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Posted Date: 6 October 2023

doi: 10.20944/preprints202310.0314.v1

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Varicella-Zoster Virus Reactivation and Increased Vascular Risk in People Living With HIV: Data from a Retrospective Cohort Study

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Abstract: Background: The increased vascular risk associated to Varicella- Zoster Virus (VZV) reactivation is extensively established in the general population. This retrospective cohort study investigates whether this observation holds true for People Living With HIV (PLWH), a group already confronting heightened cardiovascular risk. **Methods:** Among PLWH who initiated antiretroviral therapy (ART) at our center and have been under our care for > 24 months since January 1st, 2005, individuals with a history of Herpes Zoster (HZ) were identified and compared their features with those of PLWH with no history of HZ. The prevalence of ischemic events (Deep Venous Thrombosis, Stroke, Acute Myocardial Infarction) was calculated and compared using Chi Square. Odds Ratios (O.R.) with 95% Confidence Intervals (C.I.) for ischemic events following HZ were evaluated through univariate and multivariate logistic regression. **Results:** Overall, 45/581 PLWH reported HZ. Ischemic events followed HZ significantly more often than the other group (13% vs. 5%, p=0.01). Both positive serology for VZV and HZ correlated with increased ischemic risk (O.R. 4.01, 95% C.I. 1.38-11.6, p=0.01 and O.R. 3.14, 95% C.I. 1.12-7.68, p=0.02, respectively), though pre-existing heart disease demonstrated stronger predictive value in multivariate analysis(O.R. 8.68, 95% C.I. 2.49-29.50, p=0.001). **Conclusions:** VZV potentially exacerbates vascular risk for PLWH, particularly in the presence of other predisposing factors. Further research is needed to confirm our data.

Keywords: Varicella-Zoster Virus; VZV; HIV; stroke; vascular risk

1. Introduction

Herpes zoster (HZ) is defined as a painful, erythematous, maculopapular rash associated tofluid-filled lesions resulting from reactivation of the Varicella-Zoster Virus (VZV), which lies dormant in the spinal and cranial sensory ganglia after primary infection in childhood. The unilateral presentation and restriction to a single dermatome are unique features that distinguish HZ from other dermatological rashes [1]. The calculated cumulative occurrence of this phenomenon is approximately 6 instances for every 1,000 individuals in North America and Europe. Despite the availability of recombinant Zoster vaccine (Shingrix, GlaxoSmithKline, Research Triangle Park, NC), which is recommended at least for adults aged 50 years and older, data from the past decade reveals that this occurrence rate is consistently increasing [2,3]. In addition to older age and being female, family history, a physical trauma, and comorbidities such as diabetes, rheumatoid arthritis, cardiovascular diseases, renal disease, systemic lupus erythematosus, and inflammatory bowel disease have been included among the main risk factors for HZ. Immunosuppression, in particular

 doi:10.20944/preprints202310.0314.v1

due to malignancies or human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) have been associated to a significantly increased the risk of VZV reactivation [4].

Serious and common complications of HZ include acute, chronic and/or recurrent keratitis and iritis, neurotrophic keratopathy, postherpetic neuralgia [3].

A less common aspect of the phenomenon concerns the association between VZV reactivation and increased vascular risk. Recent studies conducted on the general population have indeed brought attention to a connection between HZ and the occurrence of short- and medium-term ischemic cardiac and cerebral events, particularly during the initial three months after reactivation. This association is particularly significant in individuals under the age of 50 and in those who develop ophthalmicus herpes zoster. [5,7]. There is only limited evidence available regarding the occurrence of this phenomenon in People Living With HIV (PLWH), even though VZV reactivation is quite common among this group, particularly when there is a significant depletion of CD4+ cells[8,9]. Furthermore, individuals living with HIV (PLWH) frequently face an increased risk of cardiovascular issues compared to the general population, largely due to various contributing factors[10]. In light of this, a retrospective analysis was conducted using our databases to explore the potential link between HZ and increased vascular risk in a single-center cohort of PLWH who are receiving antiretroviral treatment (ART). The goal was to ascertain whether there exists an association between both documented VZV infection and HZ clinical manifestation and the occurrence of any ischemic events within this specific population. Additionally, the study aimed to determine the extent to which chronic VZV infection contributes to heightened vascular risk in this special group, in comparison to other factors such as patients' medical histories, coexisting health conditions, and lifestyle choices.

2. Materials and Methods

2.1. Inclusion criteria and data collection

This was a retrospective observational cohort study conducted at a single center. It included all individuals with HIV-1 infection who met the following criteria, starting from January 1st, 2005:

i) Age ≥ 18 years;
ii) Initiated ART at the Infectious Diseases Clinic of the Policlinic of Bari;
iii) Were under care at our center for a minimum of 24 months;
iv) Provided written informed consent for the collection and use of clinical data for research purposes at the time of initiating ART;

From these patients, sociodemographic characteristics (gender, age, nationality, mode of HIV transmission), immunovirological and therapeutic information related to HIV infection (duration of HIV infection, AIDS diagnosis at baseline, nadir of CD4 cells count, duration of ART, history of abacavir use, current antiretroviral regimen), current comorbidities, and anamnestic information related to cardiovascular family history, smoking habits, hormonal treatment, and menopause were retrospectively collected from the computer system used at the clinic.

Data regarding VZV infections or reactivations were collected for analysis. The presence of positive G Immunoglobulins (IgG) serology for VZV was utilized as an indicator of prior infection. Detailed information regarding instances of VZV reactivation was gathered, and in cases of HZ, details such as the location of bodily reactivation, frequency of recurring episodes, and vaccination history were documented.

Subsequently, the medical records of the patients were scrutinized to identify any occurrences of ischemic events. Ischemic events included cerebral ischemia or stroke, acute myocardial infarction (AMI), a combination of previous events, and deep vein thrombosis (DVT). In PLWH having a history of VZV reactivation, only ischemic events that were documented after the date of the initial manifestation of HZ were taken into account. In such cases, the specific type of event, its outcome, and the time interval from the onset of HZ manifestation were recalled and considered for analysis.

 doi:10.20944/preprints202310.0314.v1

2.2. Statistical Analysis

The prevalence, expressed in relation to the patient population, was evaluated for:

i) Patients with positive VZV serology.
ii) Patients with a clinical history of at least one episode of VZV reactivation.

The clinical characteristics of this group are described in terms of absolute numbers and percentages (%) for categorical variables and median and interquartile range (IQR) for continuous variables. These variables were compared with the corresponding variables of the group of patients with a negative history of VZV reactivation. For categorical variables, the Chi-square test or Fischer exact test was used. The distribution of continuous variables was assessed using normality tests as Shapiro-Wilk's. The non-parametric Mann-Whitney U-test was utilized to test the null hypotesis of no difference between continuous non parametric variables between the two study groups.

The prevalence, expressed as a ratio, of ischemic events (cerebral ischemia or stroke, AMI, combination of the two, and DVT) was evaluated and compared between the VZV group and the control group via Chi-square test.

The study aimed to determine the increased likelihood of experiencing an ischemic event when individuals exhibit positive serology for VZV. This assessment involved quantifying the association using Odds Ratios (O.R.), accompanied by 95% Confidence Intervals (C.I.) to indicate the precision of the estimates. The same analysis was applied while considering the medical history of clinical HZ manifestations. Furthermore, the analysis was conducted separately to evaluate the risk of the following specific outcomes: i) the occurrence of any type of ischemic event; ii) the incidence of strokes, AMI or DVT in relation to other forms of ischemic events.

Finally, a multivariate model was constructed to assess which factors, in addition to a positive history of VZV reactivation, could predispose the patient to a cardiovascular or cerebrovascular episode among the following: male gender; age over 65 years; history of endovascular drug use; nadir CD4 count below 200; history of antiretroviral and HIV therapy exceeding 10 years; positive pharmacological history for abacavir; hypertension; type II diabetes; dyslipidemia; previous heart disease. The multivariable model incorporated all variables that demonstrated a p-value of less than 0.2 following assessment in the univariable analysis.

The analyses were performed using Jamovi version 2.3.

The level of statistical significance was set at $p < 0.05$ for all analyses.

3. Results

A total of 581 patients were included, mainly males (81%), aged median 48 (38-56) years.

Positive serology for VZV infection was reported by 371 patients (74%).

Of them, 45 (7% of total) also referred at least one physical manifestation of VZV reactivation in their clinical history.The reactivation of VZV was observed most frequently in the thoracodorsal region (17 patients, 39%), followed by the lumbosacral (7 patients, 15%), facial (5 patients, 11%), upper (4 patients, 9%) and lower limbs (3 patients, 7%) regions. In 2 cases (4%), a multidermatomal presentation was observed.

11 patients (2% of total) had received vaccination against VZV, 2 of whom due to history of recurrent HZ manifestation.

In comparison to the other group, PLWH who experienced VZV reactivation were notably older, with a lengthier history of HIV infection and ARV treatment. Additionally, among this group, a greater prevalence of individuals with a baseline AIDS diagnosis and various comorbidities (particularly hypertension and dyslipidemia) was observed (Table 1).

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Table 1. Characteristics of study population stratified in accordance to history of physical manifestation of Varicella Zoster Virus (VZV) reactivation.

Variables	Overall (N=581)	PLWH without VZV reactivation (N=546)	PLWH with VZV reactivation (N=45)	*p-value*
Male sex, n (%)	471 (81)	438 (82)	33 (73)	.16
Age ,years, median (IQR)	48 (38-56)	47 (38-55)	56 (48-61)	***<0.001***
Non Italian nationality, n (%)	63 (11)	57 811)	6 (13)	.576
Transmission route, n (%)				
Heterosexual contacts	214 (37)	200 (37)	14 (31)	
MSM	196 (34)	179 (339	17 (38)	***.003***
IDU	40 /7)	31 86)	9 (20)	
Other	126 (22)	121 (23)	5 (11)	
AIDS diagnosis, n (%)	230 (40)	203 (28)	27 (60)	***.003***
Nadir CD4, cells/mL, median (IQR)	244 (109-286)	259 (121-401)	161 (87-262)	***<0.001***
Years of HIV diagnosis, median (IQR)	9 (6-14)	9 (5-13)	15 (9-27)	***<0.001***
Years of ART, median (IQR)	8 (5-11)	8 (5-11)	11 (8-20)	***<.001***
History of Abacavir, n (%)	152 (26)	135 (25)	17 (38)	0.06
Current ARV regimen, n (%)				
2 NRTIs + NRTI	100 (17)	93 (17)	7 (16)	
2 NRTIs + PI	70 (12)	59 (11)	11 (24)	
2 NRTIs + INSTI	242 (42)	231 (43)	11 (24)	***.007***
NNRTI + INSTI	58 (10)	55 (10)	3 (7)	
PI + INSTI	8 (1)	4 (1)	2 (4)	
1 NRTI + INSTI	100 (17)	90 (17)	10 (22)	
Other	5 (1)	4 (1)	1 (2)	
Positive serology for VZV, n (%)	372 (74)	327 (61)	45 (100)	***< 0.001***
Smokers, n (%)	218 (37)	196 (42)	22 (48)	0.33
Hormonal treatment, n (%)	4 (1)	4 (1)	0 (0)	0.56
Menopause, n (%)	35 (6)	30 (6)	5 (12)	0.12
Familiarity for Cardiovascular disease, n (%)	76 (13)	67 (13)	9 (20)	0.12
Presence of co morbidities, n (%)	294 (49)	250 (46)	34 (75)	***<.001***
Hypertension	74 (26)	62 (25)	12 (35)	0.19
Dyslipidemia	160 (56)	140 (56)	20 (59)	0.75
Diabetes	43 (15)	38 (15)	5 (15)	0.94
Chronic Heart Disease	15 (5)	14 (6)	1 (3)	0.51
Other	93 (33)	81 (32)	12 (35)	0.74
Ischemic event, n (%)	31 (5)	25 (5)	6 (13)	
AMI	9 (27)	8 (30)	1 (17)	***0.01***
Stroke	7 (21)	5 (18)	2 (33)	0.08
AMI + Stroke	3 (9)	1 (4)	1 (33)	
Deep Venous Thrombosis	14 (42)	13 (48)	1 (17)	

IQR: Interquartile Range; IDU: Intravenous Drug Users; MSM: Males Who Have Sex with Males; AIDS: Acquired Immunodeficiency Syndrome; ART: Antiretroviral Treatment; ARV: Antitretroviral; NRTIs: Nucleos(t)ide Reverse Transcriptase Inhibitors; NNRTIs: Non Nucleos(t)ide Reverse Transcriptase Inhibitors; PIs: Protease Inhibitors; INSTIs: Integrase Strand Trasfer Inhibitors; VZV: Varicella Zoster Virus; AMI: Acute Miocardial Infarction.

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The overall incidence rate of ischemic events was 5% (31 subjects). Notably, the occurrence of an ischemic event was significantly more frequent among patients who also reported VZV reactivation (13% vs. 5% in the group without VZV reactivation, p=0.01).

While DVT was the most common type of ischemic event in the general population, stroke was more prevalent among PLWH who experienced HZ, although this correlation was not statistically significant (33% compared to 18% in the group without VZV reactivation, p=0.08).

Characteristics of 6 patients with history of VZV reactivation who reported at least one ischemic event are described in Table 2.

Table 2. Characteristics of 6 patients with history of Varicella Zoster Virus (VZV) reactivation who reported any Ischemic Event (Acute Miocardial Infarction, Stroke, Deep Venous Thrombosis or combination of the previous).

Patient	Sex	HBV/HCV coinfection	Smoker	AIDS diagnosis	Age at first VZV reactivation (years)	Clinical manifestation of VZV reactivation	On ART at Ischemic Stroke	Type of Ischemic Event
1	Male	No	No	Yes	67	Recurrent, multiple sites	No	Ischemic Heart Attack and Ischemic Brain Stroke
2	Male	No	No	Yes	-	Recurrent, multiple sites (vaccined with Shinrix)	No	Ischemic Heart Attack and Ischemic Brain Stroke
3	Male	No	Yes	Yes	56	Single manifestation, Ramsay Hunt Syndrome	Yes (TAF/FTC/ DRV/cobi)	Ischemic Heart Attack
4	Male	No	-	Yes	34	Single manifestation, right arm	No	Peripheral Venous Thrombosis
5	Male	No	Yes	Yes	50	Recurrent, multiple sites	No	Ischemic Brain Stroke
6	Male	Yes (both)	Yes	No	55	Recurrent, multiple sites	No	Ischemic Brain Stroke

HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; AIDS: Acquired Immunodeficiency Syndrome; VZV: Varicella Zoster Virus; ART: Antiretroviral treatment.

Two patients reported the ischemic event 7 and 13 years after the reactivation of VZV, respectively. In two other cases, ischemia occurred following herpes zoster by 45 days and 5 months, respectively. Lastly, for two subjects, although it was known that the ischemic event followed VZV reactivation, precise information about the event date was unavailable, thus making it impossible to calculate the temporal interval.

All patients who reported an ischemic event survived. As of the time of writing, 10 patients have passed away, but their deaths were attributed to other causes.

In the univariate logistic regression analysis, increased risk of developing any ischemic event could be observed in patients with positive serology for VZV infection (O.R. 4.01, 95% C.I. 1.38-11.6, p=0.01).

The same was noticed in patients with history of HZ manifestations (O.R. 3.14, 95% C.I. 1.12-7.68, p=0.02). However, any significant correlation could be outlined between history of VZV reactivation and increased risk of stroke (O.R. 5.71, 95% C.I. 0.82-38.3, p=0.06), AMI (O.R. 2.38, 95% C.I. 0.40-14.4, p=0.34) or DVT (O.R. 0.54, 95% C.I. 0.08-3.45, p=0.51) taken separately, probably due to the paucity of our population sample.

In the multivariate analysis, which was adjusted for factors including age, sex, duration of HIV infection, duration of ART and major comorbidities, the presence of previous heart disease emerged as the sole factor significantly elevating vascular risk in PLWH (O.R.9.95, 95% C.I. 2.15-45.46, p=0.003, Table 3).

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Table 3. Uni- and multivariate logistic regression estimating factor associated with higher relative risk (Odds ratio, O.R.) with 95% Confidence Interval (C.I.) of Acute Miocardial Infarction, Stroke or Deep Venous Thrombosis.

Variables	O.R. (95% C.I., p-value)	aO.R.* (95% C.I., p-value)
Male Sex	0.78 (0.34-2.01, p=0.58)	-
Age>65 years	7.35 (2.98-17.01, p<.001)	2.76 (0.83-8.36, p=0.08)
IDU	0.93 (0.15-3.25, p=0.92)	-
Positive serology for VZV	4.01 (1.54-13.71, p=0.01)	1.88 (0.56-7.54, p=0.33)
History of HZ	3.14 (1.12-7.68, p=0.018)	1.14 (0.14-6.16, p=0.89)
Baseline CD4+ <200 cells/mm3	1.37 (0.64-2.84, p=0.40)	-
>10 years of HIV infection	1.37 (0.58-3.39, p=0.47)	-
>10 years of ART	1.73 (0.35-31.33, p=0.60)	-
History of Abacavir	1.37 (0.60-2.91, p=0.43)	
Hypertension	3.23 (1.41-7.40, p=0.005)	2.84 (0.95-8.48, p=0.06)
Type II Diabetes	2.27 (0.84-5.59, p=0.09)	1.88 (0.50-6.10, p=0.32)
Dislypidemia	1.06 (0.47-2.46, p=0.88)	-
Previous Heart Disease	11.51 (3.69-35.61, p<.001)	9.95 (2.15-45.46, *p=0.003*)

O.R.: Odds Ratio; C.I.: Confidence Interval; a O.R.: adjusted Odds Ratio; IDU: Intravenous Drug User; VZV: Varicella Zoster Virus; ART: Antiretroviral Treatment. *Multivariable model includes all variables selected by backwards selection that were retained with a p-value less than 0.2.

4. Discussion

In people living with HIV, Herpes Zoster can be categorized as an opportunistic infection. In this population, its occurrence is not only more prevalent but also more likely to be accompanied by complications compared to the general population, even among individuals who are receiving effective ART [21,22]. Although limited data is available data on the current seroprevalence of VZV in PLWH, some studies indicate a prevalence of approximately 95% of VZV-positive serological patients [23].

In our study, we observed that the prevalence of positive serology for VZV exceeded 70%. Among this group of patients, approximately 12% presented with clinical manifestations of VZV reactivation. Our findings were consistent with those from previous research, showing that subjects who experienced VZV reactivation were more likely to be older, have a higher number of comorbidities, and have a longer and more complex clinical history of HIV infection. The percentage of patients who had received vaccination against VZV was 2%, but it's likely that this data is underestimated because of the retrospective nature of our study.

In addition to causing various complications, such as post-herpetic neuralgia, myelitis, and meningoencephalitis, which can significantly reduce the quality of life, especially when recurrent outbreaks occur [3,24], several studies have provided evidence that VZV infection can elevate the risk, particularly of cardiovascular and cerebral ischemic events, but also in various other sites, such as deep venous thrombosis.[25].

This phenomenon can occur even years after an episode of HZ and is associated with VZV vasculopathy, which is the chronic vascular alteration induced by the virus following VZV infection. [26–28]. Finally, there is limited available data regarding the role of vaccinations in preventing complications of HZ, particularly in relation to vascular and ischemic risks. As the prevalence of stroke is significantly higher in people who have not received vaccination compared to vaccinated individuals, some studies suggest that the protective effect of vaccinations may result from the reduced incidence of HZ infection in vaccinated individuals.[29–31].

We were able to identify an elevated risk of ischemic events among both PLWH with a positive serology for VZV and those who reported clinical manifestations of VZV reactivation. Upon examining the individual characteristics of the six patients who reported ischemic events following HZ, we noted that they were all male. Almost all of them had a history of AIDS diagnosis, and none

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of them were receiving ART at the time of the ischemic event. Notably, cerebrovascular ischemia was the most common presentation among PLWH with HZ.

Despite this remarkable result, when we examined the overall impact of VZV infection and its reactivation on increasing vascular risk among PLWH, we noticed that these factors became less significant. The only truly significant factor that remained was the history of previous heart disease. This finding doesn't come as a surprise, as it's well-documented in the literature that cardiovascular risk is elevated in individuals with HIV infection due to various illness-, treatment- and lifestyle-related factors [20]. However, in light of the results of our preliminary analysis, the history of VZV infection and the clinical history of reactivation become important factors to consider when assessing the cardiovascular risk in HIV-positive patients.

Our study has several limitations.

Firstly, the small size of the study population, which, on one hand, emphasizes the significance of our results, but on the other hand, it limited our ability to assess important correlations, such as the relationship between specific types of ischemic events and VZV. Furthermore, the retrospective design of our research impeded us from conducting a comprehensive analysis of the clinical and laboratory data obtained from pre-existing medical records, which encompassed information about the patients who were vaccinated against varicella-zoster virus (VZV). Additionally, the absence of precise time dataposed a challenge in discerning whether the associated vascular risk was short-term or long-term with regard to VZV reactivation.

Furthermore, because our study was conducted at a single center, the results should be interpreted with caution and applied primarily to the specific local context in which the study was conducted.

Nonetheless, the results of our study indicate that HZ could serve as a vascular risk marker, particularly in PLWH. This suggests the possibility that clinicians may want to reconsider the vascular risk profile of these patients. Further research is required to determine how a history of HZ can be integrated into cardiovascular risk assessments and to assess the long-term effectiveness of vaccines as a preventive measure in this context.

5. Conclusions

Similarly to the general population, VZV infection, and in particular its reactivation, represents a factor that increases vascular risk in individuals with HIV infection, especially in presence of other risk factors, such as an underlying compromised heart condition. Prospective studies involving a larger sample of patients are needed to confirm our observations and assess whether interventions, including modifications to ART, comedications and lifestyle changes, and potentially VZV vaccination, can mitigate the risk of ischemic events in this specific population.

Author Contributions: Conceptualization, D.F. and M.P.; methodology, D.F. and M.P.; software, M.P.; validation, D.F., M.P. and C.F.F..; formal analysis, M.P.; investigation, C.F.F., N.D.G., E.M., C.R.S., G.M.C., G.M., F.V.S., G.G., L.F. and G.R; data curation, C.F.F., N.D.G., E.M., C.R.S., G.M.C., G.M., F.V.S., G.G., L.F. and G.R; writing—original draft preparation, D.F. and M.P..; writing—review and editing, D.F. and M.P.; visualization, F.D.G.; supervision, F.D.G. and A.S.; project administration, F.D.G. and A.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Approved by Ethics Committee Azienda Ospedaliero Universitaria Policlinico of Bari, Study n. 7147 on January 12, 2022.

Informed Consent: Informed consent for the use of anonymized data for research purposes was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available to ensure the protection of the privacy.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Cohen J. I. Clinical practice: Herpes zoster. *The New England journal of medicine*. 2013. *369*(3), 255–263.https://doi.org/10.1056/NEJMcp1302674;
2. van Oorschot, D., Vroling, H. et al. A systematic literature review of herpes zoster incidence worldwide. *Human vaccines &immunotherapeutics*. 2021 *17*(6), 1714–1732. https://doi.org/10.1080/21645515.2020.1847582;
3. Cohen, E. J., & Jeng, B. H. Herpes Zoster: A Brief Definitive Review. *Cornea*. 2021 *40*(8), 943–949. https://doi.org/10.1097/ICO.0000000000002754].
4. Marra, F., Parhar, K et al. Risk Factors for Herpes Zoster Infection: A Meta-Analysis. *Open forum infectious diseases*, 2020. *7*(1), ofaa005. https://doi.org/10.1093/ofid/ofaa005
5. Yawn B.P., Wollan P.C., et al. Risk of stroke and myocardial infarction after Herpes Zoster in older adults in a US community population. *Mayo Clin Proc.* 2016; 91:33–44. [PubMed: 26704438]
6. Patterson B.J., Rausch D.A., et al. Analysis of vascular event risk after herpes zoster from 2007 to 2014 US insurance claims data. *Mayo Clin Proc*. 2019; 94:763–775. [PubMed: 30955916]
7. Nagel M.A., Bubak A.N. Varicella Zoster Virus vasculopathy. *J Infect Dis.* 2018; 218 (suppl 2):S107–S112. [PubMed: 30247600]
8. Marais, G., Naidoo, M., et al. Varicella-zoster virus reactivation is frequently detected in HIV-infected individuals presenting with stroke. *Journal of medical virology*, 2022.*94*(6), 2675–2683. https://doi.org/10.1002/jmv.27651
9. Ba'Omar, M., Chhetri, S., et al. Varicella Zoster Virus Vasculopathy; An HIV adult presenting with multiple strokes. *IDCases*. 2022. *30*, e01641. https://doi.org/10.1016/j.idcr.2022.e0164
10. Henning, R. J., & Greene, J. N. The epidemiology, mechanisms, diagnosis and treatment of cardiovascular disease in adult patients with HIV. *American journal of cardiovascular disease*. 2023. *13*(2), 101–121
11. Zou J., Krentz H.B., et al. Seropositivity, Risks, and Morbidity From Varicella-Zoster Virus Infections in an Adult PWH Cohort From 2000-2020. *Open Forum Infect Dis.* 2022 Aug 9;9(8):ofac395. doi: 10.1093/ofid/ofac395. PMID: 36004318; PMCID: PMC9394766;
12. Lewis D.J., Schlichte M.J., et al. Atypical disseminated herpes zoster: management guidelines in immunocompromised patients. *Cutis.* 2017 Nov;100(5):321;324;330. PMID: 29232422.
13. Ku, H.C., Tsai, Y. T., et al. Incidence of Herpes Zoster in HIV-Infected Patients Undergoing Antiretroviral Therapy: A Systematic Review and Meta-analysis. *J. Clin. Med*. 2021, 10, 2300. https://doi.org/10.3390/jcm10112300
14. Patil A., Goldust M., et al. Herpes zoster: A Review of Clinical Manifestations and Management. *Viruses.* 2022 Jan 19;14(2):192. doi: 10.3390/v14020192. PMID: 35215786; PMCID: PMC8876683
15. Salvotti F., Trapletti S., et al. Atypical varicella-zoster virus reactivation: a case report. EJCRIM 2023;10 doi:10.12890/2023_003945
16. Curhan S.G., Kawai K., et al. Herpes Zoster and Long-Term Risk of Cardiovascular Disease. *J Am Heart Assoc*. 2022 Dec 6;11(23):e027451. doi: 10.1161/JAHA.122.027451. Epub 2022 Nov 16. PMID: 36382961; PMCID: PMC9851464.;
17. Parameswaran G.I., Wattengel B.A., et al. Increased Stroke Risk Following Herpes Zoster Infection and Protection With Zoster Vaccine. *Clin Infect Dis*. 2023 Feb 8;76(3):e1335-e1340. doi: 10.1093/cid/ciac549. PMID: 35796546.;
18. Erskine N., Tran H., et al. A systematic review and meta-analysis on herpes zoster and the risk of cardiac and cerebrovascular events. *PLoS ONE.* 2017. 12(7): e0181565. https://doi.org/10.1371/ journal.pone.0181565
19. Yawn B.P., Lindsay A.C., et al. Risk of, and risk factors for, vasculopathy associated with acute herpes zoster. *J Stroke Cerebrovasc Dis*. 2023 Feb;32(2):106891. doi: 10.1016/j.jstrokecerebrovasdis.2022.106891. Epub 2022 Dec 5. PMID: 36473399.;
20. Klaric J.S., Beltran T.A., et al. An association between herpes zoster vaccination and stroke reduction among elderly individuals. *Mil Med* 2019;184:126-132.;
21. Yang Q., Chang A., et al. Herpes zoster vaccine live and risk of stroke among Medicare beneficiaries: a population-based cohort study. *Stroke* 2021;52:1712-172