Journal of Microbiology, Immunology and Infection (2018) 51, 38–44

Available online at www.sciencedirect.com

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ORIGINAL ARTICLE

Incidence and risk factors of herpes zoster in human immunodeficiency virus-positive patients initiating combination antiretroviral therapy in Taiwan

Yi-Chieh Lee [a], Chien-Ching Hung [b], Mao-Song Tsai [c], Jun-Yu Zhang [d], Pei-Ying Wu [d], Shang-Ping Yang [d], Yu-Zhen Luo [d], Hsi-Yen Chang [d], Wen-Chun Liu [b], Hsin-Yun Sun [b,*], Shan-Chwen Chang [b]

[a] *Department of Internal Medicine, Lotung Poh-Ai Hospital, Lo-Hsu Medical Foundation, I-Lan, Taiwan*
[b] *Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*
[c] *Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan*
[d] *Center of Infection Control, National Taiwan University Hospital, Taipei, Taiwan*

Received 28 January 2016; received in revised form 17 March 2016; accepted 1 April 2016
Available online 13 May 2016

KEYWORDS
AIDS;
dermatologic complications;
immunosuppression;
varicella-zoster

Abstract *Background/Purpose:* To obtain current epidemiological data for better vaccination policies, this study aimed to assess the incidence and risk factors of herpes zoster in human immunodeficiency virus (HIV)-positive patients initiating combination antiretroviral therapy (cART) in Taiwan.
Methods: Between June, 2012 and May, 2015, we prospectively identified zoster cases in HIV-positive patients initiating cART. Clinical information was collected on demographics, prior zoster, plasma HIV-1 RNA load (PVL), and CD4 count at baseline and during follow up. A case–control study by 1:2 matched pairs was used to identify the risk factors for zoster development.
Results: During the 3-year study period, 826 patients with a mean age of 32.9 years were included, and 7.7% had prior zoster. The mean baseline CD4 count and PVL were 286 cells/μL and 4.90 $\log_{10}$ copies/mL, respectively. Fifty-four (6.5%) patients developed zoster after initiation of cART, with 43 episodes (79.6%) occurring within 1 year of cART initiation, which

* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan.
E-mail address: hysun@ntu.edu.tw (H.-Y. Sun).

http://dx.doi.org/10.1016/j.jmii.2016.04.011

corresponded to an overall incidence rate of 3.61/100 person-years. The multivariate analysis revealed that prior zoster (adjusted odds ratio = 3.143; 95% confidence interval, 1.385–7.133) and baseline CD4 count < 200 cells/μL (adjusted odds ratio = 2.034; 95% confidence interval, 1.020–4.057) were independent risk factors for zoster in HIV-positive patients initiating cART. In case–control study, prior zoster and baseline PVL > 5 $\log_{10}$ copies/mL were risk factors for zoster development after cART initiation in multivariate analysis.

Conclusions: Herpes zoster occurred in 6.5% of HIV-positive Taiwanese patients after initiation of cART, which was associated with prior zoster and baseline CD4 count < 200 cells/μL or baseline PVL > 5 $\log_{10}$ copies/mL.

Introduction

Herpes zoster, also called shingles, is most often seen in the elderly population. It also commonly occurs in human immunodeficiency virus (HIV)-positive patients.[1–3] Prior to the introduction of combination antiretroviral therapy (cART), the incidence of herpes zoster was estimated to be 10–30 times greater in HIV-positive patients than in HIV-negative individuals.[1,4,5] Several studies reported incidence rates of 2.5–3.2 cases/100 person-years in different HIV-positive cohorts.[3,6] A low CD4 count was the risk factor for developement of herpes zoster.[4,7] After the introduction of cART, the incidence of herpes zoster declined significantly[7–10]; 1.2 cases/100 person-years was observed in Germany and 0.9 cases/100 person-years in the United States in the cART era.[9,10] This decrease was mainly attributable to the restoration of immunity with cART. However, the incidence remains higher in HIV-positive patients in the cART era than that in the general population of resource-rich countries, which ranges from 0.2/100 person-years to 0.5/100 person-years.[11,12] Complication rates are also higher in HIV-positive patients than in the age-matched general population (27–28% vs. 10–13%).[6,10,13,14] Therefore, use of herpes zoster vaccine may be considered in HIV-positive patients to prevent herpes zoster and its related complications.

Live attenuated herpes zoster vaccine (LAHZV) was recommended to HIV-positive adults with a CD4 count >200 cells/μL.[15,16] Recently, an adjuvanted herpes zoster subunit vaccine, called HZ/su vaccine, demonstrated significant risk reduction of herpes zoster in adults aged ≥ 50 years.[17] Given the concerns about the theoretical risk that the attenuated live vaccines may cause serious disease in immunocompromised hosts, this HZ/su vaccine has the potential to benefit HIV-positive patients.[18]

In Taiwan, Hung et al[7] reported that the incidence of herpes zoster in HIV-positive patients had declined from 17.21/100 person-years in the pre-cART era (prior to 1997) to 5.05/100 person-years in the post-cART era (between 1997 and 2003) ($p < 0.0001$), and baseline CD4 count was a significant risk factor associated with herpes zoster. To obtain current epidemiological data for better vaccination policies, this study aimed to assess the incidence and identify risk factors of herpes zoster in HIV-positive patients initiating cART in Taiwan.

Materials and methods

Patients and setting

Between June 1, 2012 and May 31, 2015, we conducted a prospective cohort study to identify cases of herpes zoster in cART-naïve HIV-positive adult patients who initiated cART at the National Taiwan University Hospital, Taipei, Taiwan. Patients were followed from the initiation of cART until the date of first episode of herpes zoster, loss to follow up, death, or end of observation (December 31, 2015). Herpes zoster was diagnosed based on the characteristic skin findings, whereas previous herpes zoster was defined as having an episode of herpes zoster prior to the initiation of cART.

In Taiwan, cART has been provided free of charge since its introduction in April 1997, and HIV-positive Taiwanese patients receive HIV care according to the national treatment guidelines at designated hospitals around Taiwan. Plasma HIV-1 RNA load (PVL) and CD4 count were determined at baseline, 4 weeks after initiation of cART, and every 12 weeks thereafter within the 1st year of cART and every 24 weeks subsequently in patients who are on stable cART with good viral suppression. All of the patients were enrolled in the case management program implemented by the Taiwan Centers for Disease Control to provide support, counseling, and linkage to and retention in HIV care fort the HIV-positive patients.

During the study period, cART was defined as combinations of two nucleos(*t*)ide reverse-transcriptase inhibitors with one non-nucleoside reverse-transcriptase inhibitor, boosted protease inhibitor or unboosted atazanavir, or integrase inhibitor. PVL and CD4 count quantified with the use of the Cobas Amplicor HIV-1 Monitor Test, version 1.5, (Roche Diagnostics Corporation, Indianapolis, IN, USA) and FACSFlow (Becton Dickinson, CA), respectively.

Study design and data collection

We used a standardized case record form to collect information on the demographic and clinical characteristics of the patients, including age, sex, risk behaviors of HIV-1 transmission, prior episode of herpes zoster, duration from

cART initiation to the development of herpes zoster, as well as PVL and CD4 count at baseline and during follow up. To better delineate the risk factor for development of herpes zoster, a case—control study was conducted with two control patients without herpes zoster who were matched for one case patient with herpes zoster with regard to age (±3 years), sex, risk behaviors, and date of cART initiation (±2 weeks). Only the first episode of herpes zoster was included for analysis. The patients were censored when herpes zoster occurred after initiation of cART, when the patients were lost to follow up, or when the observation ended (December 31, 2015), whichever occurred first.

The study was approved by the Research Ethics Committee of the hospital (Registration Number, 201003112R), and the requirement for written informed consent from participants prior to participation in the study was waived.

Statistical analysis

Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation (SD), and compared using Student *t* test. Categorical variables were expressed as percentage of the total number of patients analyzed, and compared using chi-square test. To identify the factors associated with development of herpes zoster, the variables with p values < 0.05 in univariate analysis were entered into the multivariate logistic regression analysis. The Kaplan—Meier method was used to assess time to cumulative probabilities of herpes zoster free condition by different categories of baseline CD4 count (<200 cells/μL, 200—349 cells/μL, 350—499 cells/μL, and ≥500 cells/μL, respectively), which were compared using log-rank test. A p value < 0.05 was considered statistically significant.

Table 1 Clinical characteristics of HIV-positive patients with and without herpes zoster after initiation of combination antiretrovial therapy between June 1, 2012 and May 30, 2015.

Variable	All patients	Patients with zoster	Patients without zoster	*p*
Patient no.	826 (100)	54 (6.5)	772 (93.5)	
Age (y)	32.9 ± 9.3	36.3 ± 10.1	32.7 ± 9.2	0.005
Male sex	801 (97)	53 (98.1)	748 (96.9)	0.912
Risk of HIV infection				
Homosexuals	769 (93.1)	52 (96.3)	717 (92.9)	0.326
Heterosexuals	41 (5.0)	2 (3.7)	39 (5.1)	
IDU	15 (1.8)	0 (0)	15 (1.9)	
Others	1 (0.1)	0 (0)	1 (0.1)	
Prior herpes zoster	56 (7.7)	9 (18.8)	47 (6.9)	0.007
AZT use	358 (43.3)	25 (46.3)	333 (43.1)	0.650
Switch from AZT to other agents	248 (30.0)	18 (33.3)	230 (29.8)	0.583
Duration from ART initiation to the development of zoster (d)	227 ± 265	227 ± 265	NA	NA
<1 mo of ART use	NA	8 (14.8)	NA	NA
1—3 mo of ART use	NA	13 (24.1)	NA	NA
3—6 mo of ART use	NA	11 (20.4)	NA	NA
6—12 mo of ART use	NA	11 (20.4)	NA	NA
>12 mo of ART use	NA	11 (20.4)	NA	NA
Baseline CD4 (cells/μL)	286 ± 187	208 ± 156	292 ± 187	0.001
≥500 cells/μL	86 (10.5)	3 (5.6)	83 (10.8)	0.013
350—499 cells/μL	199 (24.2)	8 (14.8)	191 (24.9)	
200—349 cells/μL	271 (33.0)	15 (27.8)	256 (33.3)	
<200 cells/μL	266 (32.4)	28 (51.9)	238 (31.0)	0.002
CD4 1 mo post-ART (cells/μL)	401 ± 212	344 ± 179	405 ± 214	0.043
<200 cells/μL	139 (17.9)	13 (24.5)	126 (17.4)	0.193
CD4 4 mo post-ART (cells/μL)	453 ± 224	403 ± 213	457 ± 225	0.091
<200 cells/μL	101 (14.0)	11 (20.8)	90 (13.5)	0.142
Baseline PVL ($\log_{10}$ copies/μL)	4.90 ± 0.73	5.22 ± 0.72	4.87 ± 0.72	0.001
>5 $\log_{10}$ copies/μL	340 (41.3)	33 (61.1)	307 (39.9)	0.002
PVL 1 mo post-ART $\log_{10}$ copies/μL ($\log_{10}$ copies/μL)	2.60 ± 0.82	2.93 ± 0.84	2.58 ± 0.81	0.002
>2 $\log_{10}$ copies/mL	617 (78.5)	45 (84.9)	572 (78.0)	0.240
<200 copies/mL	288 (36.6)	11 (20.8)	277 (37.8)	0.013
PVL 4 mo post-ART ($\log_{10}$ copies/μL)	2.60 ± 0.82	2.16 ± 1.09	1.74 ± 0.79	0.008
>2 $\log_{10}$ copies/μL	165 (22.9)	21 (40.4)	144 (21.5)	0.002
<200 copies/mL	616 (85.4)	39 (73.6)	577 (86.4)	0.011

Data are presented as mean ± SD or *n* (%).
ART = antiretroviral therapy; AZT = zidovudine; HIV = human immunodeficiency virus; IDU = injected drug user; NA = not available; PVL = plasma HIV-1 RNA load; SD = standard deviation.

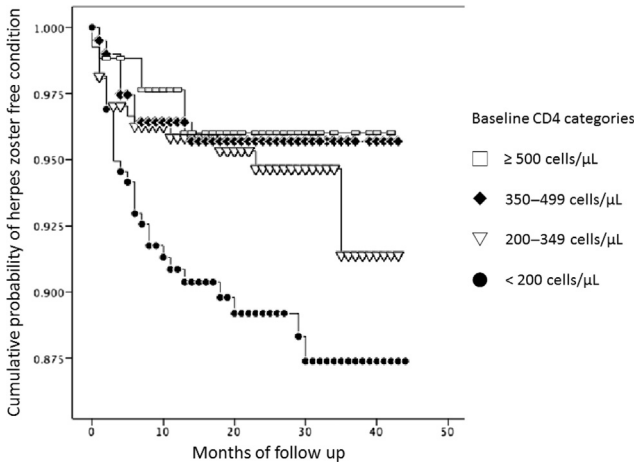

Figure 1. Kaplan–Meier plots showing the cumulative probability of herpes zoster-free condition in human immunodeficiency virus (HIV)-positive patients initiating combination antiretroviral therapy with different categories of baseline CD4 counts.

Results

During the 3-year study period, a total of 826 patients initiated cART at National Taiwan University Hospital. The patients had a mean age of 32.9 years; 97.0% were men; 93.1% were men who have sex with men; and 7.7% had prior herpes zoster. The mean baseline CD4 count and PVL were 286 cells/μL and 4.90 $\log_{10}$ copies/mL, respectively. Almost one-third of the patients (32.4%) had a baseline CD4 count $<$ 200 cells/μL (Table 1). cART containing zidovudine/lamivudine was initiated in 43.3% (358/826) of the patients; however, 69.3% of those 358 patients initiating zidovudine-containing regimens had to switch from zidovudine/lamivudine to other nucleoside reverse transcriptase inhibitors.

After a mean observation duration of 634 days (SD, 348), herpes zoster developed in 54 patients (6.5%) after cART initiation, and nine (18.8%) of them had had herpes zoster prior to cART initiation. This corresponded to an overall incidence rate of 3.61/100 person-years. The mean interval from cART initiation to onset of herpes zoster was 227 days (SD, 265). Most of the episodes (79.6%) occurred within 1 year of cART initiation.

Demographic data and clinical characteristics between patients with and without development of herpes zoster after initiation of cART are shown in Table 1. Compared with patients without herpes zoster after cART, those with herpes zoster were older (mean age, 36.3 years vs. 32.7 years, $p = 0.005$) and more likely to have had prior herpes zoster (18.8% vs. 6.9%, $p = 0.007$), and had a lower mean baseline CD4 count (208 cells/μL vs. 292 cells/μL, $p = 0.001$) and a higher mean baseline PVL (5.22 $\log_{10}$ copies/mL vs. 4.87 $\log_{10}$ copies/mL, $p = 0.001$).

One month after initiation of cART, patients with herpes zoster continued to have a lower mean CD4 count (344 cells/μL vs. 405 cells/μL, $p = 0.043$) and a higher mean PVL (2.93 $\log_{10}$ copies/mL vs. 2.58 $\log_{10}$ copies/mL, $p = 0.002$). Four months after initiation of cART, patients with herpes zoster tended to have a lower mean CD4 count (403 cells/μL vs. 457 cells/μL, $p = 0.091$) but had a higher mean PVL (2.15 $\log_{10}$ copies/mL vs. 1.74 $\log_{10}$ copies/mL, $p = 0.010$).

Kaplan–Meier plots for cumulative probability of herpes zoster in patients with different categories of baseline CD4 counts during observation are shown in Figure 1. Patients with lower baseline CD4 counts were more likely to develop zoster (log-rank test $p = 0.012$; Figure 1). In multivariate analysis, prior herpes zoster [adjusted odds ratio (AOR) = 3.143; 95% confidence interval (CI), 1.385–7.133; $p = 0.006$] and baseline CD4 count $<$ 200 cells/μL (AOR 2.034, 95% CI 1.020–4.057, $p = 0.044$) were independent risk factors for herpes zoster in HIV-positive patients initiating cART (Table 2).

In the case–control study, the clinical characteristics of the matched pairs (1:2) of patients with and without development of herpes zoster after initiation of cART are shown in Table 3. Six case patients did not have suitable controls, and only one matched control was identified for each of 10 patients. Compared with control patients, case patients were more likely to have prior herpes zoster (18.8% vs. 3.8%, $p = 0.012$), and had a lower mean baseline CD4 count (208 cells/μL vs. 284 cells/μL, $p = 0.015$) and a higher mean baseline PVL (5.22 $\log_{10}$ copies/mL vs. 4.80 $\log_{10}$ copies/mL, $p < 0.001$). One month and 4 months after initiation of cART, case patients had a higher mean PVL [2.93 $\log_{10}$ copies/mL vs. 2.51 $\log_{10}$ copies/mL ($p = 0.004$) and 2.15 $\log_{10}$ copies/mL vs. 1.71 $\log_{10}$ copies/mL ($p = 0.014$), respectively]. Associated factors with development of herpes zoster in multivariate analysis included prior herpes zoster (AOR = 4.735; 95% CI, 1.122–19.990; $p = 0.034$) and baseline PVL $>$ 5 $\log_{10}$ copies/mL (AOR = 2.963; 95% CI, 1.001–8.774; $p = 0.050$) (Table 4).

Discussion

In this cohort of ART-naive HIV-positive patients, 6.5% experienced herpes zoster after cART initiation. Other studies of similar populations (homosexual males aged

Table 2 Multivariate analysis for risk factors associated with the development of zoster in HIV-positive patients after initiation of combination antiretroviral therapy.

Variable	Reference	OR	95% CI	*p*
Prior zoster	No prior zoster	3.143	1.385–7.133	0.006
Age	Continuous variables	1.016	0.985–1.047	0.317
Baseline CD4 count <200 cells/μL	Baseline CD4 < 200 cells/μL	2.034	1.020–4.057	0.044
Baseline PVL > 5 $\log_{10}$ copies/mL	Baseline PVL < 5 log copies/mL	1.542	0.789–3.013	0.205

CI = confidence interval; HIV = human immunodeficiency virus; OR = odds ratio; PVL = plasma HIV-1 RNA load.

Table 3 Clinical characteristics in matched pairs (1:2) of HIV-positive patients with and without herpes zoster after initiation of combination antiretroviral therapy.

Variable	Patients with zoster	Patients without zoster	*p*
No. of patients	54 (38.6)	86 (61.4)	
Age (y)	36.3 ± 10.1	34.3 ± 7.8	0.191
Male	53 (98.1)	86 (100)	0.386
Risk of HIV infection			
Homosexuals	52 (96.3)	85 (98.8)	0.681
Heterosexuals	2 (3.7)	1 (1.2)	
IDU	0 (0)	0 (0)	
Others	0 (0)	0 (0)	
Prior zoster	9 (18.8)	3 (3.8)	0.012
Baseline CD4 (cells/μL)	208 ± 156	284 ± 192	0.015
≥500 cells/μL	3 (5.6)	19 (13.8)	0.022
350–500 cells/μL	8 (14.8)	30 (21.7)	
200–349 cells/μL	15 (27.8)	49 (35.5)	
<200 cells/μL	28 (51.9)	28 (32.6)	0.023
AZT use	25 (46.3)	29 (33.7)	0.137
Switch from AZT to other agents	18 (33.3)	25 (29.1)	0.595
CD4 1 mo post-ART (cells/μL)	344 ± 179	374 ± 201	0.368
<200 cells/μL	13 (24.5)	15 (18.5)	0.403
CD4 4 mo post-ART (cells/uL)	403 ± 213	417 ± 210	0.705
<200 cells/μL	11 (20.8)	15 (18.5)	0.749
Baseline PVL (log_{10} copies/mL)	5.22 ± 0.72	4.80 ± 0.59	<0.001
>5 log_{10} copies/mL	33 (61.1)	28 (32.6)	0.001
PVL 1 mo post-ART (log_{10} copies/mL)	2.93 ± 0.84	2.51 ± 0.81	0.004
>2 log_{10} copies/mL	45 (84.9)	64 (78.0)	0.324
<200 copies/mL	11 (20.8)	36 (43.9)	0.006
PVL 4 mo post-ART (log_{10} copies/mL)	2.15 ± 1.08	1.71 ± 0.82	0.014
>2 log_{10} copies/mL	21 (39.6)	13 (16.3)	0.002
<200 copies/mL	39 (73.6)	72 (90.0)	0.013

Data are presented as mean ± SD or *n* (%).
ART = antiretroviral therapy; AZT = zidovudine; HIV = human immunodeficiency virus; IDU = injection drug user; PVL = plasma HIV-1 RNA load; SD = standard deviation.

approx.30–40 years) in the cART era reported a relatively higher prevalence of herpes zoster, ranging from 7.9% to 14.1%.[8,9,19] The discrepancy may be attributable to the different ethnicities and baseline CD4 counts of the patient populations.[8] Compared with a previous observational study in Taiwan,[7] this study showed lower incidence (6.5% vs. 10.7%, $p = 0.006$) with a significantly lower incidence rate than that in the pre-cART era (3.61/100 person-years vs. 17.2/100 person-years, $p = 0.004$) but a similar incidence rate when compared with that in the post-cART era (3.61/100 person-years vs. 5.05/100 person-years, $p = 0.754$). The decline in the incidence of herpes zoster was also demonstrated in other recent studies,[8,10,19] which could reflect the benefit of restoration of immunodeficiency and viral suppression by cART.

Our study found that baseline CD4 count < 200 cells/μL and prior herpes zoster were independent risk factors for the development of herpes zoster in patients initiating cART. Several recent studies also demonstrated a clear association between the CD4 counts and the risk of herpes zoster.[9,10,19,20] In the French study using insurance databases, Grabar et al[19] found an inverse dose–response relationship between the CD4/CD8 ratio < 0.9 and the risk of herpes zoster, independent of the CD4 count and PVL, in multivariate analysis. An association between CD8 count and the risk of herpes zoster has also been described by other studies.[21,22]

In the case–control study, we found that prior herpes zoster and baseline PLV > 5 log_{10} copies/mL were risk factors associated with development of herpes zoster, which was different from those (prior herpes zoster and baseline CD4 count < 200 cells/μL) identified in the overall study population. Blank et al[10] found that starting cART within 90 days of the zoster episode, having a PVL > 400 copies/mL, and a CD4 < 350 cells/μL were associated with increased risk of herpes zoster. These findings suggested that markers of poor immune function, such as high PVL and low CD4 count, were predisposing factors to the development of herpes zoster, and early initiation of appropriate regimens of cART may reduce the burden of herpes zoster in HIV-positive patients.

Because of higher incidence and complications of herpes zoster in HIV-positive patients, vaccination could provide potential benefits. LAHZV is recommended to HIV-positive adults with a CD4 count >200 cells/μL.[15,16] Despite concerns of causing disease in immunocompromised hosts, including HIV-positive populations, by LAHZV,[23,24] a recent study by Shafran[15] recommended the administration of LAHZV to HIV-positive adults with a CD4 count >200 cells/μL, which was safe and immunogenic with no cases of vaccine strain infection. However, the lower CD4 counts, the higher the probability of herpes zoster in HIV-positive patients. For HIV-positive patients with CD4 counts < 200 cells/μL, a recombinant subunit vaccine might be an appropriate choice to prevent herpes zoster.[25] A recent phase 1/2a clinical trial by Berkowitz et al[18] noted that an adjuvanted herpes zoster subunit candidate vaccine was immunogenic in both humoral and cellular immunity and had a clinically acceptible safety profile in HIV-positive adults, including patients with cART and CD4 count < 200 cells/μL.

This study should be viewed with necessary caution in light of several limitations. First, self-reported prior herpes zoster was not documented by a health professional, but high validity to self-reports of herpes zoster suggested that herpes zoster misclassification was likely to be very low.[26] Second, as patients might present with herpes zoster in a local primary care facility, the incidence of herpes zoster experienced by patients in this cohort was likely to be underestimated. Third, information on complications of herpes zoster were unavailable, such as postherpetic neuralgia, disseminated herpes zoster, bacterial superinfection, ocular involvement, and meningoencephalitis. This precludes us from evaluating the impact of herpes zoster on HIV-positive patients. Fourth, our results were derived from patients followed at a single, urban institution with a high proportion of men who have sex with men, and the results may not be generalized to other clinical settings.

Table 4 Multivariate analysis for risk factors associated with the development of zoster in matched pairs of HIV-positive patients after initiation of combination antiretroviral therapy.

Variable	Reference	OR	95% CI	*p*
Age	Continuous variables	1.403	0.931–2.114	0.106
Prior zoster	No prior zoster	4.735	1.122–19.990	0.034
Baseline PVL >5 $\log_{10}$ copies/mL	Baseline PVL <5 $\log_{10}$ copies/mL	2.963	1.001–8.774	0.050
Baseline CD4 <200 cells/μL	Baseline CD4 >200 cells/μL	1.191	0.389–3.645	0.760

CI = confidence interval; HIV = human immunodeficiency virus; OR = odds ratio; PVL = plasma HIV-1 RNA load.

In conclusion, 6.5% of HIV-positive Taiwanese patients developed herpes zoster after initiation of cART, with an overall incidence rate of 3.61/100 patient-years. The associated factors of zoster development included prior herpes zoster and baseline CD4 count < 200 cells/μL or baseline PVL > 5 $\log_{10}$ copies/mL.

Conflicts of interest

C.-C.H. has received research support from Janssen, Abbvie, and ViiV; and speaker honoraria from Bristol-Myers Squibb, ViiV, Abbvie, and Gilead Sciences; and served on advisory boards for Gilead Sciences and Abbvie. All other authors declare no conflicts of interest.

Acknowledgments

We thank the patients for participating in this survey and Taiwan Centers for Disease Control for the research grant support. This study was supported by grants from Taiwan Centers for Disease Control (MOHW103-CDC-C-114-000405 to C.-C. H.). The funding source played no role in study design and conduct, data collection, analysis or interpretation, writing of the manuscript, or the decision to submit it for publication.

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