrated incidence rates of 2.5–3.2 cases per 100 person-years in various cohorts [4, 5]. The incidence, complications, and recurrences of HZ increase with lower CD4 T-cell counts in HIV-infected subjects [4–6]. Although HZ incidence is higher with advancing age in the HIV-negative population, it might be lower in the case of HIV-infected patients [5, 7]. In addition, HZ incidence is likely to be higher in subjects who acquire HIV via sexual contact vs intravenous drug abuse [8].

There have been conflicting reports in the literature about the incidence of HZ in HIV-infected subjects in the HAART era compared to the pre-HAART era. The objective of our study is to evaluate the incidence and risk factors for HZ in a large cohort of HIV-infected persons in the pre-HAART and HAART eras.

METHODS

To evaluate the incidence of HZ in HIV-infected subjects, we included patients from the HIV Atlanta VA Cohort Study (HAVACS) who had an episode of HZ between 1982 and 2011; this patient population is 99% male (see Supplementary Data for full information on HAVACS). All patients with an episode of HZ were included in the case series. HZ was defined as a clinical diagnosis made by the provider and supported by the typical description of a painful unilateral rash, often with vesicular component. Only 5 cases of HZ were confirmed by polymerase chain reaction testing. Pertinent data collected included year of diagnosis, race, HIV risk factor, age, CD4 count, and antiretroviral treatment at the time of diagnosis.

The Clinical Case Registry of the Veterans Health Administration provided pertinent denominator data for this cohort including number of patients seen per year, age and risk factor distribution, distribution of CD4 by year, and number of patients on antiretroviral therapy by year. Incidence data were developed from the appropriate numerator and denominator or weighted data were developed for data, which changed per year to produce standardized incidence rates (SIRs). We used SIRs for our calculations as our demographics, including race and median age, prevalence of antiretroviral therapy, mean CD4 counts, and mean HIV viral loads, have changed dramatically over the study period. This made it problematic to choose appropriate controls. Thus, we were not able to calculate odds ratios or perform multivariate analyses.

RESULTS

Between January 1982 and December 2011, 650 episodes of HZ were documented in 3816 patients with an overall rate of 17.0 cases per 100 patients. During this time period, 25 patients had 2 episodes and 1 patient had 3 episodes of HZ. The overall incidence of HZ has decreased significantly from 28.6 cases per 100 patients in the pre-HAART era to 14.1 cases per 100 patients in the HAART era, reflecting a change in HZ risk factors (Supplementary Table 1). The date of the episode was available for 94%
of the episodes and the annual incidence decreased significantly from 6.3 episodes in 1987 to 1.0 episode in 2011 per 100 person-years (Figure 1).

The incidence of HZ varied by race, HIV risk factor, age, and CD4 count (Supplementary Table 2). White patients had a higher incidence of HZ compared to black patients (SIR, 4.40 vs 3.07 per 100 patients; \( P = .00002 \)). MSM had higher incidence rate when compared to intravenous drug abusers or heterosexual HIV-infected individuals (SIR, 4.53 vs 2.69 and 2.00, \( P < .000001 \)). The incidence of HZ decreased with increasing age despite the aging of this cohort (\( P < .000001 \)); the median age of our HIV population increased from 37 in 1990 to 51 in 2011 (Supplementary Figure 1). Subjects on HAART had a lower incidence of HZ compared to those who were not on HAART (3.56 vs 4.22), but the difference was not statistically different (\( P = .055 \)). Subjects with a CD4 count <50 cells/\( \mu L \) had a higher incidence of HZ in this cohort, especially compared to those with a CD4 count of >500 cells/\( \mu L \) (SIR, 1.45 vs 0.47; \( P < .000001 \)). Of the 192 patients (73.8%) who were ever on HAART and for whom we had a date of the HZ episode, most began HAART >12 months before the episode of HZ. Very few cases occurred within 1–4 months of the initiation of HAART (Supplementary Figure 2).

The site of HZ rash was listed for 223 patients and the dermatomes involved (listed in descending order) were thoracic (108 cases), lumbar (37 cases), trigeminal (32 cases), cervical (27 cases), and sacral (9 cases). Seven patients had multiple dermatomes involved, 2 patients had zoster encephalitis, and 1 patient had progressive outer retinal necrosis. The frequency of the dermatomes involved did not differ between white patients compared to black patients.

**DISCUSSION**

The extent of follow-up in this cohort allowed us to evaluate the incidence of HZ over a long period of the pre-HAART and HAART eras. The annual incidence decreased significantly from 6.3 episodes in 1987 to 1.0 episode per 100 person-years in 2011. There were fluctuations in the incidence of HZ in the pre-HAART era, but these are probably related to relatively low numbers. A similar decrease in the incidence of HZ has been observed in children with HIV infection in the HAART era [9–11]. A few studies in adults infected with HIV reported a similar decrease in the incidence of HZ in the HAART era [5, 12, 13], but some reported no significant change [14–16]. Moreover, some reports suggested an increase in the incidence of HZ in HIV-infected individuals who were initiated on HAART; this was postulated to be due to immune reconstitution [17–19]. However, these studies did not assess the incidence of HZ long after HAART initiation. Additionally, they did not examine the incidence of HZ in the pre-HAART era compared to the HAART era, as we did in this study. We did not observe an increase of HZ incidence due to immune reconstitution within a few months after HAART initiation.

We found that the incidence of HZ is higher in white patients compared to black patients, an observation made previously [20]. MSM had a higher incidence of HZ compared to subjects who acquired HIV through intravenous drug abuse or through other routes; this finding also has been reported previously [5, 8]. Interestingly, the incidence of HZ decreased with increasing age, a finding previously reported in an HIV cohort [5]. This finding is especially striking compared to the clear-cut increasing incidence of HZ with increasing age in the general population.
Veteran population [21]. The likely explanation is that although our study population is aging, more patients are on antiretroviral therapy and have higher CD4 cell counts. A higher incidence of HZ was seen in our study in patients with CD4 cell count <200 cells/µL, consistent with other previous studies [13, 15, 22]. We believe that a higher CD4 count, reflecting improved immune function, is probably the main factor driving the decreasing rates of HZ in our study population.

Our data document that the most common dermatomes involved with HZ in HIV-positive patients are the thoracic and the trigeminal cranial, followed by lumbar and cervical. These results are consistent with reports from HIV-negative populations that date back to 1965 [23].

Some limitations should be mentioned. We may have missed cases of HZ in Veterans who were diagnosed and treated by non–Veterans Affairs providers. These numbers are hard to estimate but are probably small. In addition, we defined HZ as a dermatomal rash. Rarely, reactivation of herpes simplex virus infection can occur in a dermatomal fashion in the lumbosacral area and mimic HZ, especially in HIV-infected MSM [24]. A third limitation is that we did not examine the incidence of complications of HZ such as postherpetic neuralgia. Our prospective data collection did not include a history of postherpetic neuralgia. Finally, we could not examine the effect of HAART on the incidence of HZ in women with HIV infection because our study population is 99% male. Previous studies that had a higher percentage of female participants with HIV infection reported an overall decrease in the incidence of HZ with HAART [12, 13].

In summary, this study documents a significant decrease in the incidence of HZ in an HIV-infected cohort in the HAART era. This decrease, we believe, is mainly due to decreased immunosuppression and increased CD4 count related to HAART. However, the incidence remains higher than in the general population [12, 15, 25]. Hence, it is necessary to consider the use of the zoster vaccine in HIV-infected patients with higher CD4 cell counts, regardless of their age, to limit HZ and its related complications (see Supplementary Data for more discussion on zoster vaccine).

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

Potential conflicts of interest. Both authors: No reported conflicts.

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References


