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Impact of Antiretroviral Therapy on the Risk of Herpes Zoster among Human Immunodeficiency Virus-Infected Individuals in Tanzania

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Abstract. We examined the incidence of herpes zoster (HZ) before and after the initiation of antiretroviral therapy (ART), and risk factors for HZ among human immunodeficiency virus (HIV)-infected individuals in Tanzania. A cohort study was conducted among HIV-positive individuals enrolled in HIV care and treatment clinics in Dar es Salaam, Tanzania. A Cox proportional hazard model was used to examine the effect of ART on the risk of HZ after adjusting for sociodemographics and time-varying clinical and nutritional factors. Among 72,670 HIV-positive individuals, 2,312 incident cases of HZ (3.2%) occurred during the median follow-up of 15 months (interquartile range: 3–35). The incidence rate of HZ significantly declined from 48.9 (95% confidence interval [CI] = 46.7–51.0) per 1,000 person-years before ART to 3.7 (95% CI = 3.3–4.1) per 1,000 person-years after the initiation of ART ($P < 0.001$). The risk of HZ declined with longer duration on ART. Low CD4 cell count, older age, female sex, district of Dar es Salaam, and year of enrollment were independently associated with the risk of HZ in the multivariate analysis. Low body mass index and anemia were not associated with the risk of HZ. The risk of HZ substantially declined after ART initiation in this large cohort of HIV-infected individuals. Earlier initiation of ART could reduce the risk of HZ and other opportunistic infections among HIV-infected individuals in sub-Saharan Africa.

INTRODUCTION

Herpes zoster (HZ), also known as shingles, is a human immunodeficiency virus (HIV)-associated opportunistic infection. HZ causes a painful, blistering rash and results from reactivation of varicella-zoster virus (VZV).[1–3] Because of impaired cell-mediated immunity, HIV-positive individuals have 3 to ≥ 10-fold higher risk of HZ than HIV-negative individuals.[4–7] HIV-positive individuals frequently suffer from serious complications, including post-herpetic neuralgia, disseminated zoster, bacterial superinfection, and HZ ophthalmicus.[8–11]

Substantial efforts have been made to increase access to the treatment and care of people with HIV/acquired immunodeficiency syndrome (AIDS) in sub-Saharan Africa, the region most heavily affected by the HIV epidemic.[12] Prior studies found a reduction in the risk of HZ from the initiation of antiretroviral therapy (ART) in North America and Europe.[6,13–17] Although prior studies examined the risk of HZ in sub-Saharan Africa, there are a few studies comparing the incidence of HZ before and after the initiation of ART.[18,19] The incidence of HIV-associated opportunistic infections often varies widely by geographic region.[20] Understanding the risk factors for HZ may provide valuable information for health-care practitioners. Previously identified risk factors for HZ include low CD4 cell counts, female sex, and race/ethnicity[14–17,21]; however, other potential risk factors, such as poor nutritional status have not been well studied.

The objective of our study was to examine the incidence of HZ before and after the initiation of ART in this large cohort of HIV-infected individuals who enrolled in HIV/AIDS treatment and care in Tanzania. We also investigated the risk factors for HZ, including sociodemographic, clinical, and nutritional factors.

METHODS

Study design and population. A prospective cohort study was conducted at the Management and Development for Health (MDH), the President's Emergency Plan For AIDS Relief–supported HIV care and treatment clinics in Dar es Salaam, Tanzania.[22,23] The MDH program was established in 2004 and has provided infrastructure, laboratory, and technical support to HIV care and treatment centers; integrated prevention of mother to child transmission; and HIV and tuberculosis (TB) services. The present study was conducted among HIV-infected adults who enrolled in 30 MDH-supported HIV care and treatment clinics in three districts of Dar es Salaam from November 2004 to September 2011. The study was approved by institutional review boards at the Harvard School of Public Health and Muhimbili University of Health and Allied Sciences.

Criteria for the initiation of ART treatment were based on the National AIDS Control Program in Tanzania at the time of the study. Patients were initiated on ART, if they had CD4 cell count < 200 cells/mm^3, clinical World Health Organization (WHO) stage IV, or clinical WHO stage III with a CD4 cell count of < 350 cells/mm^3. At the time of this study, standard first-line ART regimens included stavudine (d4T) or zidovudine (ZDV) plus lamivudine (3TC) and efavirenz (EFV) or nevirapine (NVP). Tenofovir plus either 3TC or emtricitabine was introduced as an alternative nucleoside reverse transcriptase inhibitor combination in 2009 to d4T and 3TC. The recommended treatment of HZ includes analgesics and acyclovir five times daily for 7–10 days.

After ART initiation, patients were evaluated monthly by a physician and received adherence and nutrition counseling, and ART refills. When patients did not meet initiation criteria for

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ART, clinic visits were scheduled every 4–6 months. Physicians and nurses collected data on patient demographic, clinical, and laboratory data using standard case report forms. Cases of HZ were identified through physicians' examination and diagnosis. Nurses measured the patient's height, weight, and middle upper arm circumference (MUAC) using standard techniques. Laboratory tests for CD4 cell counts and hemoglobin (Hgb) concentrations were performed at enrollment and every 6 months thereafter. According to the WHO clinical staging, the occurrence of HZ is regarded as clinical stage 2; therefore, not all were eligible for ART initiation.

Data analysis. The incidence rate of HZ was calculated as cases per 1,000 person-years. Follow-up time was defined as enrollment until a diagnosis of HZ, death, loss to follow-up, or the last visit date. We evaluated CD4 cell count (cells/mm^3), gender/pregnancy, age category, marital status, district of residence (Kinondoni, Ilala, and Temeke), body mass index (BMI), MUAC, anemia status, year of enrollment, and season of clinical visits.

We used Cox proportional hazard modeling to examine the impact of ART on the risk of HZ. The following time interval categories were used: < 3 months, 3–5 months, 6–11 months, or ≥ 12 months since the initiation of ART treatment. The Andersen–Gill formulation of the Cox proportional hazards model was used to model time-varying covariates. ART treatment, recent CD4 cell count, BMI, MUAC, and anemia status were evaluated as time-varying covariates. Missing indicator was used for missing values. All factors associated with the risk of HZ with $P \leq 0.20$ in the univariate analysis were introduced into the multivariate model. *P* values for trend were based on the median score for ordered categorical variables. All statistical analyses were conducted using the SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

There were 80,199 HIV-infected individuals ≥ 15 years of age enrolled in the HIV care and treatment program between November 2004 and September 2011 (Figure 1). We excluded 3,223 patients (4.0%) who had HZ at enrollment or within 2 years before enrollment. We further excluded 4,306 patients without follow-up visits.

Among 72,670 HIV-positive individuals included in our study, the median age was 35 years (interquartile range [IQR]: 29–41) at enrollment and 72% were women (Table 1). The median CD4 cell count was 219 cells/mm^3 (IQR: 88–394). About 24% of the patients had low BMI (< 18.5 kg/m^2) and 54% had moderate to severe anemia (Hgb < 11.0 g/dL). The median follow-up time was 15 months (IQR: 3–35; mean of 21 months). During the study period, 60% of the study patients initiated ART. The median time from enrollment to initiation of ART was 2.3 months (IQR: 1.5–4.2). Among patient on ART, the median CD4 cell count at the time of ART initiation was 144 (IQR: 62–242) and the median BMI was 20.7 (IQR: 18.2–23.8).

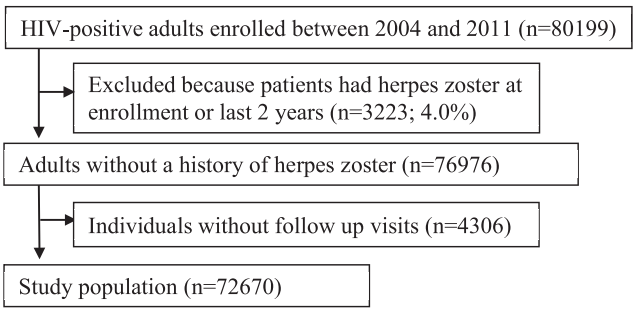

FIGURE 1. Study population.

TABLE 1
Baseline characteristics of 72,670 human immunodeficiency virus–positive individuals

Characteristics	*N* (%)
Age (years), median (IQR)	35.0 (29–41)
Gender	
Women	52,306 (72.0%)
Men	20,364 (28.0%)
Pregnancy among women	10,226 (19.6%)
Married	30,539 (42.0%)
Initiated ART	43,328 (59.6%)
ART regimens	
ZDV, 3TC, and EFV	12,055 (34.7%)
ZDV, 3TC, and NVP	4,841 (13.9%)
d4T, 3TC, and EFV	11,696 (33.7%)
d4T, 3TC, and NVP	2,679 (7.7%)
District	
Ilala	28,449 (39.4%)
Kinondoni	24,192 (33.5%)
Temeke	19,597 (27.1%)
CD4 cell counts (cells/mm^3), median (IQR)	219 (88–394)
CD4 cell counts (cells/mm^3)	
< 100	15,442 (27.5%)
100–199	10,718 (19.1%)
200–349	12,872 (22.9%)
350–499	8,506 (15.2%)
≥ 500	8,592 (15.3%)
BMI (kg/m^2), median (IQR)	21.2 (18.6–24.6)
BMI (kg/m^2)	
< 18.5	16,836 (24.1%)
18.5–24.9	37,258 (53.4%)
25.0–29.9	11,186 (16.0%)
≥ 30.0	4,535 (6.5%)
MUAC (cm), median (IQR)	25.0 (23.0–28.0)
Hgb (g/dL), median (IQR)	10.8 (9.3–12.1)
Year at enrollment	
2004–2006	15,456 (21.3%)
2007–2009	39,022 (53.7%)
2010–2011	18,192 (25.0%)

3TC = lamivudine; ART = antiretroviral therapy; BMI = body mass index; d4T = stavudine; EFV = efavirenz; Hgb = hemoglobin; IQR = interquartile range; MUAC = middle upper arm circumference; NVP = nevirapine; ZDV = zidovudine.

A total of 2,312 incident cases of HZ (3.2%) occurred during the study period. The incidence rate of HZ declined from 48.9 (95% confidence interval [CI] = 46.7–51.0) per 1,000 person-years before ART to 3.7 (95% CI = 3.3–4.1) per 1,000 person-years after the initiation of ART. Compared with those who were not on ART, the risk of HZ was significantly lower among patients who were on ART (Table 2). The risk of HZ declined with longer duration on ART in the multivariate model (adjusted hazard ratios [HRs] of 0.14 [95% CI = 0.12, 0.18] during the first 3 months, 0.05 [95% CI = 0.04, 0.08] between 3 and 5 months, 0.06 [95% CI = 0.05, 0.09] between 6 and 11 months, and 0.04 [95% CI = 0.03, 0.05] after 12 months). The risk of HZ did not differ by ART regimen. HR for patients receiving d4T-containing regimen compared with ZDV-containing regimen was 1.16 (95% CI = 0.82, 1.64). The risk of HZ did not differ by NVP versus EFV-containing regimen (HR = 1.25; 95% CI = 0.86, 1.81).

CD4 cell count, age, female sex, district, and year of enrollment were independently associated with the risk of HZ in

TABLE 2
Predictors of herpes zoster among human immunodeficiency virus–positive individuals

	Unadjusted HR	(95% CI)	P	Adjusted HR	(95% CI)	P
Antiretroviral therapy (ART)			< 0.001			< 0.001
Before ART	Reference	–		Reference	–	
0–3 months	0.19	(0.16, 0.23)		0.14	(0.12, 0.18)	
3–6 months	0.07	(0.05, 0.10)		0.05	(0.04, 0.08)	
6–12 months	0.08	(0.06, 0.11)		0.06	(0.05, 0.09)	
≥ 12 months	0.04	(0.04, 0.05)		0.04	(0.03, 0.05)	
ART regimen						
NRTI						
ZDV	Reference	–	–	–	–	–
d4T	1.16	(0.82, 1.64)	0.40	–	–	–
TDF	0.91	(0.33, 2.50)	0.85	–	–	–
NNRTI						
EFV	Reference	–	–	–	–	–
NVP	1.25	(0.86, 1.81)	0.25	–	–	–
Gender/pregnancy			< 0.001			< 0.001
Nonpregnant women	1.43	(1.29, 1.59)		1.18	(1.05, 1.31)	
Pregnant women	1.31	(1.05, 1.64)		0.86	(0.68, 1.09)	
Men	Reference	–		Reference	–	
Married			0.026			0.06
Yes	1.10	(1.01, 1.20)		0.92	(0.84, 1.00)	
No	Reference	–		Reference	–	
District			0.004			< 0.001
Ilala	1.17	(1.06, 1.30)		1.16	(1.04, 1.28)	
Kinondoni	1.04	(0.93, 1.17)		0.96	(0.85, 1.07)	
Temeke	Reference	–		Reference	–	
Number of children			0.43			
None	Reference	–		–	–	–
1–2	1.06	(0.97, 1.15)		–	–	–
≥ 3	0.99	(0.86, 1.14)		–	–	–
Age (years)			< 0.001			0.029
15–29	1.19	(1.08, 1.31)		0.91	(0.83, 1.00)	
30–39	Reference	–		Reference	–	
40–49	0.89	(0.80, 1.00)		1.09	(0.97, 1.22)	
≥ 50	0.79	(0.67, 0.94)		1.01	(0.85, 1.19)	
CD4 cell counts (cells/mm^3)			< 0.001			< 0.001
< 100	0.72	(0.61, 0.85)		2.11	(1.76, 2.53)	
100–199	0.67	(0.57, 0.78)		2.19	(1.85, 2.58)	
200–349	1.19	(1.06, 1.33)		1.95	(1.74, 2.18)	
350–449	1.08	(0.96, 1.21)		1.27	(1.12, 1.43)	
≥ 500	Reference	–		Reference	–	
BMI (kg/m^2)			0.011			0.11
< 18.5	0.88	(0.76, 1.02)		0.93	(0.80, 1.09)	
18.5–24.9	Reference	–		Reference	–	
25.0–29.9	1.06	(0.95, 1.19)		0.94	(0.84, 1.05)	
≥ 30.0	1.12	(0.97, 1.29)		0.85	(0.74, 0.99)	
MUAC (cm)			0.002			0.99
< 22	0.64	(0.44, 0.92)		1.00	(0.69, 1.45)	
22–24.9	0.82	(0.62, 1.09)		1.26	(0.95, 1.69)	
25–34.9	0.98	(0.76, 1.28)		1.35	(1.04, 1.76)	
≥ 35	Reference	–		Reference	–	
Anemia			0.014			0.90
Severe	1.16	(0.98, 1.38)		1.03	(0.87, 1.23)	
Moderate	1.10	(0.99, 1.22)		1.05	(0.95, 1.16)	
Mild	1.04	(0.93, 1.16)		1.03	(0.93, 1.16)	
No	Reference	–		Reference	–	
Year of enrollment			< 0.001			< 0.001
2004–2006	Reference	–		Reference	–	
2007	1.42	(1.26, 1.61)		1.40	(1.24, 1.59)	
2008	1.42	(1.24, 1.61)		1.49	(1.31, 1.71)	
2009	1.80	(1.57, 2.06)		1.85	(1.61, 2.13)	
2010	2.31	(1.99, 2.68)		2.58	(2.21, 3.02)	
2011	2.41	(1.87, 3.10)		2.78	(2.15, 3.60)	
Season			< 0.001			0.012
Long dry (June to September)	1.02	(0.91, 1.15)		1.09	(0.97, 1.23)	
Short rain (October to November)	0.82	(0.71, 0.95)		0.90	(0.78, 1.05)	
Short dry (December to March)	0.95	(0.84, 1.07)		0.96	(0.85, 1.08)	
Long rain (April to May)	Reference	–		Reference	–	

BMI = body mass index; CI = confidence interval; d4T = stavudine; EFV = efavirenz; HR = hazard ratio; MUAC = middle upper arm circumference; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; TDF = tenofovir; ZDV = zidovudine. Based on a multivariate Cox model that includes ART, age, gender, pregnancy, marital status, CD4 cell counts, district, BMI, anemia status, year, and season of clinical visits. In a separate model, BMI was replaced by MUAC and entered into the multivariate model. *P* values for trend were based on the median score for ordered categorical variables. *P* values for gender/pregnancy, district, and season were based on the likelihood ratio test. Following cutoffs were used to define severe, moderate, or mild anemia, or normal: for men, hemoglobin < 8.0, 8.0–10.9, 11.0–12.9, and ≥ 13.0 g/dL and for women, < 8.0, 8.0–10.9, 11.0–11.9, and ≥ 12.0 g/dL.

the multivariate analysis (Table 2). Compared with patients with CD4 cell counts greater than 500 cells/mm^3, patients with CD4 cell counts less than 100 and 100–199 cells/mm^3 had more than two times greater risk of HZ in the multivariate model (adjusted HR = 2.11 [95% CI = 1.76, 2.53] and 2.19 [95% CI = 1.85, 2.58], respectively). Nonpregnant women had 1.18 times (95% CI = 1.05, 1.31) greater risk of HZ than men. Patients < 15–29 years of age tend to have lower risk of HZ than patients > 30 years of age, although the difference in the risk of HZ across age group was marginal. Later year of enrollment was associated with greater incidence of HZ (P < 0.001). BMI, MUAC, and anemia status were not associated with the risk of HZ in the multivariate model.

DISCUSSION

In this large cohort of HIV-positive individuals in Tanzania, the incidence of HZ substantially declined from 48.9 per 1,000 person-years before ART to 3.7 per 1,000 person-years after the initiation of ART. Our findings are consistent with prior studies (Table 3). A study of the French National Hospital database reported that the incidence of HZ declined from 30 per 1,000 person-years in 1992–1996 to 6 per 1,000 person-years in 2009–2011, and this decline was primarily due to the initiation of ART.[6] The Veterans Affairs study in the United States showed that the incidence rate of HZ significantly declined from 63 to 10 per 1,000 person-years between 1987 and 2011.[13] Prior studies in sub-Saharan Africa showed low incidence of HZ among patients who initiated ART.[18,19] In South Africa, overall incidence of HZ among HIV-infected patients who initiated ART was 7.4 per 1,000 person-years.[18] A study in Uganda reported that the prevalence of HZ declined from 13.4 to 3.3 per 1,000 persons between 2002 and 2013 from the rollout of ART program.[19]

Consistent with prior studies, low CD4 cell counts and female sex were associated with an increased risk of HZ.[6,15,18] Women are heavily affected by HIV/AIDS in Tanzania and they had a higher risk of HZ than men in our study. Increased risk of HZ among women has been shown in both HIV-infected and uninfected populations, most likely because of differences in health-seeking behavior or biological response to VZV infection.[6,24] Contrary to what we hypothesized, BMI, MUAC, and anemia status were not associated with the risk of HZ. A study in South Africa also found that BMI and anemia status were not associated with the risk of HZ.[18] The higher rates of HZ that we observed in patients enrolled in more recent years may be due to shorter time being on ART or increased reporting over time, although we were unable to assess this possibility.

Our study found that the risk of HZ substantially declined after ART initiation. Furthermore, ART was previously associated with reduction in risks of TB, *Pneumocystis* pneumonia, Kaposi's Sarcoma, and other opportunistic infections.[20,25,26] WHO recently recommended initiating ART immediately for all HIV-positive individuals regardless of WHO clinical stage or CD4 cell count level.[27] Further efforts based on the updated WHO's "test and treat" approach could reduce the risk of HZ and other opportunistic infections among HIV-infected

TABLE 3
Prior studies on herpes zoster (HZ) during antiretroviral therapy (ART) era in HIV-positive patients

Reference	Study design	Study population	Incidence rates of HZ	Risk factors for HZ
Present study	Individuals enrolled in HIV care and treatment program in Tanzania	2,312 cases of HZ among 72,670 individuals	Incidence declined from 48.9 per 1,000 person-years pre-ART to 3.7 per 1,000 person-years post-ART	Low CD4 cell counts, age, female sex, district, and year of enrollment
Grabar et al.[6]	French National Hospital Database on HIV 1992–2011	7,167 cases of HZ among 91,044 patients	Incidence declined from 29.6 per 1,000 person-years in 1992–1996 to 6.3 per 1,000 person-years in 2009–2011	Low CD4 cell counts, high HIV RNA levels, low CD4/CD8 ratios, age, female
Rubaihayo et al.[19]	HIV care program in Uganda 2002–2013	5,972 individuals	Incidence declined from 13.4 to 3.3 per 1,000 persons between 2002 and 2013	–
Shearer et al.[18]	Adult patients on ART in South Africa 2004–2011	340 episodes of HZ among 15,025 patients	Incidence of 7.4 per 1,000 person-years	Low CD4 cell counts, and prior episode of HZ
Moanna and Rimland[13]	HIV Atlanta Veterans Affairs cohort study 1982–2011	650 cases of HZ among 3,816 patients	Incidence declined from 63 to 10 per 1000 person-years between 1987 and 2011	Low CD4 cell counts, age, race, and MSM
Jansen et al.[15]	Nationwide HIV cohort in Germany 1985–2010	362 episodes of HZ among 3,757 patients	Incidence of 17 per 1,000 person-years	Low CD4 cell counts
Liu et al.[17]	Women's interagency HIV study in the U.S. 1994–2009	389 matched pairs of participants	Incidence of 25 per 1,000 person-years in ART group vs. 35 per 1,000 person-years in ART naive group	CD4 cell counts, quality of life, and acyclovir use
Blank et al.[16]	A retrospective cohort study in Maryland, U.S. 2002–2009	183 new and 138 recurrent cases of HZ among 4,353 patients	Incidence of 9.3 per 1,000 person-years	HIV RNA, and low CD4 cell counts
Gebo et al.[21]	A retrospective cohort study in Maryland, U.S. 1997–2001	158 new and 124 recurrent cases of HZ among 2,543 patients	Incidence of 32 per 1,000 person-years	Low CD4 cell counts
Hung et al.[14]	A prospective cohort study in Taiwan, 1994–2003	103 episodes of HZ among 716 patients	Incidence declined from 172.1 per 1,000 person-years pre-ART to 50.5 per 1,000 person-years post-ART	Low CD4 cell counts

HIV = human immunodeficiency virus; MSM = men who had sex with men.

individuals in sub-Saharan Africa. Prevention of these infections through early initiation of ART could substantially improve the quality of life among HIV-infected individuals.

The strength of our study is that it is one of the largest cohorts from sub-Saharan Africa, with a median follow-up period of 15 months and an IQR of 3–35 months. More than 60% of patients initiated ART during the follow-up, which allowed us to evaluate the incidence rate of HZ before and after the initiation of ART. However, our study has several limitations. Cases of HZ were based on clinical diagnosis. Occasionally, presentation of HZ may be atypical and may require laboratory confirmation,[4] and this could have potentially led to underreporting of HZ. Our study did not evaluate the risk of complications or recurrence. More than 28% of patients with HZ developed complications among HIV-positive patients.[16] We excluded patients without follow-up visits and patients with a prior history of HZ. Excluded patients may have had more advanced HIV disease and may have been at a greater risk of HZ than those included in our study cohort. Therefore, we may have underestimated the overall incidence of HZ, which may have potentially biased our results. Several studies demonstrated that patients with a prior episode of HZ have increased risk of recurrent episode of HZ.[18] Because we were unable to determine whether cases identified during follow-up were incident or prevalent cases, we could not evaluate the risk of recurrence among patients who had HZ at or before enrollment. Because this study included patients in an HIV care and treatment program, there may be a potentially differential ascertainment from differences in a frequency of visits before and after ART. Our study was conducted in an urban setting in Tanzania and our findings may not necessarily be generalizable to rural or other setting in sub-Saharan Africa.

In conclusion, we found that the risk of HZ substantially declined after ART initiation in this large cohort of HIV-infected individuals in Tanzania. Further efforts based on the WHO's "test and treat" approach could reduce the risk of HZ and other opportunistic infections among HIV-infected individuals in sub-Saharan Africa.

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