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BRIEF REPORT

Herpes Zoster Rates Continue to Decline in People Living With Human Immunodeficiency Virus but Remain Higher Than Rates Reported in the General US Population

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In the antiretroviral therapy era, herpes zoster incidence continued to decline in people living with HIV (PLWH). However, at 0.9 cases/100 person-years, rates in PLWH are substantially higher than the general US population; emphasizing the needs for studies of the subunit vaccine in PLWH.

Keywords. herpes zoster; HIV; declining incidence.

With the widespread availability of antiretroviral therapy (ART), herpes zoster (HZ) incidence declined by more than 40% in people living with human immunodeficiency virus (PLWH) [1–3]. However, HZ rates in PLWH remain 3 to 5 times higher than in the general population, and the infection typically more severe in PLWH [4]. The US Food and Drug Administration has licensed the following 2 vaccines against HZ: a live attenuated vaccine (LAHZV; Zostavax), approved in 2006, and a recombinant subunit vaccine (RZV; Shingrix), approved in 2017. Despite the higher burden of disease, the Advisory Committee on Immunization Practice (ACIP) has not made any specific recommendations for HZ vaccination in PLWH. Lack of effectiveness and efficacy studies in this population is a limiting factor [5, 6]. There is also limited information on the incidence of HZ in PLWH after 2001 [1–3]. Our purpose in this study is to provide updated epidemiologic data to help inform vaccine recommendations. Using data from the US Military HIV Natural History Study (NHS), we examined HZ incidence and risk factors.

METHODS

Study Population

The NHS is a well-characterized cohort comprised of more than 6100 HIV-infected Department of Defense beneficiaries followed longitudinally at 1 of 6 military treatment facilities [7]. During visits, clinical diagnoses (to include HZ) are captured by participant interview and medical record abstraction. For the incidence estimates, we included all first episodes of HZ diagnosed among NHS participants. Participants were included in the Cox proportional hazards models if they contributed follow-up time between 1 January 2001 and 31 December 2016.

Statistics

Incidence was estimated by dividing the number of first cases of HZ by person-years (PY) of follow-up; rates are presented per 100 PY of follow-up with 95% confidence intervals (CIs). Incidence was evaluated across calendar time and age groups. Comparisons between participants with and without HZ used χ^2 or Fisher exact tests for categorical variables and Wilcoxon 2-sample tests for continuous variables. For the Cox model, follow-up time was estimated from 1 January 2001, and observations were censored when a participant had their first HZ diagnosis or at last follow-up. Multivariate Cox proportional hazards models were used to examine risk factors associated with incident HZ. Factors examined included demographic (time updated age, gender, ethnicity) and HIV-specific variables (HIV diagnosis era, ART use, time to ART initiation, and time-updated CD4 count and viral load [VL]). We also examined vaccine coverage by identifying the number of vaccine-eligible participants who were immunized. All analyses were conducted using SAS version 9.4.

RESULTS

Herpes Zoster Incidence

Since the inception of the NHS, 858 incident cases of HZ have been recorded (624 occurred before 2001). Incidence of HZ was highest before 1996 at 3.2 cases (3–3.5) and declined significantly over time with 1.9 (1.6–2.3), 1.4 (1.2–1.8), 1.3 (1.1–1.7), and 0.9 (0.7–1.1) cases recorded in 1996–2000, 2001–2005, 2006–2010, and 2011–2016, respectively (P = .001). When restricted to cases diagnosed after 2001, HZ incidence varied by age and was highest in those aged 20–30 years at 1.5 (1.11, 1.98). Rates were 1.36 (1.08, 1.7), 1.08 (0.84, 1.37), 1.09 (0.74, 1.54),

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and 0.51 (0.17, 1.2) in those aged 30–40, 40–50, 50–60, and >60 years, respectively. These trends were significant ($P < .001$).

For the risk factor analysis, 2954 participants contributed 19 382 PY of follow-up; 234 (8%) participants had their first episode of HZ after 2001. At the time of first HZ diagnosis, the median age was 38.8 years (interquartile range [IQR], 30.9, 45.8), CD4 count was 459 cells/uL (IQR, 333, 637), and VL was 1950 copies/mL (IQR, 50, 19 023), respectively. The median time from ART initiation to HZ diagnosis was 5.6 years (IQR, 2.6, 9.2). About three-quarters (76.5%) of the participants with HZ were receiving ART at the time of HZ diagnosis. Of the 234 participants, 21 (9%) had a subsequent episode and 7 (3%) were hospitalized for HZ. The median time between the episodes was 1.8 years; 16 participants (75%) were receiving ART at the second episode. Median CD4 count was 477 cells/uL and VL was 48 copies at the subsequent episode.

Comparison of Participants With and Without HZ

When compared to participants without HZ, those with HZ were older at HIV diagnosis (median age 29.5 vs 28 years), more likely to have been diagnosed with HIV in an earlier calendar period (53.8 vs 39.8%; before 2000), had lower median CD4 counts at ART initiation (350 vs 369 cells/uL) and nadir CD4 counts (244 vs 312 cells/uL), and had waited longer from HIV diagnosis to initiate ART (median 3.2 vs 0.8 years); all P values < .05.

Independent Predictors of HZ

In the multivariate model, delays in ART initiation (hazard ratio [HR], 1.04 for each year delay in initiation of ART; 95% CI, 1.01, 1.09) and higher VL (HR, 1.76 for each log increase in VL [Table 1]; 95% CI, 1.56, 1.99) were associated with HZ. Higher CD4 counts (HR, 0.92 for each 100 cell increase; 95% CI, 0.87, 0.98) and older age were protective (HR, 0.95 for each year increase in age; 95% CI, 0.93, 0.96; Table 1).

Vaccine Coverage

By 2011 (when LAHZV was approved for individuals aged ≥50 years), 707 of the 2954 participants were aged ≥50 years and eligible; however, only 79 (11%) received LAHZV. At vaccination, all recipients were on ART, with preserved CD4 counts (median 768 cells/uL; IQR 562,915), 74 participants had an undetectable viral load, VL was detectable in 1 participant and missing in 3 (Supplementary Table 1). One participant developed HZ 3.5 years after vaccine receipt; at HZ diagnosis, his CD4 count was 197 cells/uL, VL was undetectable, and he was receiving radiation for his cancer. Of note, only 8 (3.4%) of the 234 participants with HZ received LAHZV.

DISCUSSION

In the NHS, HZ incidence is decreasing but remains a common diagnosis, with about 1 in 10 affected; approximately 10% have a recurrence and 3% have been hospitalized. Our rates are comparable to those reported in recent studies of PLWH [1–3]. However,

Table 1. Factors Associated With Herpes Zoster in US Military HIV Natural History Study Participants Who Contributed Follow-up Time After 2001

	Unadjusted Hazard Ratio (95% CI)	*P* Value	Adjusted Hazard Ratio (95% CI)	*P* Value
Age (for each year increase)[a]	0.95 (0.93–0.96)	<.0001	0.95 (0.93–0.96)	<.0001
Gender				
Male	0.83 (0.53–1.31)	.4258	…	…
Race				
Caucasian	Reference	…	…	…
African-American	0.85 (0.64–1.13)	.2734	…	…
Other	1.17 (0.82–1.68)	.3874	…	…
HIV diagnosis era				
Prior to 1996	Reference	…	…	…
1996–2000	1.11 (0.78–1.59)	.5591	…	…
2001–2005	1.08 (0.75–1.54)	.6927	…	…
2006–2010	1.36 (0.95–1.95)	.0971	…	…
2011–2016	0.34 (0.15–0.78)	.0113	…	…
Current ART use	0.51 (0.26–0.99)	.0462	…	…
Time to ART initiation from HIV diagnosis (for each year increase)	1.03 (1.01–1.06)	.0218	1.04 (1.01–1.07)	.0293
HIV-1 viral load (for each log increase)[a]	2.06 (1.9–2.24)	<.0001	1.76 (1.56–1.99)	<.0001
CD4 count (for each 100 cell increase)[a,b]	0.78 (0.74–0.82)	<.0001	0.92 (0.87–0.98)	.0091
CD4 nadir[c]	0.84 (0.77–0.92)	<.0001	…	…

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus.

[a]Time-updated.

[b]CD4 count: measurement of CD4 T lymphocyte cells.

[c]CD4 nadir: lowest ever CD4 cell count.

these rates are significantly higher than rates reported in the general US population [4]. NHS participants with HZ were usually in the fourth/fifth decades of life. This is in keeping with the average age of 39 years reported in 2 US-based studies of PLWH [1, 2]. HZ in PLWH is associated with higher rate of complications and post-herpetic neuralgia [8]. Hence, had we used the threshold of 50 years to vaccinate PLWH, a significant number at risk of disease would be missed, exposing them to significant morbidity [9]. ACIP recommended against LAHZV use in immunocompetent individuals aged <60 years in part to ensure that the rapidly waning protection would cover a longer risk period. However, our data show an inverse relationship between age and rates of HZ in PLWH and along with the approval of a RZV with longer expected duration of immunity, suggest a different approach is warranted.

As anticipated, our results demonstrated that higher CD4 count and lower VL at time of HZ diagnosis afforded protection (Table 1). Delays in ART initiation were associated with HZ, emphasizing the need to initiate ART upon HIV diagnosis, unless contraindicated. Most prior HZ studies have shown increasing HZ incidence with older age; however, we observed a protective effect of aging. Universal childhood varicella vaccination and lack of exposure to exogenous varicella infection may lead to waning cell-mediated responses to varicella zoster, resulting in HZ diagnoses at a younger age [10]. Another potential explanation is that individuals who contributed data after 2001 survived the pre-ART era and are likely different from individuals who did not (hence not included in our analysis) in unmeasured ways (including better cell-mediated responses to VZV), which may have led to our observation. Interestingly, our results are in keeping with 2 recent database studies (French and US) that also noted increased HZ incidence in younger HIV-positive adults when compared with HIV-negative adults [2, 3]. In the French study, the risk was greatest in those aged 15–34 years where the risk was 6-fold higher in HIV-positive patients [3].

Primary care guidelines for the treatment of PLWH encourage consideration of HZ vaccination for PLWH aged >60 years except those with a CD4 count <200 cells/uL [11]. Despite these recommendations, vaccination rates are low. The NHS rate of 10% is in keeping with recent reports that suggest rates of between 1.5% and 42.4% in PLWH [12]. Vaccination remains a proven way for HZ prevention, and the advent of RZV should reduce concerns associated with LAHZV. The barriers to vaccinations in the NHS population need further study.

The NHS is a well-characterized cohort with extensive follow-up, which allowed us to assess incidence in the pre- and post-ART eras, a strength of this analysis. The retrospective nature is a limitation as there might have been case-ascertainment errors and missed diagnosis, although the centralized military healthcare system and active endpoint evaluation are expected to minimize this. In addition, we evaluated all HZ cases in participants aged <35 years and found no ascertainment errors.

In conclusion, HZ remains a significant problem among PLWH even in the ART era, and rates are 3 times higher than in the general US population. There is an urgent need to study the safety, efficacy, and adverse effect profile of the RZV vaccine in PLWH. These studies should include PLWH aged <50 years, given that HZ occurs a decade earlier in PLWH.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. G. and L. G. conceived the idea for this analysis. A. G., C. S., T. L., T. F., R. M., K. K., R. D., J. O., and B. A. implemented the study, collected data, and oversaw the individual participating sites. A. G. and L. G. drafted the manuscript. X. W. performed the statistical analysis. All authors provided critical review that helped shape the manuscript.

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