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Incidence and predictors of herpes zoster among antiretroviral therapy-naïve patients initiating HIV treatment in Johannesburg, South Africa ☆☆

Kate Shearer [a,*], Mhairi Maskew [a], Toyin Ajayi [b], Rebecca Berhanu [c], Pappie Majuba [c], Ian Sanne [a,c,d], Matthew P. Fox [a,b,e]

[a] Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand,, Johannesburg, South Africa
[b] Center for Global Health and Development, Boston University, Boston, Massachusetts, USA
[c] Right to Care, Johannesburg, South Africa
[d] Clinical HIV Research Unit, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[e] Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts, USA

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SUMMARY

Objectives: To describe the characteristics of HIV-infected patients experiencing herpes zoster after antiretroviral therapy (ART) initiation and to describe the incidence and predictors of a herpes zoster diagnosis.
Methods: Adult patients initiating ART from April 2004 to September 2011 at the Themba Lethu Clinic in Johannesburg, South Africa were included. Patients were followed from ART initiation until the date of first herpes zoster diagnosis, or death, transfer, loss to follow-up, or dataset closure. Herpes zoster is described using incidence rates (IR) and predictors of herpes zoster are presented as subdistribution hazard ratios (sHR) and 95% confidence intervals (95% CI).
Results: Fifteen thousand and twenty-five patients were included; 62% were female, the median age was 36.6 years, and the median baseline CD4 count was 98 cells/mm^3. Three hundred and forty patients (2.3%) experienced herpes zoster in a median of 26.1 weeks after ART initiation. Most (71.5%) occurred within 1 year of initiation, for a 1-year IR of 18.1/1000 person-years. In an adjusted model, patients with low CD4 counts (<50 vs. ≥200 cells/mm^3; sHR: 1.71, 95% CI: 1.21–2.47) and with a prior episode of herpes zoster (sHR: 1.53, 95% CI: 0.97–2.28) were at increased risk of incident herpes zoster.
Conclusions: While only 2% of patients were diagnosed with herpes zoster in this cohort, patients with low CD4 counts and those with prior episodes of herpes zoster were at higher risk for a herpes zoster diagnosis.

1. Introduction

While in immune competent populations, herpes zoster, also called shingles, is most often seen in elderly persons, it is also commonly reported among HIV-infected persons.[1–5] After primary infection with varicella zoster virus (VZV), usually during childhood (chickenpox), the virus remains dormant in the sensory

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* Corresponding author. Tel.: +27 0 10 001 2653; fax: +27 0 86 668 0358.
E-mail address: kshearer@heroza.org (K. Shearer).

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nerve roots. Reactivation of latent virus occurs in the elderly or immunocompromised and results in herpes zoster, a painful vesicular rash that is self-limited.[2,6,7] In HIV-infected patients, herpes zoster can be more severe and prolonged, and may involve the eye or central nervous system.[6]

While data are lacking for low-resource settings, statistics from resource-rich environments suggest that while the lifetime risk of a herpes zoster episode in the general population is between 25% and 35%,[8–10] the burden is substantially higher in HIV-infected populations.[3] Although some studies have found that the incidence of herpes zoster has been decreasing since the scale-up of antiretroviral therapy (ART), the risk of a herpes zoster episode remains elevated in HIV-infected populations. In a recent study of HIV-infected patients conducted in Germany, the incidence of herpes zoster was 12/1000 person-years, while a cohort in the USA experienced herpes zoster at a rate of 9/1000 person-years.[11,12] These estimates are both substantially higher than the incidence rate in the general population of resource-rich countries, which ranges from 2/1000 person-years to approximately 5/1000 person-years.[10,13]

To describe the characteristics of patients experiencing episodes of herpes zoster after ART initiation, we assessed the incidence of herpes zoster in a large cohort of ART-naïve HIV-infected patients initiating ART in Johannesburg, South Africa. We further sought to identify characteristics that were associated with an increased risk for a herpes zoster episode and the timing of these episodes after initiation of ART.

2. Methods

2.1. Study site

The study was conducted at the Themba Lethu Clinic in Johannesburg, South Africa. Themba Lethu is a large outpatient, public sector HIV treatment clinic located within the Helen Joseph Hospital that receives non-governmental organization (NGO) support through the President's Emergency Plan for AIDS Relief (PEPFAR) program. ART at Themba Lethu has been provided in accordance with South Africa's national treatment guidelines since it was first made available in the public sector in 2004 and currently follows the 2013 guidelines.[14,15] Since 2004, approximately 30 000 patients have received HIV care at Themba Lethu and over 21 000 patients have initiated ART.[16]

Prior to April 2010, patients were initiated on ART when they reached a CD4 count of <200 cells/mm^3 or if they experienced a World Health Organization (WHO) stage IV condition. The primary ART regimen was stavudine, lamivudine, and efavirenz, with options to substitute zidovudine for stavudine, emtricitabine for lamivudine, and nevirapine for efavirenz when indicated.[14] After April 2010, tenofovir was chosen to replace stavudine in first-line regimens and in August 2011, the ART eligibility threshold was raised to a CD4 count of ≤350 cells/mm^3.[17,18]

Patient details including demographic information, laboratory test results, medications prescribed, clinical conditions, and other clinical details are captured in an electronic medical record system called TherapyEdge-HIV^{TM}.[16] Data are entered into the database at the time of the clinical encounter by the treating clinician. Patients are typically seen every month for the first 6 months after ART initiation and then every 2 months thereafter for either antiretroviral medication pick-ups and/or medical visits. The CD4 count is assessed at ART initiation, 1 year after ART initiation, and yearly thereafter, while viral load is assessed 4–6 months after ART initiation, at 1 year, and then yearly thereafter.

While herpes zoster can be identified at regularly scheduled visits, it is often diagnosed at an unscheduled medical visit or retrospectively at the medical visit following the episode. Herpes zoster is diagnosed clinically, and treatment for the lesions is provided with acyclovir and pain medication. Start and stop dates of the episode are entered into TherapyEdge-HIV^{TM} by the clinician.

2.2. Study population

We conducted a cohort analysis using data collected prospectively as part of routine patient care. We included all ART-naïve adult patients (≥18 years old) who initiated any of the standard public sector first-line regimens listed above between April 2004 and August 2011 and had at least one visit after ART initiation at the Themba Lethu Clinic. Loss to follow-up was defined as ≥3 months late for a scheduled visit with no subsequent visit. Death was ascertained through patient tracing. In addition, for patients with a valid South African national identification number (61%), deaths were identified through linkage with the National Vital Registration System.[19] The last linkage occurred in September 2011.

2.3. Study variables

Patients were followed from the date of ART initiation until the date of first herpes zoster diagnosis, or death, transfer, loss to follow-up, or dataset closure (September 6, 2012). Incident herpes zoster was defined as any herpes zoster episode occurring after the date of ART initiation.

We defined the baseline CD4 count to be the CD4 count conducted closest to the date of ART initiation, from 6 months prior to 7 days after ART initiation; this was categorized as <50 cells/mm^3, 50–99 cells/mm^3, 100–199 cells/mm^3, and ≥200 cells/mm^3. Classification by WHO stage was done by the clinician. If the clinician did not enter a classification, the WHO stage was determined according to the conditions present at ART initiation. Body mass index (BMI) was categorized according to standard categories (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2). Before defining anemia, recorded hemoglobin values were adjusted downward by 0.65 g/dl to account for the elevation of Johannesburg.[20] Anemia was then defined using WHO guidelines as severe, moderate, mild, and none, which differ by sex (male: <8, 8–10, 11–12, ≥13 g/dl) and pregnancy status (female, pregnant: <7, 7–9, 10, ≥11 g/dl; female, not pregnant: <8, 8–10, 11, ≥12 g/dl).[20] Finally, a prior episode of herpes zoster was defined as an episode that occurred prior to, or was present at, ART initiation.

2.4. Statistical analysis

The demographic and baseline characteristics of all patients included in the cohort are presented using frequencies for categorical variables and medians with corresponding interquartile ranges (IQR) for continuous variables. Incident herpes zoster rates per 1000 person-years and the corresponding 95% confidence intervals (95% CI) and predictors of herpes zoster within 12 months of ART initiation and herpes zoster ever on treatment are also presented.

Fine and Gray's method for competing risks regression was used to estimate the subdistribution hazard ratios (sHR) of predictors of herpes zoster for each model, accounting for the competing event of mortality.[21] Age, gender, and the baseline CD4 count were included as covariates in each model. Other potential confounding variables were included if they were plausible confounders based on prior knowledge and were associated with herpes zoster ($p <$ 0.2) in the crude analyses.

In order to determine whether an incident herpes zoster diagnosis within 12 months of ART initiation had any impact on short-term treatment outcomes, we matched each patient with a herpes zoster diagnosis within 12 months of follow-up to eight