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# Herpes Zoster among Persons Living with HIV in the Current ART Era

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**Abstract**

*Background:* Previously, herpes zoster (HZ) was found to occur at a higher rate in the HIV population than the general population. There are, however, limited data about the incidence, risk factors, and clinical outcomes of HZ in the current antiretroviral therapy (ART) era.

*Methods:* We identified HZ episodes in an urban HIV clinic cohort between 2002-2009. Three controls were matched to each case and conditional logistic regression was used to assess for risk factors associated with incident HZ cases. Logistic regression to assess for factors associated with complicated HZ.

*Results:* 183 new HZ cases were identified in 4,353 patients with 19,752 person-years (PY) of follow-up—an incidence rate 9.3/1000 PY. Cases were majority male (62%), and African-American (75%), with a mean age of 39 (IQR 32-44). 50 patients (28%) had complicated HZ with 12% developing post-herpetic neuralgia. In multivariate regression, having started ART within 90 days of the episode (Adjusted OR 4.02, 95% CI:[1.31,12.41]), having a viral load of > 400 copies/mL (1.49, [1.00,2.24]), and having a CD4 <350 cells/$mm^3$ (2.46, [1.42,4.23]) or 350-500 (2.02, [1.14,3.57]) as compared to CD4 > 500 were associated with increased risk of HZ.

*Conclusions:* The incidence of HZ is lower than previously reported in HIV cohorts, but remains higher than the general population. Over one-fourth of patients developed complicated HZ, which is remarkable given the young age of our population. Risk factors for HZ include markers of poor immune function, suggesting that appropriate ART may reduce the burden of HZ in this population.

## Introduction

It is estimated that over one million cases of herpes zoster (HZ) occur in the United States each year.(1) Most cases of HZ occur in adults over 60 years of age.(2) While over 90% of adults have serologic evidence of varicella-zoster infection and are therefore at risk for developing HZ, HIV-infected patients have been repeatedly found to have higher incidence rates than the general population.(3-8) Even after the institution of antiretroviral therapy (ART), the high rate of HZ persisted in persons living with HIV (PLWH).(3, 9)

Furthermore, studies suggested that PLWH were particularly susceptible to complicated HZ particularly recurrence, multidermatomal involvement, and systemic disease. Studies suggested that early in the combination ART era, ART did not correct the disparity between PLWH and the general population.(3) Some studies suggest that ART initiation and the resultant immune reconstitution syndrome might even increase a patient's risk of developing HZ.

As advances in HIV therapy allow patients to live longer and the HIV infected population ages, it would be plausible to think that the burden of herpes zoster would increase in the HIV-infected population. Moreover, a new varicella vaccine to protect against zoster was FDA-approved in 2006 and could greatly impact the epidemiology of this disease. In this study, we re-evaluated the incidence, risk factors and incidence of complicated HZ in our urban cohort of HIV patients.

## Methods

*Population and data collection*

The Johns Hopkins University AIDS Service provides both primary and sub-specialty care for PLWH in the Maryland region. The clinic maintains an observational database on patients. Trained monitors use structured forms to extract extensive information including demographics, clinical and laboratory data, pharmaceutics, and deaths. Institutional electronic sources supplement the record abstraction.(10) Maintenance of the database and use of its contents for analysis is approved by the

Institutional Review Board of the Johns Hopkins University School of Medicine. All patients receiving primary HIV care enrolled in this clinic were eligible for inclusion in this study.

For this study, we identified all cases of clinically diagnosed HZ diagnosed between January 1, 2002 and December 31, 2009 in this cohort. Charts were systematically reviewed for the clinical characteristics, treatment and sequelae of all new cases of HZ.

*Definitions*

We defined HZ as a rash that a healthcare provider verified as HZ. HZ was considered a first episode if there was no evidence in the medical record of a previous occurrence. Complicated HZ was defined as the occurrence of one or more of the following: disseminated zoster (zoster involving three or more dermatomes); ocular, visceral or neurologic complication consistent with HZ but not attributable to an independent pathologic process; or a recurrence of HZ within 180 days of presentation. Consistent with prior literature post-herpetic neuralgia (PHN) was defined as pain lasting more than 120 days from the initial onset of the herpes rash.(11)

ART was defined as a prescribed multiclass regimen of three or more antiretroviral agents, This definition of ART was highly inclusive, and thus unlikely to exclude any preferred drug combinations. Time on ART was defined as the time between the date of ART initiation and the date of zoster presentation. If ART was initiated within 90 days prior to HZ the patient was considered to have "recently started." Finally, AIDS was defined as a previous CD4 count of < 200 cells/$mm^3$ or by a prior AIDS-defining illness based on Centers for Disease Control and Prevention criteria.(12)

HIV risk factors were defined as past or present exposure to injection drug use (IDU), men who have sex with men (MSM), or high-risk heterosexual contact. Substance use was categorized as current if use was recorded in the medical record within one year of the HZ episode.

Comorbidities were assessed through the patient's medical record. Depression was defined as a diagnosis of depression previously made by a medical or psychiatric provider. Hepatitis C was defined

as chronic hepatitis C infection, and hepatitis B as chronic, active hepatitis B infection.

The data we collected were entered and managed using a REDCap (Research Electronic Data Capture) electronic data capture tools hosted by the Johns Hopkins Biostatistics Center.(13)

*Data analysis*

For normally distributed variables, means and standard deviations were calculated. For non-parametric data, medians and inter-quartile ranges are reported. Normally distributed, continuous variables were compared using the Student *t*-test, categorical variables with the Fisher exact test, and non-parametric data with the Wilcoxon rank-sum test.

Incidence rates were calculated using annual totals of person-time in the cohort. We compared herpes zoster incidence rates over time using Poisson regression. Risk factors were identified using a nested case-control analysis. Three controls were randomly selected for each case from the patients in the cohort based on year of enrollment, baseline CD4, and duration of follow-up. Conditional multivariate logistic regression was used to assess risk factors for zoster.

In order to determine predictors of complicated HZ, we also used logistic regression methods. Individual risk factors were first identified using univariate analyses, with a *p*-value cut-off for significance of 0.2. The variables that were identified in univariate analysis were then combined in a multivariable logistic regression model. Potential interactions between variables were evaluated by adding interaction terms to the multivariate models. The final model was selected using a modified backwards stepwise selection method for non-significant *p*-values, and then choosing the model with the lowest Akaike information criterion. All analyses were performed using STATA 11.0 (Stata Corp, TX)

**Results**

*Patient demographics, clinical characteristics, and incidence of zoster*

Between January 1, 2002 and December 31, 2009, there were 4,353 patients with 19,752

person-years of follow-up time. During this period there were 321 cases of HZ in 262 individuals. One hundred and eighty-three cases (57%) were incident cases. The remaining 138 cases were recurrences that occurred during the study period. Incident cases were less likely than recurrent cases to be on ART at the time of the event (OR 0.42, p=0.004). The incidence rate over the entire study period was 9.3 events per 1,000 person-years of follow-up, and varied from 4.7 per 1,000 person-years in 2009 to 13.1 in 2003 (Figure 1). There was no statistically significant difference between the annual incidence rates and the overall rate for the study period ($p$ >0.1).

Among incident HZ, the majority of patients were male (62%), African-American (75%), and had heterosexual sex as their HIV risk factor (52%) (Table 1). The median age was 39 years (range: 18-68 years). Most patients actively used tobacco (63%), alcohol (46%), or illicit drugs (27%).

The median CD4 count at HZ was 278 cells/mm$^3$ (IQR: 153-444; 18% with CD4 < 350 cells/mm$^3$) and the median HIV-1 RNA was 2,581 copies/mL (range: <400 to > 700,000 copies/mL; 37% undetectable).

Most patients (75%) were on ART at the time of their zoster event. Of the 137 patients on ART, 10 (5.5%) had started ART within the past 90 days. Most patients (86%) had at least one comorbid condition. The most common conditions were hepatitis C (53%), depression (42%), and hepatitis B (26%) (Table 1). Notably, none of the patients in this study received the HZ vaccine in our clinic during the study interval.

Thirty cases were seen by an outside provider at the time of their diagnosis and had unknown dermatomal involvement. Among the remaining 153 patients, 67% had single dermatomal involvement, with the most common location being the thorax (involved in 60% of patients). Nineteen patients (11%) had disseminated HZ (Table 2).

Among 168 cases for whom we had treatment data, 158 (94%) were treated with antiviral therapy for HZ. The most commonly prescribed antiviral was valacyclovir (77%). Thirty-six patients

(20%) were hospitalized for their HZ. The hospitalized patients had a mean CD4 count of 233 cells/mm$^3$, 68% were already on ART at the time of the episode, and 26 patients (74%) were treated with intravenous acyclovir.

In multivariate analysis, factors associated with an initial HZ outbreak included having initiated ART within 90 days of the episode (Adjusted Odds Ratio (AOR): 4.02, 95% CI: [1.31-12.41]), having a detectable HIV-1 RNA at the time of the episode (AOR 1.49, [1.00-2.24]), and having a CD4 count between 350 and 500 cells/mm$^3$ (AOR 2.02, [1.14-3.57]) or a CD4 count below 350 cells/mm$^3$ (AOR 2.46, [1.42-4.23]) as compared to patients with CD4 count above 500 cells/mm$^3$ (Table 3). Age, sex, race, HIV risk factor, current ART use, and comorbid depression, hepatitis B, or hepatitis C were not associated with a zoster outbreak in univariate or multivariate analyses.

*Presenting symptoms, complications of zoster*

Not all patients initially presented within the Johns Hopkins system with their episode of HZ. For patients whose available medical records included their initial presentation (n=133), the majority complained of pain (82.0%), rash (53.4%), and pruritis (33.8%). Over one quarter of patients (28.3%) had complicated zoster. The most common complications were PHN (11.9%), disseminated zoster (10.7%), bacterial superinfection (6.3%), ocular involvement (5.7%) and meningioencephalitis (2.8%). In univariate logistic analysis, having a CD4 count < 50 cells/mm$^3$ (Odds Ratio 2.86, 95%CI [1.01-8.09]) was significantly associated with developing complicated zoster (Table 4). However, this finding was no longer statistically significant after adjusting for age and viral load.



**Discussion**

In this study, the incidence of herpes zoster among an urban cohort of HIV-infected persons was 9.3 per 1,000 person-years. This rate has decreased significantly since a previous study conducted earlier in the combination ART era using this same cohort (32 cases/ 1,000 PYs, between 1997 and

2001), and now appears to be approaching that of the general population—estimated at approximately 3.5 cases per 1,000 person-years.(3, 14) This finding is in contrast to data from two other cohorts—the Veterans Health database and Olmsted County, Minnesota—that both showed small but significant increases in HZ over time (2000-2007 and 1996-2001, respectively).(15, 16)

The observed decrease in incidence rate in our clinic might be explained by improvements in addressing the risk factors for HZ specific to PLWH,. Consistent with our earlier study and other studies, we found that a lower CD4 count was associated with increased risk of incident HZ. (3, 4, 8) Indeed, immune suppression is consistently a risk factor for herpes zoster outbreak in this population, with a CD4 count below 350 cells/$mm^3$ conferred greater risk than a CD4 count between 350 and 500 cells/$mm^3$. Given that the median CD4 count of our population has steadily increased from 2000 through 2009 from 298 to 431 cells/mm3, this finding highlights the importance of restoring immune function in protecting against HZ. The effectiveness of contemporary ART in improving immune function is likely to be the primary reason for the decline in HZ incidence.

Unlike our earlier study, we also found that the recent ART initiation was strongly associated with incident disease, suggesting a possible role of immune dysregulation during immune reconstitution in producing HZ outbreaks. The association between early immune reconstitution after starting ART and HZ outbreaks has been previously observed in smaller studies, and may be at least partially mediated through an increase in CD8 cells.(17, 18)

Although the incidence rate has decreased in our population, it is still greater than the general population, especially when age is considered, and we continue to observe a significant complication rate (28%) among cases. If one excludes PHN, the rate is still 21%—far more than the 10-13% rate observed in the general population.(16, 19, 20) Our data are consistent with previous reports of higher complication rates in PLWH; however, the complication rate observed in this study was less than the 53% complication rate previously described in our clinic population.(3, 7) Importantly, since the

earlier analysis, the definition of PHN has become more conservative now only including pain 120 days after the onset of rash, as compared to the previous definition which included pain that persisted 28 days after the disappearance of the rash. This change in definition might also account for the large decrease in the proportion of patients experiencing PHN (from 28% to 12% in this study). We identified a CD4 count <50 cells/mm$^3$ as a factor associated with complications on univariate analysis, but no factors were statistically significant on multivariate regression. Past studies have identified low CD4 count, older age, and particular HIV risk factors to be associated with complications.(3, 19) Only 50 of our patients experienced complications, which was perhaps not a sufficient number to detect risk factors with only a small effect size. Our results are nevertheless consistent with the literature suggesting a higher complication rate in PLWH. Better access to improved HIV-related care may reduce the gap in complication rates between PLWH and the general population. Age was not a risk factor for either an HZ episode or an HZ complication in this study. Age is a known risk factor for HZ in the general population, but our population is still relatively young.

There are several potential limitations to this study. Our results are derived from patients followed at a single, urban institution with a relatively high proportion of injection drugs users and minority ethnicity and may not generalize to other clinical settings. We were unable to assess the impact of the two varicella vaccines. Although young, our population is still old enough to have had very low rates of varicella vaccination in childhood. Both the varicella and zoster vaccines are live attenuated vaccines and as such could potentially be dangerous in an immunosuppressed population. Data on the use of the vaccine in HIV-infected adults is limited, though suggest that the vaccine can be immunogenic in HIV infected patients. (21) Based on expert opinion, vaccination of HIV-infected persons >8 years of age who are in CDC clinical class A or B and have CD4 counts > 200 cells/mm$^3$ may be considered.(22) Though not currently licensed for this use, the zoster vaccine can be given to those who do not have AIDS or clinical manifestations of HIV, and a CD4 > 200 cells/mm$^3$ or >15% of

total lymphocytes.(23) No patient in our clinical cohort had received a dose of zoster vaccine during the study period. Finally, our results rely on documentation in the medical record although we have no reason to believe that the clinical documentation of events and complications has decreased during our or the previous study periods. In addition, our methods of abstracting these data have not changed over time.

In summary, this study offers several important findings. First, incidence rates of HZ have decreased significantly since earlier in the combination ART era, moving closer to the general population rate, but still remain elevated. Second, complication rates of HZ remain high in PLWH despite this group's much younger median age. Despite the high complication rate, and the high incidence rate in PLWH, not a single patient in our study population had been vaccinated against HZ. Finally, and perhaps most importantly, there are several modifiable risk factors for incident HZ, including having a detectable HIV-1 RNA level and a low CD4 count. However, HZ does appear to be associated with immune reconstitution, so that the clinician should be aware of the higher risk of HZ shortly after ART is started. Although age was not a risk factor for HZ in this study, it is a known risk factor for HZ in the general populations, and as the HIV-infected population continues to age on effective ART, we may see a greater burden of HZ.



**Figure Legend:**

**Figure 1. Annual incidence rates of herpes zoster between 2002 and 2009**

Orange lines mark the point estimate (dotted) and 95% confidence intervals (solid) for the overall 2002-2009 herpes zoster incidence rate.

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**Table 1.** Patient demographic and clinical characteristics by case status

| | **Cases of HZ (n=183)** | **Controls (n=549)** | **P-value*** |
|---|---|---|---|
| Gender- N (%) | | | 0.448 |
| Male | 114 (62.3) | 359 (65.4) | |
| Race- N (%) | | | 0.619 |
| African American | 137 (75.3) | 403 (73.4) | |
| Age- yrs | | | 0.579[H] |
| Mean | 38.6 | 39.0 | |
| Standard deviation | 9.2 | 9.1 | |
| HIV risk factor- N(%) | | | |
| Injection drug use (IDU) | 64 (35.0) | 214 (39.0) | 0.333 |
| Men who have sex with men (MSM) | 49 (26.8) | 160 (29.1) | 0.539 |
| High risk heterosexual sex | 95 (51.9) | 284 (51.7) | 0.966 |
| ART use at HZ onset-N (%) | | | 0.843 |
| On ART | 137 (74.9) | 415 (75.6) | |
| CD4 count at HZ onset-N (%) | | | 0.001 |
| CD4 < 350/mm3 | 112 (61.2) | 268 (48.8) | |
| CD4 350-500/mm3 | 38 (20.8) | 107 (19.5) | |
| CD4 >500/mm3 | 33 (18.0) | 174 (31.7) | |
| HIV-1 RNA at HZ onset- N(%) | (n=183) | (n=542) | 0.007 |
| Undetectable < 400 copies/mL | 67 (36.6) | 261 (48.2) | |
| Detectable ≥ 400 copies/mL | 116 (63.4) | 281 (51.9) | |
| Recent ART use- N (%) | | | 0.009 |
| Started ART <90 days before event | 10 (5.5) | 10 (1.8) | |
| Comorbidities- N (%) | | | |
| Hepatitis B | 48 (26.2) | 131 (23.9) | 0.519 |
| Hepatitis C | 96 (52.5) | 286 (52.1) | 0.932 |
| Diabetes | 19 (10.4) | 68 (12.4) | 0.468 |
| Cancer | 60 (32.8) | 138 (25.1) | 0.044 |

* P-value calculated using Pearson's $\chi^2$ test unless otherwise indicated.
H P-value calculated using a two sample t-test.

**Table 2.** Clinical characteristics of patients with a first episode of herpes zoster.

| | N (%) |
|---|---|
| Substance use at HZ onset | |
| Tobacco (n=139) | 88 (63.3) |
| Alcohol (n=142) | 65 (45.8) |
| Illicit drugs (n=135) | 37 (27.4) |
| Location of dermatomes involved (n=153) | |
| Cranial | 33 (21.6) |
| Cervical | 31 (20.3) |
| Thoracic | 91 (59.5) |
| Lumbar and/or sacral | 15 (9.8) |
| Number of dermatomes involved (n=151) | |
| 1 | 101 (66.9) |
| 2 | 31 (20.5) |
| 3 + | 19 (12.6) |
| Any complication (n=177) | 50 (28.3) |
| Post-herpetic neuralgia | 21 (11.9) |
| Disseminated zoster | 19 (10.7) |
| Bacterial superinfection | 11 (6.3) |
| Ocular involvement | 10 (5.7) |
| Meningioencephalitis | 5 (2.8) |
| Confusion | 1 (0.6) |
| Antiviral used for treatment (n=168) | |
| IV acyclovir | 26 (15.5) |
| Oral acyclovir | 23 (13.7) |
| Valacyclovir | 129 (76.8) |
| Famciclovir | 10 (6.0) |
| Steroids prescribed (n=168) | 9 (5.4) |
| Hospitalized for herpes zoster (n=181) | 36 (19.9) |

Abbreviations: number of patients (N), total number of patients (n)

**Table 3. Conditional logistic regression analysis of factors associated with first herpes zoster outbreak**

| Characteristic | Unadjusted Odds Ratio (OR) (95% Confidence Interval (CI)) | Adjusted OR (95% CI) |
|---|---|---|
| Recent ART initiation | | |
| No | 1.0 (Ref) | 1.0 (Ref) |
| Yes | 4.67 (1.54-14.16) | 4.02 (1.31-12.41) |
| Detectable HIV-1 RNA | | |
| No (<400 copies/mL) | 1.0 (Ref) | 1.0 (Ref) |
| Yes (>400 copies/mL) | 1.75 (1.20-2.56) | 1.49 (1.00-2.24) |
| CD4 count | | |
| >500 cells/$mm^3$ | 1.0 (Ref) | 1.0 (Ref) |
| 350-500 cells/$mm^3$ | 2.08 (1.18-3.65) | 2.02 (1.14-3.57) |
| <350 cells/$mm^3$ | 3.01 (1.79-5.08) | 2.46 (1.42-4.23) |
| Age | | |
| <40 years | 1.0 (Ref) | 1.0 (Ref) |
| 40-49 years | 1.03 (0.70-1.52) | 1.06 (0.71-1.58) |
| >50 years | 1.00 (0.57-1.75) | 1.11 (0.62-1.98) |

**Table 4. Factors associated with complicated zoster**

| Characteristic | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|
| Detectable HIV-1 RNA | | |
| No <400 copies/mL | 1.0 (Ref) | 1.0 (Ref) |
| Yes >400 copies/mL | 1.70 (0.84-3.47) | 1.50 (0.66-3.40) |
| CD4 count | | |
| >50 cells/$mm^3$ | 1.0 (Ref) | 1.0 (Ref) |
| <50 cells/$mm^3$ | 2.86 (1.01-8.09) | 2.47 (0.75-8.20) |
| Presented with headache | | |
| No | 1.0 (Ref) | 1.0 (Ref) |
| Yes | 3.87 (0.88-17.06) | 3.14 (0.69-14.41) |
| Age | | |
| <30 years | 1.0 (Ref) | 1.0 (Ref) |
| 30-49 years | 1.21 (0.50-2.95) | 0.96 (0.33-2.82) |
| >50 years | 0.85 (0.23-3.04) | 1.01 (0.24-4.29) |