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# Comparative gender analysis of the seroprevalence of varicella zoster virus among HIV-infected individuals receiving care at Offa, north-central Nigeria

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## Abstract:

**Background:** Varicella zoster virus (VZV) infections are common and contribute substantially to morbidity and mortality among HIV-infected patients. This study was conducted to determine the level of exposure, compare the gender distribution pattern and correlate with CD4 count, history of chicken pox and demographics among HIV patients.

**Methodology:** Blood samples were collected from 273 randomly selected HIV-positive patients (93 males and 180 females) receiving care and management at the General Hospital Offa, Kwara State, Nigeria, between September 2019 and March 2020, after obtaining informed consent. Sera were separated from the blood samples and tested for the presence of VZV-specific IgG antibodies using Enzyme Linked Immunosorbent Assay (ELISA).

**Results:** The seroprevalence rate of VZV in the selected HIV patients was 76.9% (210/273), which was similar in both male (83.9%, 78/93) and female (73.3%, 132/180) patients ( $\chi^2=3.265$ ,  $p=0.071$ ). The seroprevalence rates of VZV in both male and female patients were significantly associated with marital status, occupational status, and CD4<sup>+</sup> cell count ( $p<0.05$ ), however, age group was not significantly associated with VZV seroprevalence in both male ( $\chi^2=8.014$ ,  $p=0.155$ ) and female ( $\chi^2=4.689$ ,  $p=0.455$ ) patients. The seroprevalence of VZV in males (32%) who reported history of chicken pox was about twice that of females (17.4%) (OR=2.235, 95% CI=1.162-4.302,  $p=0.023$ ).

**Conclusion:** The level of exposure of HIV-infected individuals to VZV in Offa, Nigeria is high and is similarly distributed in both male and female genders. However, more males with VZV exposure reported history of chicken pox (acute infection) than their female counterparts.

**Keywords:** Seroprevalence; VZV; HIV; gender; Nigeria

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## Analyse comparée selon le sexe de la séroprévalence du virus varicelle-zona chez les personnes infectées par le VIH recevant des soins à Offa, dans le centre-nord du Nigeria

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## Résumé:

**Contexte:** Les infections par le virus varicelle-zona (VZV) sont courantes et contribuent considérablement à la morbidité et à la mortalité chez les patients infectés par le VIH. Cette étude a été menée pour déterminer le

niveau d'exposition, comparer le schéma de répartition entre les sexes et établir une corrélation avec le nombre de CD4, les antécédents de varicelle et les données démographiques chez les patients atteints VIH.

**Méthodologie:** Des échantillons de sang ont été prélevés sur 273 patients séropositifs sélectionnés au hasard (93 hommes et 180 femmes) recevant des soins et une prise en charge à l'hôpital général d'Offa, dans l'État de Kwara, au Nigéria, entre septembre 2019 et mars 2020, après avoir obtenu leur consentement éclairé. Les sérums ont été séparés des échantillons de sang et testés pour la présence d'anticorps IgG spécifiques au VZV à l'aide d'un dosage immuno-enzymatique (ELISA).

**Résultats:** Le taux de séroprévalence du VZV chez les patients VIH sélectionnés était de 76,9% (210/273), ce qui était similaire chez les patients masculins (83,9%, 78/93) et féminins (73,3%, 132/180) ( $\chi^2=3,265$ ,  $p=0,071$ ). Les taux de séroprévalence du VZV chez les hommes et les femmes étaient significativement associés à l'état matrimonial, au statut professionnel et au nombre de cellules CD4<sup>+</sup> ( $p<0,05$ ), cependant, le groupe d'âge n'était pas significativement associé à la séroprévalence du VZV chez les hommes ( $\chi^2=8,014$ ,  $p=0,155$ ) et de sexe féminin ( $\chi^2=4,689$ ,  $p=0,455$ ). La séroprévalence du VZV chez les hommes (32,0%) ayant déclaré des antécédents de varicelle était environ le double de celle des femmes (17,4%) (OR=2,235, IC à 95%=1,162-4,302,  $p=0,023$ ).

**Conclusion:** Le niveau d'exposition des personnes infectées par le VIH au VZV à Offa, au Nigeria, est élevé et est réparti de manière similaire chez les hommes et les femmes. Cependant, plus d'hommes exposés au VZV ont signalé des antécédents de varicelle (infection aiguë) que leurs homologues féminins.

**Mots clés:** Séroprévalence; VZV; VIH; genre; Nigeria

## Introduction:

Herpes group of viruses constitute the major viral opportunistic infections (OIs) among HIV-1 infected individuals. Opportunistic infections occur as a result of immune deficiency and have been recognised as the main reason for hospitalization and substantial morbidity in HIV-infected patients (1). Currently eight human herpes viruses belonging to herpesviridae family are known; herpes simplex virus 1, herpes simplex virus 2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus 6, human herpesvirus 7, and human herpesvirus 8 (HHV-8). These viruses share a characteristic ability to remain latent within the body over a long period of time.

Varicella zoster virus, a member of the  $\alpha$ -herpesvirinae subfamily is exclusively human pathogen. It is highly infectious virus and is endemic worldwide. Primary infection with VZV leads to acute varicella or "chicken pox". Infection is usually through direct contact with skin lesion or through airborne spread from respiratory droplets (2). Initial infection is followed by establishment of lifelong latency in cranial nerves and dorsal root ganglia from where reactivation can occur years to decades later as herpes zoster or "shingles" which is characterized by painful, localized, vesicular rash in one or adjacent dermatomes.

In HIV-infected individuals, reactivation of VZV causes prolonged and severe manifestation of herpes zoster (3). Although zoster is not viewed as AIDS-defining illness, it can indicate immunodeficiency and tends to occur more often in patients with HIV (4). In fact, herpes zoster occurs at all stages of the HIV infection (5), with reactivation occurring as a result of HIV-induced immunodepression. Other risk factors of herpes zoster include cancers and chronic medical conditions (6). Zoster is said to afflict about 20% of the gene-

ral population during their lifetime, especially the elderly, and about 8% to 11% of patients with AIDS (7). While recurrent episodes of zoster in non-immunocompromised patients are rare, occurring in about 1%-4% of cases (8), recurrence increases in AIDS patients to about 10%-27% of zoster cases (9).

Reactivation in the trigeminal ganglion also results in herpes zoster ophthalmicus (HZO) which may likely be the initial manifestation of HIV infection. The rate of reactivation is higher in immunocompromised patients and older people (10). Incidence of HZO is believed to be six times greater in HIV/AIDS patients than in healthy people and occurs in 5%-15% of HIV-positive patients (11). Studies have increasingly shown gender bias in the incidence of zoster with females more likely to acquire zoster than males. This has been highlighted by review of several epidemiological studies (12). Hitherto attributed to the greater longevity of females than males, research by Fleming et al., (13) however showed greater female incidence in almost all age groups, indicating involvement of factors other than age which are yet to be fully understood.

Although reports have it that over 60% of patients with HZO in Nigeria are HIV-positive (14,15), there is paucity of data showing the true burden of the infection among HIV infected persons in the country. In this study, we determined the seroprevalence of VZV in a cross section of HIV-1 infected patients who are receiving treatment at the General Hospital Offa, Kwara State, north-central Nigeria. We also compared male cum female distribution patterns as well as other associated risk factors.

## Materials and method:

### Study setting, design and population:

This comparative cross-sectional hospital-based study was conducted among HIV-

infected individuals accessing antiretroviral treatment at the General hospital Offa, Kwara State, northcentral Nigeria.

#### **Sample size and method of sampling:**

A total of 273 HIV-infected patients were selected by simple random sampling technique, comprising 93 (34.1%) males and 180 (65.9%) females. The sample size of 273 was determined using the Fischer's formula (16).

#### **Data and sample collection:**

Relevant socio-demographic and clinical information including age, marital status, occupation, CD4<sup>+</sup> cell count, history of chicken pox and history of vaccination against VZV were recorded using well-structured questionnaire forms. These information were obtained both directly from the patients and their clinical record books.

About 5ml of venous blood was obtained from each patient into a sterile bottle and allowed to clot at room temperature. The serum was aspirated into a new Eppendorf tube, appropriately labelled and stored at -20°C until tested.

#### **Serological assay:**

Serum samples were tested for the presence of IgG antibodies using commercially available Enzyme Linked Immunosorbent Assay (ELISA) kit (Diagnostic Automation, Inc., Calabasas, CA, USA) for the detection of VZV specific IgG antibodies. The tests were performed and interpreted according to the manufacturer's instructions.

#### **Ethical clearance:**

Ethical clearance for the study was obtained from the Ethical Review Committee (ERC) of Kwara State Ministry of Health, Nigeria (MOH/KS/EU/777/174). The ethical standards of the committee and the Helsinki Declaration of 1975 (revised 2000) were strictly adhered to in carrying out the study. Prior to the study, informed consent was obtained from each patient participant and from the parents where the participants were below 18 years of age.

#### **Statistical analysis:**

Data were analysed using Statistical Package for Social Sciences version 22 (SPSS Inc., Chicago, USA). Pearson's Chi-square or Fisher's exact test was used where appropriate to test association at 95% confidence interval. P value <0.05 was considered statistical significance.

## **Results:**

#### **Comparative seroprevalence of VZV in male & female patients with respect to other socio-demographic characteristics:**

Over the period of September 2019 to

March 2020, a total of 273 HIV-infected patients were randomly selected for the study with 93 males (mean age 47.4 years) and 180 females (mean age 43.3 years). Of these, 210 (76.9%) were seropositive for VZV infection, 78 (83.9%) of 93 and 132 (73.3%) of 180 male and female patients tested positive to anti-VZV IgG antibodies ( $\chi^2=3.265$ ,  $p=0.071$ ).

The seroprevalence of VZV was not significantly associated with the age group in both male ( $\chi^2=8.014$ ,  $p=0.155$ ) and female ( $\chi^2=4.689$ ,  $p=0.455$ ) patients. However, the highest seroprevalence (100%) was recorded among patients in age group  $\leq 20$  years in both the male and female patients, while the lowest seroprevalence (70.0%) among the males was recorded among patients in both age groups 21-30 and >60 years. Among the females, the lowest seroprevalence (67.7%) was recorded among patients in age group 31-40 years (Table 1).

The VZV seroprevalence was strongly associated with marital status in both male ( $\chi^2=12.46$ ,  $p=0.006$ ) and female ( $\chi^2=12.139$ ,  $p=0.007$ ) patients. While the highest seroprevalence (89.8%) was seen among married male participants, the highest seroprevalence (100%) was recorded among widows and single (unmarried) female patients. The lowest seroprevalence (40%) in the males was recorded among the widowers while in the females, the lowest seroprevalence (50%) was recorded among the divorced women (Table 1).

Analysis also showed strong association of VZV seroprevalence with occupation in both male ( $\chi^2=21.515$ ,  $p=0.0007$ ) and female ( $\chi^2=11.173$ ,  $p=0.025$ ) patients. While artisans, civil servants and participants whose occupation were not determined all had 100% VZV seroprevalence, the lowest seroprevalence was recorded among the students in the male patients. In the female patients, the highest seroprevalence (86.4%) was recorded among patients with undetermined occupation while the lowest seroprevalence (57.1%) was recorded among the artisans (Table 1).

#### **Comparative seroprevalence of VZV in male & female patients with respect to CD4<sup>+</sup> count:**

The seroprevalence of VZV infection was statistically associated with the CD4<sup>+</sup> cell count in both male ( $\chi^2=5.648$ ,  $p=0.017$ ) and female ( $\chi^2=6.448$ ,  $p=0.011$ ) patients. The highest seroprevalence (88.2% for males and 78.7% for females) were recorded among patients with CD4<sup>+</sup> cell count  $\leq 350/\mu\text{L}$  while the lowest seroprevalence rates (64.7% for males and 60.4% for females) were recorded among patients with CD4<sup>+</sup> count  $>350/\mu\text{L}$  (Table 2).

#### **Comparative seroprevalence of VZV in male & female patients with respect to past history of chicken pox:**

Records showed that males seroposi-

tive for VZV were about twice more likely to have suffered from chicken pox than their female counterparts. Out of 78 males who were seropositive for VZV, 25 (32%) had history of chicken pox either as a child or adult,

while out of 132 females who were seropositive for VZV, 23 (17.4%) had previous history of chicken pox ( $\chi^2=5.148$ , OR=2.235, 95% CI=1.162-4.302,  $p=0.023$ ) (Fig 1).

Table 1: Comparative seroprevalence of VZV among male and female HIV patients in relation to demographic variables

Variable	Males		$\chi^2$ (p-value)	Females		$\chi^2$ (p-value)
	Total	Positive (%)		Total	Positive (%)	
<b>Age group (years)</b>						
≤20	8	8 (100)	8.014 (0.155)	3	3 (100)	4.689 (0.455)
21-30	10	7 (70.0)		19	13 (68.4)	
31-40	14	11 (78.6)		65	44 (67.7)	
41-50	37	34 (91.9)		34	28 (82.4)	
51-60	14	11 (78.6)		34	25 (73.5)	
>60	10	7 (70.0)		25	19 (76.0)	
<b>Total</b>	<b>93</b>	<b>78 (83.9)</b>		<b>180</b>	<b>132 (73.3)</b>	
<b>Marital status</b>						
Single	22	19 (86.4)	12.46 (0.006)	6	6 (100)	12.139 (0.007)
Married	59	53 (89.8)		148	112 (75.7)	
Widow/widower	5	2 (40.0)		2	2 (100)	
Divorced	7	4 (57.1)		24	12 (50.0)	
<b>Total</b>	<b>93</b>	<b>78 (83.9)</b>		<b>180</b>	<b>132 (73.3)</b>	
<b>Occupation</b>						
Trading	49	43 (87.8)	21.52 (0.0007)	103	79 (76.7)	11.173 (0.025)
Artisan	6	6 (100)		35	20 (57.1)	
Civil servant	12	12 (100)		20	14 (70.0)	
Student	6	3 (50.0)		-	-	
Professionals	14	8 (57.1)		-	-	
Undetermined	6	6 (100)		22	19 (86.4)	
<b>Total</b>	<b>93</b>	<b>78 (83.9)</b>		<b>180</b>	<b>132 (73.3)</b>	

Table 2: Comparative seroprevalence of VZV infection among male and female HIV-infected patients in relation to CD4+ count

Variable	Males		$\chi^2$ (p-value)	Females		$\chi^2$ (p-value)
	Total	Positive (%)		Total	Positive (%)	
<b>CD4+ count</b>						
≤350	76	67 (88.2)	5.648 (0.017)	127	100 (78.7)	6.448 (0.011)
>350	17	11 (64.7)		53	32 (60.4)	
<b>Total</b>	<b>93</b>	<b>78 (83.9)</b>		<b>180</b>	<b>132 (73.3)</b>	

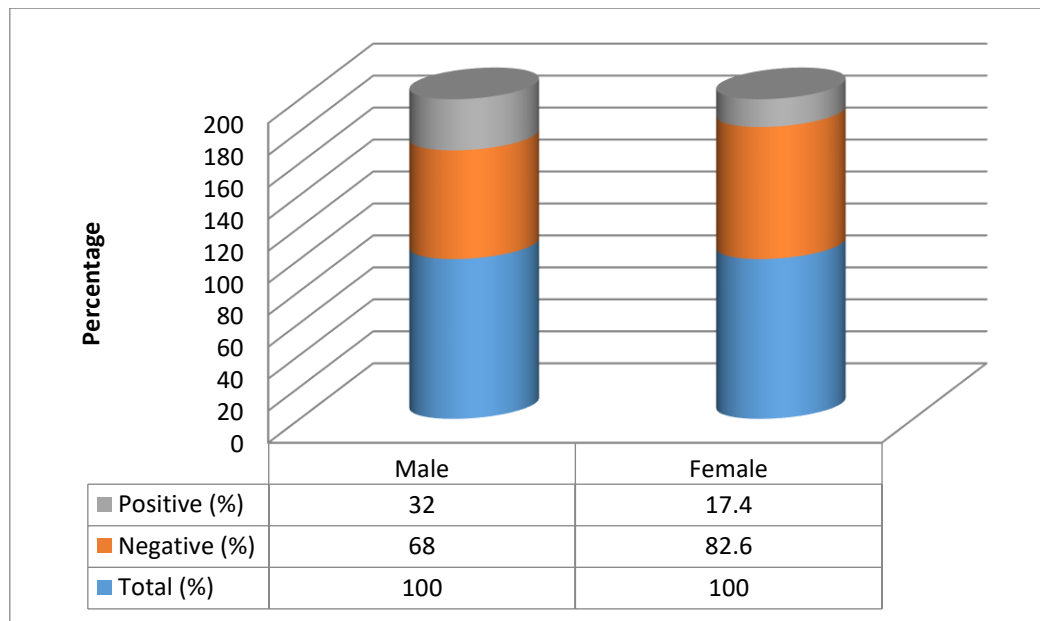


Fig 1: Gender-specific seroprevalence of varicella zoster virus infection with respect to history of chicken pox

**Discussion:**

Varicella zoster virus infection is common and contributes significantly to morbidity and mortality especially among HIV-infected individuals. Despite this, it has not been given adequate recognition especially in Nigeria. In this study, prevalence of 83.9% and 73.3% were recorded for male and female patients respectively. As far as it can be ascertained, there has not been any previous epidemiological study on VZV infection among HIV-positive patients in Nigeria thus comparing our result with any local finding is difficult. This reflects how neglected the infection is in Nigeria. Since vaccination against VZV is not yet routine in Nigeria and since none of the study participants reported having received VZV vaccination, the seroprevalence obtained in this study indicates the level of previous natural exposure to the virus.

The 83.9% and 73.3% VZV seroprevalence rates recorded for male and female participants in this study indicates similar rates of exposure of both genders to the infection and is comparable to report from similar study in Italy (17). Although a lower prevalence has been reported in India (18), the rates obtained in this study are appreciably lower compared to the reported 90% -100% seroprevalence in more developed regions of the world such as North America, Western Europe, New Zealand and Japan (19,20). It has earlier been noted that about 50% of young adults in tropical regions have not been exposed to primary VZV infection (20). High ambient temperature and humidity (22) as well as high ultraviolet radiation (23) such as seen in tropical regions like Nigeria have all

been reported to have deleterious effect on the virus. This may partly explain the relatively lower seroprevalence in this study compared to more developed regions of the world.

The age group of the patients was not significantly associated with the seroprevalence of VZV infection, and this was observed for both male and female participants in this study. Other similar studies did not find any association between age and prevalence of VZV antibodies (24,25). High seroprevalence in the younger age group in this study is not out of place since the virus is known to be acquired at very young age. In the temperate countries, most of the infections are known to occur before adolescence (26), while in the tropical regions, primary infection is usually delayed till adolescence (27). Seroprevalence of 66.3% has been previously reported in Kaduna, Northern Nigeria among children ≤15 years (28).

On the other hand, marital and occupational status were significantly associated with the seroprevalence of VZV infection in both male and female patients in our study. While being students and professionals correlated with low VZV seroprevalence among the male patients, this was not so among the female patients. Few studies have looked into the association between occupation and acquisition of VZV. In one of such studies conducted in a healthcare setting, positive association was observed between VZV sero-negativity and job of the patients (29). Although no immediate reason can be advanced for the observed association of prevalence with marital and occupational status of the patients in our study, it may not be unconnected with increased risk of contact with infected individuals in

certain group of individuals than the others. Some other studies however, did not find any association with these variables (25).

Immunologically, significant association was observed between VZV seroprevalence and CD4<sup>+</sup> count in both the male ( $p=0.017$ ) and female ( $p=0.011$ ) patients in our study. Cell-mediated immunity is believed to play significant role in maintaining the latent state of VZV infection (30), the lower seroprevalence observed among patients with higher CD4<sup>+</sup> count may therefore be as a result of their relatively strong cellular immunity. On the other hand, individuals with more advanced HIV with decreased CD4<sup>+</sup> cell count ( $\leq 350$  cells/ $\mu$ L) had higher seroprevalence of VZV due to their low cellular immunity and therefore stand higher chances of developing zoster in the near future (31).

We also looked into the medical history of the participants and discovered that males are twice as likely to suffer from chicken pox following VZV infection than their female counterparts (ratio 1.8:1). Thirty-two percent of the males seropositive for the virus had history of chicken pox while 17.4% of the females had history of chicken pox indicating that more females had subclinical infection (without chicken pox) than their male counterparts following exposure. Whether ability to suffer from more acute infection (leading to chicken pox) as observed among males in this study translates to reduced chances of suffering from zoster in the future remains to be investigated.

## Conclusion:

The seroprevalence rate of VZV in HIV-infected individuals in Offa, Kwara State, Nigeria, is high and the rate is similar in both male and female patients in our study. However, greater percentage of seropositive males than females reported history of chicken pox.

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## Contributions of authors:

AU conceived, designed and supervised the study. AU and MO were involved in the recruitment of participants, sample and data collection and analysis. AU drafted the manuscript. AU and MO read and approved the final manuscript.

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## Conflict of interest:

Authors declare no conflict of interest

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