Herpes Zoster in Antiretroviral Therapy

Subjects: Biology

Contributor: Sriyani Padmalatha Konara Mudiyanselage

The incidence of herpes zoster (HZ) in patients infected with HIV is higher than that of the general population. However, the incidence of HZ in HIV patients receiving antiretroviral therapy (ART) remains unclear.

incidence herpes zoster HIV-infected patients highly active antiretroviral therapy meta-analysis

1. Introduction

Herpes zoster (HZ), also known as shingles, is caused by the reactivation of varicella zoster virus (VZV), which remains latent in the sensory ganglia following varicella infection [1]. HZ is a human immunodeficiency virus (HIV)-associated opportunistic infection. HIV infected populations have a 3- to 20-fold higher risk of contracting HZ than HIV seronegative individuals [2][3][4][5][6]. A systematic review and meta-analysis of the HZ incidence in ART-naive patients was 9.4%. During the first year of ART, the incidence was 2.3%, but this reduction was not statistically significant [7].

Even though the introduction of ART has improved the survival of those living with HIV, the incidence of HZ among HIV cohorts remains higher than that of the general population [4][8]. The incidence of HZ in the HIV cohort was 9.3–141 per 1000 patient years (PY)s [8][9][10]; but the incidence of HZ in the general population is only 3–5 per 1000 PYs [11]. The general population lifetime risk for HZ is between 23.8% and 30% and affects approximately one in four people in Europe; however, for those aged >85 years, the risk increases to one in two people [12].

ART was previously associated with reduced risk of herpes zoster and other opportunistic infections and could substantially improve the quality of life among HIV infected patients [7]. The long-term effects of ART on HZ incidence among HIV infected cohorts have been inconsistent across previous studies. A study in 2005 noted that the HZ incidence has not significantly decreased since the advent of ART [9]. Conversely, other prior studies found a reduction in the risk of HZ after the initiation of ART in North America, Europe, Taiwan and Africa [4][8][10][13][14][15][16][17]. Several studies have shown an increase in the HZ incidence during the first to fourth months following ART therapy, which suggests that HZ may be a feature of immune reconstitution inflammatory syndrome (IRIS) [9][18][19].

A better understanding of the risk factors for HZ for the HIV infected population may provide valuable information for health care professionals to identify adult patients at a heightened risk and could help formulate appropriate policies for vaccination strategies for the HIV-infected population [20]. Therefore, the objective of meta-analysis

aimed to systematically review studies estimating the incidence and risk factors for HZ in the post-ART era among people living with HIV (PLWH) and discuss implications based on the updated evidence.

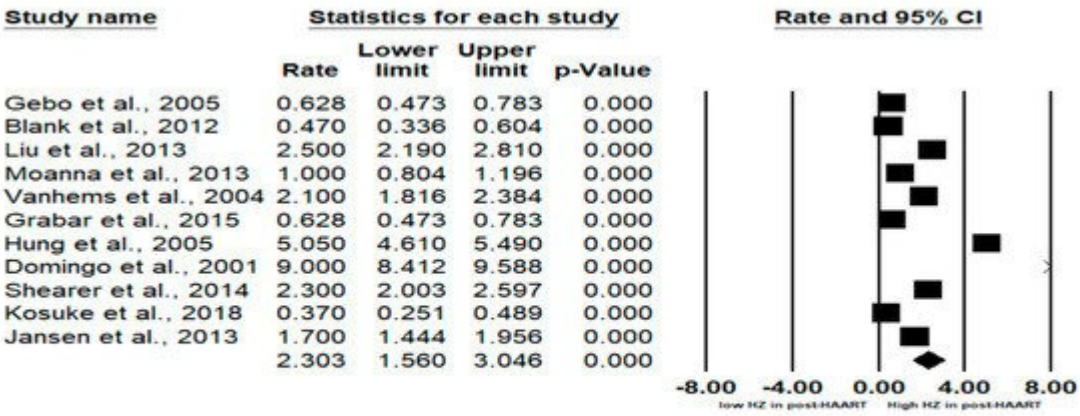
2. Results

2.1. Study Characteristics

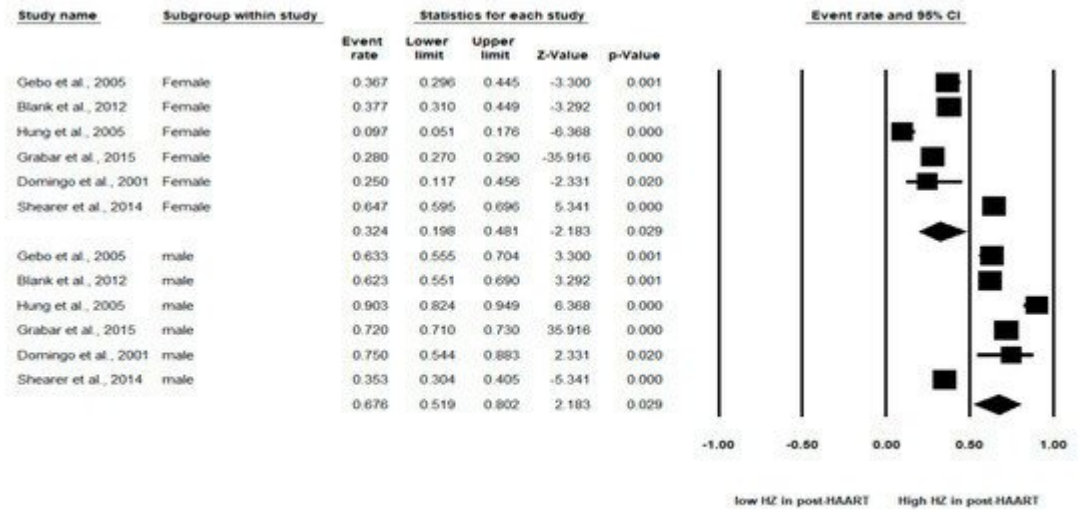
During the period from 1 January 2000 to 28 February 2021, we identified 2111 records: 221 from PubMed, 1793 from Embase, 23 from Cochrane Library and 74 from CINAHL. After removing duplications and the initial screening, 45 articles were eligible for full-text review (Figure 1).

Eleven studies met the inclusion criteria for the meta-analysis. The 11 studies received a quality score of ≥8, with nine studies receiving a score of >10 out of 12 (Table 1). The 11 studies included 10 cohort studies and 1 clinical observational study. Overall, the study quality was acceptable. These 11 studies included 195,190 total HIV infected participants. The incidence was reported for populations in America (four studies), Europe (four studies), Asia (one study) and Africa (two studies).

The pooled incidence rate of HZ in the 11 studies was 2.30 (95% CI: 1.56–3.05) per 100 person years (PYs) (Figure 2a). Due to high heterogeneity, subgroup analyses were conducted and stratified by gender, income, AIDS history, study observational years, HIV risk factors and CD4 cell count (Table 2). Among the 10 studies, patients with high income (pooled RR, 2.64; 95% CI, 1.62–3.65) had the pooled HZ incidence greater than those with low income (pooled RR, 1.33; 95% CI, −0.56–3.22). Among the 4 studies, patients without AIDS history (pooled RR, 0.60; 95% CI, 0.46–0.72) had the pooled HZ incidence greater than those who had AIDS history (pooled RR, 0.40; 95% CI, 0.28–0.54). Among the 4 studies, patients being heterosexual had the pooled HZ incidence (pooled RR, 0.41; 95% CI, 0.31–0.52) greater than IDUs and MSM. Of the 4 studies, patients with a CD4 count < 200 cells/mm^3 (pooled RR, 0.78; 95% CI, 0.55–0.91) were at increased risk of HZ compared with those with a CD4 count > 200 cells/mm^3 (pooled RR, 0.21; 95% CI, 0.06–0.51).


Study name
Statistics for each study
Rate and 95% CI
Rate
Lower limit
Upper limit
p-Value
Gebo et al., 2005 0.628 0.473 0.783 0.000
Blank et al., 2012 0.470 0.336 0.604 0.000
Liu et al., 2013 2.500 2.190 2.810 0.000
Moanna et al., 2013 1.000 0.804 1.196 0.000
Vanhems et al., 2004 2.100 1.816 2.384 0.000
Grabar et al., 2015 0.628 0.473 0.783 0.000
Hung et al., 2005 5.050 4.610 5.490 0.000
Domingo et al., 2001 9.000 8.412 9.588 0.000
Shearer et al., 2014 2.300 2.003 2.597 0.000
Kosuke et al., 2018 0.370 0.251 0.489 0.000
Jansen et al., 2013 1.700 1.444 1.956 0.000
2.303 1.560 3.046 0.000
-8.00 -4.00 0.00 4.00 8.00
low HZ in post-HAART
High HZ in post-HAART

(a)


Study name
Subgroup within study
Statistics for each study
Event rate and 95% CI
Event rate
Lower limit
Upper limit
Z-Value
p-Value
Gebo et al., 2005 Female 0.367 0.296 0.445 -3.300 0.001
Blank et al., 2012 Female 0.377 0.310 0.449 -3.292 0.001
Hung et al., 2005 Female 0.097 0.051 0.176 -6.368 0.000
Grabar et al., 2015 Female 0.280 0.270 0.290 -35.916 0.000
Domingo et al., 2001 Female 0.250 0.117 0.456 -2.331 0.020
Shearer et al., 2014 Female 0.647 0.595 0.696 5.341 0.000
0.324 0.198 0.481 -2.183 0.029
Gebo et al., 2005 male 0.633 0.555 0.704 3.300 0.001
Blank et al., 2012 male 0.623 0.551 0.690 3.292 0.001
Hung et al., 2005 male 0.903 0.824 0.949 6.368 0.000
Grabar et al., 2015 male 0.720 0.710 0.730 35.916 0.000
Domingo et al., 2001 male 0.750 0.544 0.883 2.331 0.020
Shearer et al., 2014 male 0.353 0.304 0.405 -5.341 0.000
0.676 0.519 0.802 2.183 0.029
-1.00 -0.50 0.00 0.50 1.00
low HZ in post-HAART
High HZ in post-HAART

(b)

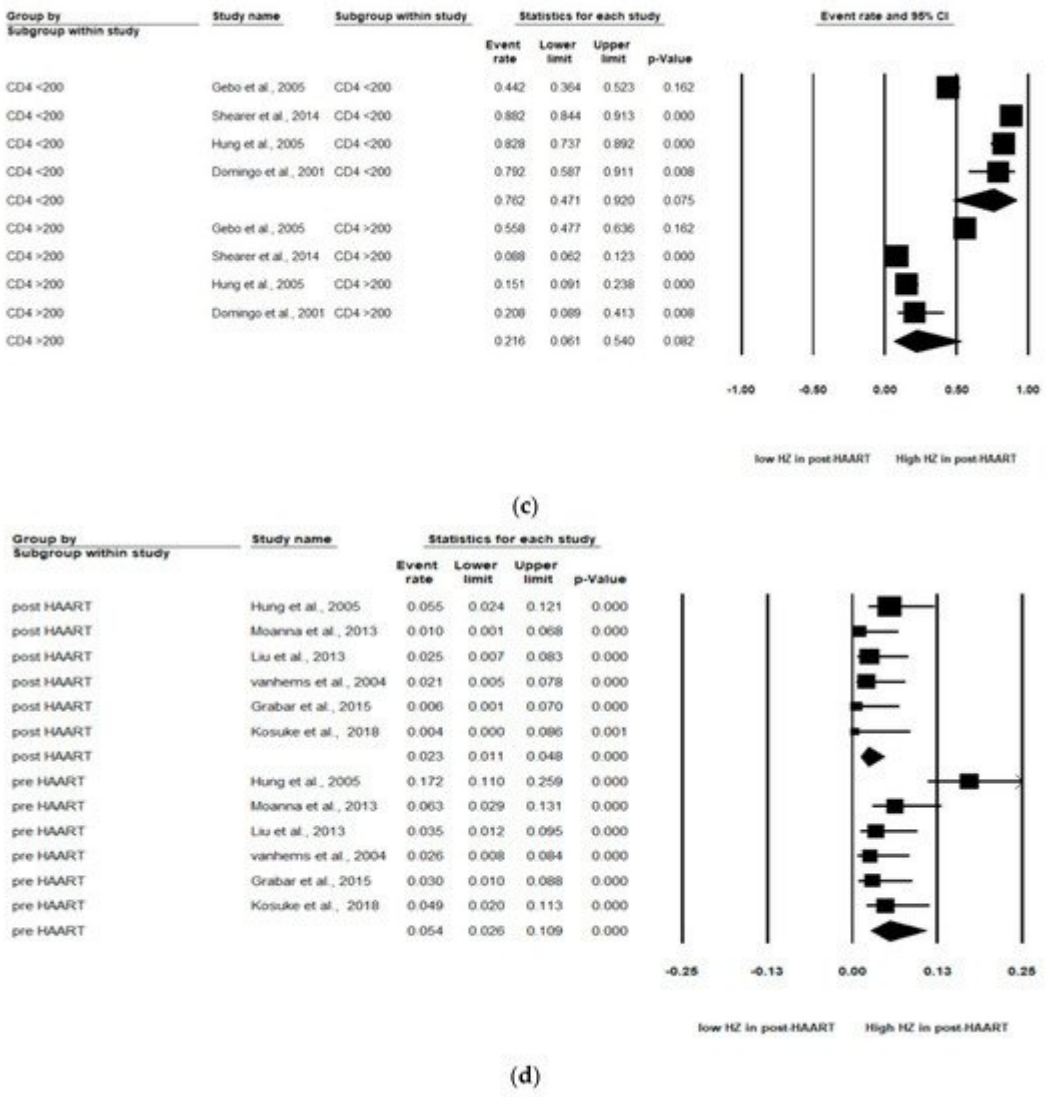


Figure 2. Meta-analyses of (**a**) HZ incidence of HIV-infected patients among ART-era therapy, (**b**) subgroup segmented by sex, (**c**) subgroup segmented by CD4 count level and (**d**) subgroup segmented by ART use. (Note: in the graph, the square represents the effect size of each study. The bigger the square, the more participants in the study. A horizontal line represents the 95% confidence intervals of the study result, with each end of the line representing the boundaries of the confidence interval. The diamond represents the combined effect. Pre-ART = not receiving ART. Post-ART = receiving ART).

Table 2. Subgroup analysis of HZ incidence in different categories.

Subgroup Category	No. of Studies	RR (95% Confidence Interval)	I^2 (%)	*p* Value
Overall HZ	11	2.30 (1.56–3.05)	99.3	0.001
Sex				
Male	6	0.68 (0.52–0.80)	97.5	0.001
Female	6	0.32 (0.20–0.48)	97.5	0.001

Subgroup Category	No. of Studies	RR (95% Confidence Interval)	I^2 (%)	*p* Value
Income				
High income	8	2.64 (1.62–3.65)	99.5	0.001
Low income	2	1.33 (−0.56–3.22)	99.3	0.001
AIDS history				
Yes	4	0.40 (0.28–0.54)	98.3	0.001
No	4	0.60 (0.46–0.72)	98.3	0.001
Observation years				
>7 years	5	2.50 (1.29–3.71)	99.6	0.001
≤7 years	5	2.24 (1.09–3.40)	99.1	0.001
HIV risk factor				
Heterosexual	4	0.41 (0.31–0.52)	76.5	0.005
IDUs	4	0.35 (0.20–0.54)	88.7	0.001
MSM	4	0.32 (0.19–0.49)	90.2	0.001
CD4 count				
CD4 < 200	4	0.78 (0.55–0.91)	95.6	0.001
CD4 > 200	4	0.21 (0.06–0.51)	97.0	0.001
ART use				
Pre-ART	6	6.22 (3.59–8.85)	99.6	0.001
Post-ART	6	2.00 (1.04–2.95)	99.2	0.001

2.2. Meta-Regression Analyses of Overall HZ Moderators

Performed several meta-regression analyses, by which samples were segmented by sex, CD4 count level and ART use.

2.3. Subgroup Analyses by Sex

In six studies, males and females were analyzed. The subgroup analyses revealed that males were at significantly higher HZ risk than females (Pooled RR = 0.32 (female) and 0.68 (male); 95% CI: 0.20–0.48 (female) and 0.52–

References

1. Hope-Simpson, R.E. The nature of herpes zoster: A long-term study and a new hypothesis. Proc. R. Soc. Med. 1965, 58, 9–20.
2. Buchbinder, S.P.; Katz, M.H.; Hessol, N.A.; Liu, J.Y.; O'Malley, P.M.; Underwood, R.; Holmberg, S.D. Herpes zoster and human immunodeficiency virus infection. J. Infect. Dis. 1992, 166, 1153–1156.
3. Glesby, M.J.; Hoover, D.R.; Tan, T.; Shi, Q.; Gao, W.; French, A.L.; Toby, M.; Mary, Y.; Jack, D.; Jenny, R.; et al. Herpes zoster in women with and at risk for HIV: Data from the Women's Interagency HIV Study. J. Acquir. Immune Defic. Syndr. 2004, 37, 1604–1609.

4.80 (male)). Larger effect sizes were observed for the HZ incidence in females than for males in the HIV-infected population (Figure 2b).

2.4. Subgroup Analyses by CD4 Count Level

As stated, two levels of CD4 count (CD4 count < 200 and CD4 count > 200 cells/mm^3) were analyzed in these studies. Of the four studies, patients with a CD4 count < 200 cells/mm^3 (pooled RR, 0.76; 95% CI, 0.47–0.92, p < 0.001) were at increased risk of HZ compared with patients with a CD4 count > 200 cells/mm3 (pooled RR, 0.22; 95% CI, 0.06–0.54, p < 0.001). A significant effect was noted in that CD4 count < 200 cells/mm^3 among HIV-infected population that would increase the risk of HZ (Figure 2c).

2.5. Subgroup Segmented by ART Use

Among the six studies that enrolled patients in the pre-ART (not receiving ART) and post-ART (receiving ART) era, the subgroup analyses showed that those in the pre-ART era (pooled RR, 0.05 PYs; 95% CI, 0.03–0.11, p < 0.001) were at significantly higher HZ risk than those in the post-ART era (pooled RR, 0.02 PYs; 95% CI, 0.01–0.05, p < 0.001). The HIV-infected population who was not receiving ART was at higher HZ risk than the HIV-infected population receiving ART (Figure 2d).

2.6. Meta-Regression Analysis

We found a high level of heterogeneity in the HZ incidence across the 11 studies (I^2 = 99.3%) (Figure 2a). Publication bias was analyzed by generating a funnel plot (Figure 3) and using Egger's test.

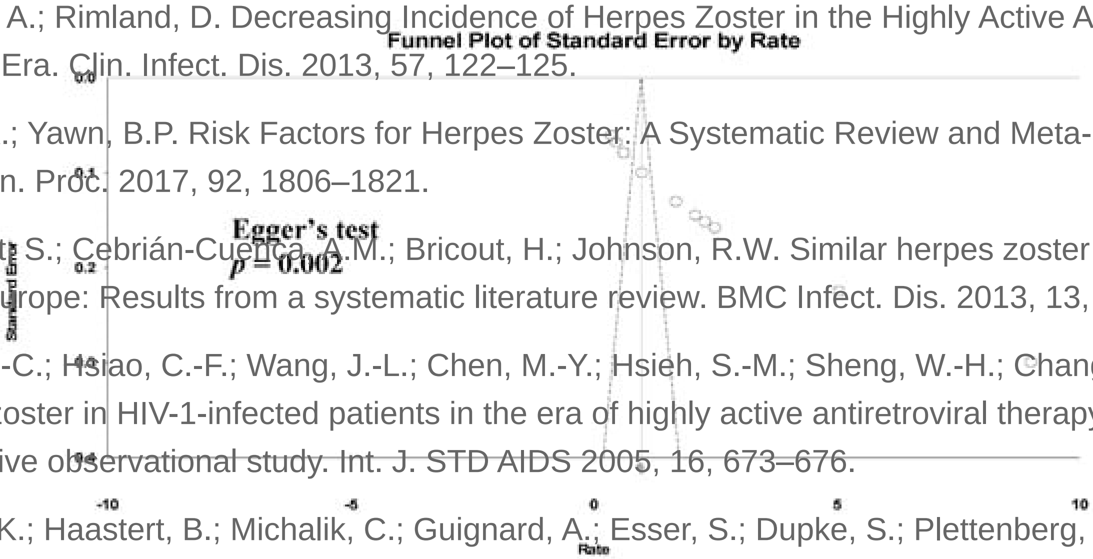


Figure 3. Funnel plot of HZ incidence. (Note: in the graph, the observed studies are shown as open circles and the observed point estimate in log units us shown as a diamond).

Furthermore, significant publication bias existed based on the Egger's regression analysis (p = 0.002). A univariate analysis was conducted to identify significant independent covariates as potential sources of heterogeneity to be

4. Grabar, S.; Tattevin, P.; Selinger-Leneman, H.; De La Blanchardiere, A.; De Truchis, P.; Rabaud, C.; Rey, D.; Daneluzzi, V.; Ferret, S.; Lascaux, A.-S.; et al. Incidence of Herpes Zoster in HIV-Infected Adults in the Combined Antiretroviral Therapy Era: Results From the FHDH-ANRS CO4 Cohort. Clin. Infect. Dis. 2015, 60, 1269–1277.
5. Morgan, D.; Mahe, C.; Malamba, S.; Okongo, M.; Mayanja, B.; Whitworth, J. Herpes zoster and HIV-1 infection in a rural Ugandan cohort. AIDS 2001, 15, 223–229.
6. Veenstra, J.; Krol, A.; Van Praag, R.M.; Frissen, P.M.J.; Schellekens, P.T.; Lange, J.M.; Coutinho, R.A.; Van Der Meer, J.T. Herpes zoster, immunological deterioration and disease progression in HIV-1 infection. AIDS 1995, 9, 1153–1158.
7. Low, A.; Gavriilidis, G.; Larke, N.; B-Lajoie, M.R.; Drouin, O.; Stover, J.; Muhe, L.; Easterbrook, P. Incidence of opportunistic infections and the impact of antiretroviral therapy among HIV-infected adults in low- and middle-income countries: A systematic review and meta-analysis. Clin. Infect. Dis. Off. Publ. Infect Dis. Soc. Am. 2016, 62, 1595–1603.
8. Blank, L.J.; Polydefkis, M.J.; Moore, R.D.; Gebo, K.A. Herpes Zoster among Persons Living With HIV in the Current Antiretroviral Therapy Era. JAIDS J. Acquir. Immune Defic. Syndr. 2012, 61, 203–207.
9. Gebo, A.K.; Kalyani, R.; Moore, R.D.; Polydefkis, M.J. The Incidence of, Risk Factors for, and Sequelae of Herpes Zoster among HIV Patients in the Highly Active Antiretroviral Therapy Era. JAIDS J. Acquir. Immune Defic. Syndr. 2005, 40, 169–174.
10. Moanna, A.; Rimland, D. Decreasing Incidence of Herpes Zoster in the Highly Active Antiretroviral Therapy Era. Clin. Infect. Dis. 2013, 57, 122–125.
11. Kawai, K.; Yawn, B.P. Risk Factors for Herpes Zoster: A Systematic Review and Meta-analysis. Mayo Clin. Proc. 2017, 92, 1806–1821.
12. Pinchinat, S.; Cebrián-Cuenca, A.M.; Bricout, H.; Johnson, R.W. Similar herpes zoster incidence across Europe: Results from a systematic literature review. BMC Infect. Dis. 2013, 13, 170.
13. Hung, C.-C.; Hsiao, C.-F.; Wang, J.-L.; Chen, M.-Y.; Hsieh, S.-M.; Sheng, W.-H.; Chang, S.-C. Herpes zoster in HIV-1-infected patients in the era of highly active antiretroviral therapy: A prospective observational study. Int. J. STD AIDS 2005, 16, 673–676.
14. Jansen, K.; Haastert, B.; Michalik, C.; Guignard, A.; Esser, S.; Dupke, S.; Plettenberg, A.; Skaletz-Rorowski, A.; Brockmeyer, N.H. Incidence and risk factors of herpes zoster among hiv-positive patients in the german competence network for HIV/AIDS (KompNet): A cohort study analysis. BMC Infect. Dis. 2013, 13, 372.
15. Kawai, K.; Hawkins, C.A.; Hertzmark, E.; Francis, J.M.; Sando, D.; Muya, A.N.; Ulenga, N.; Fawzi, W.W. Impact of Antiretroviral Therapy on the Risk of Herpes Zoster among Human

included in the meta-regression model were the risk factors for HZ incidence including male sex (AOR: 4.35 (95% CI: 0.54–2.41), $p = 0.002$), CD4 count < 200 cells/μL (AOR: 11.59 (95% CI: 0.53–4.38), $p = 0.013$) and not receiving ART (AOR: 2.89 (95% CI: −0.44–2.56), $p = 0.16$) (Table 3).

Immunodeficiency Virus-Infected Individuals in Tanzania. Am. J. Trop. Med. Hyg. 2018, 98, 396–400.
16. Liu, C.; Wang, C.; Glesby, M.J.; D'Souza, G.; French, A.; Minkoff, H.; Maurer, T.; Karim, R.; Young, M. Effects of highly active antiretroviral therapy and its adherence on herpes zoster incidence: A longitudinal cohort study. AIDS Res. Ther. 2013, 10, 34.

Table 3. Meta-regression analysis of HZ risk factors affecting heterogeneity.

Variable	Coefficient	Standard Error	OR (95% CI)	*p* Value
Sex				
Female	Reference			
Male	1.47	0.48	0.54–2.41	0.002 *
HIV risk factor				
Heterosexual	Reference			
IDU	−0.77	0.51	−1.76–0.22	0.13
MSM	0.19	0.48	−0.76–1.13	0.70
CD4 count				
CD4 > 200	Reference			
CD4 < 200	2.45	0.98	0.53–4.38	0.013 *
AIDS history				
No	Reference			
Yes	−0.57	0.42	−1.39–0.25	0.17
ART use				
With ART	Reference			
Absence of ART	1.06	0.77	−0.44–2.56	0.16

* $p < 0.05$.