Prevalence of Herpes Simplex Virus (HSV) type II antibodies in Human Immunodeficiency Virus (HIV)-infected patients in Benin City, Nigeria

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ABSTRACT

Background: HSV and HIV infections are frequently acquired through the sexual route and infection with HSV increases the risk of transmission and acquisition of HIV infection. Aim: To determine the prevalence of HSV 2 antibodies in HIV infected patients in Benin City, Nigeria. Methods: One hundred and seventy-four persons (92 HIV+ patients/39 males, 53 females and 82 HIV-/44 males, 38 females) were enrolled into this cross-sectional study and screened for HSV-2 antibodies using the HERPESELECT ELISA kit. HIV infection was confirmed using the double ELISA technique. The mean age was 38.91±9.42 and 36.77±11.64 for HIV+ and HIV- persons respectively with age range 18-65 for the two groups. Results: The prevalence of HSV-2 antibodies in HIV infected patients was 92.4% compared to 40.2% in HIV negative persons and this was statistically significant (p<0.05). Age group 31-40 years constituted the most with HSV seropositivity and there was an increasing relative percentage in HSV-2 seropositivity with increasing age from 21-30 years and above. This was statistically significant (p<0.05). Gender and marital status were found to be predictors of HSV-2 acquisition with more females (71) than males (47) and more married subjects in the marital status group being positive for HSV-2 antibodies and this was statistically significant (p<0.05). Conclusion: The prevalence of HSV-2 antibodies in HIV infected persons (92.4%) was significantly higher than that in HIV negative persons (40.2%). HSV type specific testing and counseling should be offered to all HIV positive patients in order to reduce the risk of transmission of HIV.

Key words: Antibodies, HSV, HIV, seropositivity, epidemic, infectious disease

INTRODUCTION

Herpes simplex virus type 2 (HVS-2), a DNA virus and a sexually transmitted infection (STI), is the major cause of herpes genitalis. HSV-2 infection is an independent risk factor for the acquisition and transmission of infection with human immunodeficiency virus 1(HIV-1). Among co-infected persons, HIV-1 virions can be shed from herpetic lesions of the genital region. This shedding may facilitate the spread of HIV through sexual contact. HSV-2 infection
doubles the risk of acquiring HIV. In addition, co-infection with HSV-2 may accelerate HIV disease progression by increasing the HIV viral load.

The worldwide incidence of genital infection due to HSV-2 has progressively increased over the past two decades. In a study of female patients attending the sexually transmitted infection (STI) clinic of the University College Hospital, Ibadan, Nigeria, a prevalence rate of 4.3% was noted for HSV infections. Most of the studies on HSV infections were done on immune competent patients.

There are geographical variations in the prevalence of HSV-2 worldwide. In Europe, seroprevalence differs in many countries, with Bulgaria having about 23.9% relative to England and Wales with 4.2%. Seroprevalence in US has increased from 16.4% in 1976 to 21.8% in 1994 and is still rising. The highest HSV-2 prevalence (60%) in Central and South America was found in Colombian middle-aged women although similar prevalence (54%) was observed in younger women in Haiti. Seroprevalence in developing Asian countries is comparable (10-30%) to that observed in North America and Northern Europe; however there are variations in different countries in Asia. Notably, the prevalence in Thailand (37%) is higher than that observed in other Eastern Asian countries.

In Africa, some sub-Saharan countries have much higher prevalence rates than countries in Europe or the North America. About 80% of women and 50% of men in sub-Saharan Africa are seropositive for HSV-2, representing the highest levels of HSV-2 infection in the world, although exact levels vary from country to country in Africa. In most African countries, HSV-2 prevalence increases with age, however age-associated decreases in HSV-2 seroprevalence has been observed for women in Uganda and Zambia, as in men in Ethiopia, Benin and Uganda.

From studies done in USA and around the world, age and sexual behaviour were found to be independent risk factors for the acquisition of HSV-2 infection. On the average, women were about 45% more likely than men to be infected with HSV-2. Potential explanations being that there is a higher transmission from men to women and differences between women and men in sexual behaviour. Women are more likely than men to choose sexual partners who are older than themselves and who therefore have an increased risk of HSV-2 infection.

Blacks (especially women) were also noted to be more susceptible to be infected with HSV-2. The disparities may be due to a variety of factors, both current and historical, which include racial and ethnic differences in the prevalence of poverty and low socio-economic status, access to health care, sexual behaviour, health related behaviour and illicit drug use as well as the age and sex composition of the population. Among HIV-1 infected individuals, HSV-2 infections are common with prevalences that approximate or exceed those in the general population. Studies done in recent years found seroprevalences of 50-90% in HIV-1 positive populations, which was significantly higher than among those who are HIV negative. The two viruses’ shared route of sexual transmission may explain this finding. It has been observed that heterosexual men and women in the sub-Saharan Africa and homosexuals in Americas have the highest prevalences of co-infection HSV-2 and HIV-1.

Increasing evidences have shown that genital HSV-2 is facilitating the perseverance of the global HIV-1 epidemic. A recent meta-analysis reported that HSV-2 infection increases the susceptibility to HIV-1 and also increases the contraction of the disease by about 3-fold.

Two parallel prospective studies in northern France, using HIV-1 infected outpatients, demonstrated seroprevalences of HSV-2 in HIV-1 of 51% and 66%. Seroprevalence of HSV-2 in HIV-1 was reported to be 47.9% from another study in Germany. Interestingly, 69% of the study population in the 1st cohort study in France had no clinical history of herpes virus infection. This finding demonstrated high proportion of subclinical and undiagnosed HSV-2 infection in HIV-1 infected individuals and infer that HSV type specific serological testing could be an efficient strategy to diagnose clinically asymptomatic HSV-2 infection.
In dually infected (HIV-1/HSV-2) individuals, the clinical presentation of symptomatic HSV-2 infection vary significantly.[2] HSV reactivation presents with vesicular and ulcerative lesions of the oral and anogenital regions in both HIV positive and negative individuals.[3]

Infection by HSV-2 virus can present in a variety of ways, the commonest of which is genital herpes, with or without ulcers. Other presentations are herpetic whitlow, mollaret’s meningitis, neonatal herpes and occasionally orofacial herpes. In most cases, infections are asymptomatic.

Genital herpes is generally classified as primary, recurrent and atypical.[18] HSV-2 is the commonest cause of genital ulcers worldwide[18] however HSV-1 has been increasingly implicated as the causative agent in as many as 30% of cases of primary genital herpes infections possibly secondary to orogenital contact.[19] Genital infections present as clusters of inflamed papules and vesicles on the outer surface of the genitals. These represent the typical symptoms of either a primary HSV-2 or HSV-1 genital infection. Papules and vesicles usually appear 2-14 days after sexual exposure to HSV for the first time,[18] and may resemble cold sores.

In HIV-positive individuals, the atypical mucocutaneous manifestations of genital HSV reactivation is common and usually undiagnosed.[20] The severity of genital herpes infection is similar in both HSV-1 and HSV-2 infections but predilection for recurrences is much lower for HSV-1. Among patients with documented newly acquired HSV-1 infection, the median time to first recurrence was 310 days compared to 49 days among patients with newly acquired HSV-2 infection.[21] This means that about 50% of patients with genital HSV-1 will not have even one recurrence in the initial year after infection, compared with patients with HSV-2 infection who will have, on average, 4-5 recurrences. Recurrent genital herpes infections are almost exclusively caused by HSV-2.[22] Most cases (about 90%) of genital herpes are asymptomatic, although viral shedding may still occur.[22]

Neonatal HSV disease, a rare but serious condition, can be caused by either HSV-1 or HSV-2. Commonest mode of transmission is usually vertical transmission of the virus from mother to newborn child, although an estimated 10% of cases may be acquired post-nataly from a parent, caretaker or sibling.[23] Approximately 22% of pregnant women in the USA have had a previous exposure to HSV-2 and a further 2% or more acquire the virus during pregnancy.[23] Amongst young adults, genital herpes infections are increasingly caused by HSV-1.[24]

Infection by HSV-1 is the most common cause of herpes that affect the face and mouth, although HSV-2 causing orofacial infection is becoming increasingly common probably as a result of orogenital sex.[25] Orofacial herpes presents with inflammation of mucosa of cheek and gums— gingivostomatitis; other symptoms may also develop including fever, sore throat and painful ulcers.[25] Primary HSV infection in adolescents frequently manifests as severe pharyngitis.[25] Recurrences also occur with HSV-2 although less frequently.[25] Recurrences are usually preceded by a prodrome comprising erythema of the skin around infected site, and subsequent ulceration to form blisters that affect the lip tissue and the area between the lip and the skin (vermilion border).[25]

The recurrent infection is thus often called herpes simplex labialis.[25] Rare re-infection occur inside the mouth (intraoral HSV stomatitis) affecting the gums, alveolar ridge, hard palate, and the back of the tongue-this may be accompanied by the herpes labialis.[25]

HSV infection predates the advent of HIV infection. Persistent HSV-2 infection was one of the original opportunistic infections that resulted in the identification of HIV. A report had shown the association between prevalent and incident HSV-2 infection and risk of HIV acquisition.[26] Most people worldwide with sexually acquired HIV have virologically active HSV-2 infection.[27]

Assessing the extent of HSV-2 infection is difficult for several reasons.[28] HSV infection is not a reportable disease.[28] Furthermore, most people with HSV-2 are asymptomatic of the infection hence serologic methods have
increasingly been used to study the epidemiology of HSV-2.\textsuperscript{[28]}

Human immunodeficiency virus (HIV) is a member of the genus Lentivirus, part of the family of retroviridae.\textsuperscript{[29]} HIV causes acquired immune deficiency syndrome (AIDS) and it was first identified as the cause of AIDS by a French scientist Luc Montagnier in 1983.\textsuperscript{[30]}

Two strains of HIV are known to exist- HIV-1 and HIV-2. HIV-1 is more virulent, relatively easily transmissible and is the cause of majority of HIV infections globally. HIV-2 is less transmissible and largely confined to West Africa.\textsuperscript{[31]} The combination of Nigeria’s population size, projected at >160 million by the World Bank in 2011\textsuperscript{[32]} and estimated HIV prevalence of 3.34\% (ages 15-49 years) for the same year,\textsuperscript{[33]} is the second highest burden of HIV/AIDS worldwide, with an estimated 3.2 million people living with HIV in 2011 and an estimated 2.4 million children orphaned by HIV/AIDS.\textsuperscript{[33]}

This study was carried out to determine the prevalence of human herpes virus type II antibodies in human immunodeficiency virus infected patients in Benin City, Nigeria.

**METHODOLOGY**

**Study design and patients**

This study was a cross-sectional study carried out in both the in-patient and out-patient units of the Department of Internal Medicine, University of Benin Teaching Hospital (UBTH), Benin City, Edo state from April to June 2010.

HIV positive patients both antiretroviral naïve and or experienced admitted or referred into the unit during the period of study, aged 15 years and above were included in this study while age and sex matched controls were pooled from other patients attending the out-patient clinic and from hospital/departmental staff who were HIV negative on screening.

Patients with other immunosuppressive illnesses such as diabetes mellitus, chronic kidney diseases, patients on immunosuppressive drugs for whatever reasons and pregnant women irrespective of their HIV status were all excluded from the study.

**Sample size**

The sample size was determined using the Fisher’s formula

\[
 n = \frac{Z^2pq}{d^2}
\]

- \( n \) = Minimum sample size
- \( Z \) = Normal standard deviation 95\% confidence interval \( = 1.96 \)
- \( p \) = Prevalence \( = 0.6 \)
- \( q \) = \( 1-p \)
- \( d \) = Margin of error (Degree of precision desired) \( \approx 0.1 \) (one-fifth of \( p \))

Studies on prevalence of HSV-2 infection described a geographical variation, ranging between 4-80\% worldwide. In some African countries, prevalence is between 50-80\% however researches done in recent years on HSV-2 in HIV found seroprevalence of 50-90\% in some populations, significantly higher than among those without HIV.\textsuperscript{[6]}

There is paucity of data on HSV-2 infection in HIV patients in Nigeria. Using a prevalence of 60\% obtained from studies done worldwide, minimum sample size using the Fisher’s formula was

\[
 N = \frac{1.96^2 \times 0.6 \times 0.4}{0.1^2} = 92
\]

A sample size of 184 (92 HIV+,92 HIV-) was estimated to be used for this study however due to the very high cost of reagents and challenges of maintaining a cold chain of the reagents for a long period, a total of 174 patients (92 HIV+, 82 HIV-) were used in the study.

**Ethical consideration**

Ethical approval was sought from the Ethical Committee of the University of Benin Teaching Hospital. Approval was given for research to be carried out on the patients. Informed consent was also obtained from persons that were used for this study. Voluntary counselling and testing (VCT) was explained to them after which a pre and post testing counselling was offered to the patients.

**Data collection**

A simple random sampling of patients attending the HIV/AIDS clinic and the general out-patient...
clinics was done. After obtaining an informed consent, a data acquisition sheet (structured questionnaire) was self-administered to collect information, including the presence or absence of symptoms suggestive of HSV-2 infections both in the past and or during the period of study and these include ulcers in the genitalia/gluteal region, mouth and fingers, genital itching, burning sensation or pain on genitalia, mouth or fingers, penile or vaginal discharge and dysuria especially in women. A physical examination of these patients for vesicles and ulcers at the genitalia/gluteal region, mouth, fingers in addition to examination for regional lymph nodes was carried out by the researcher after which they were counseled and tested for HIV and HSV-2 antibodies.

**Laboratory assay**

**Antibody response to HSV**

HSV 1 and 2 share many common antigens however each has a unique glycoprotein G (gG1 found only in HSV-1 and gG2 only in HSV-2). Antibodies to these antigens are produced by individuals infected with HSV and these antibodies persist for life. Detection of these antibodies is indicative of infection with HSV and capability of transmission of the virus to others.

**IgM positivity**

Individuals infected with HSV also develop IgM antibodies which are usually transient however the presence of these antibodies may indicate a primary infection, a reactivated infection or a super-infection with a different serotype. IgM tests are not type specific and therefore cannot be used to distinguish between the serotypes.

**HSV-2 antibody testing**

Five mls of blood, collected aseptically from a peripheral vein, was put into a plain bottle. It was allowed to clot at room temperature following which serum was separated by centrifugation at 2000 cycles/min for 5 minutes. Serum was removed into another tube where it was frozen at ≤-20°C.

A glycoprotein G2 type-specific enzyme immunoassay technique (Herpeselect Elisa Kit) was used for the serologic evaluation of HSV-2 antibodies. The kit is a 96 well plate and diluted serum samples (100ul of 1:101 dilution) were inoculated into the antigen gG2 coated wells at room temperature. Presence of specific antibodies in the serum react with the antigen. Peroxidase-conjugated anti-human IgG was added and this reacts with specific IgG. Enzyme substrate and chromogen were subsequently added and colour was allowed to develop. Spectrophotometric reading of optical density (OD) was used to quantify colour change and results determined by comparing sample OD readings with reference cutoff OD readings. Index values greater than 1.10 were POSITIVE, values less than 0.90 NEGATIVE and values between 0.90 - 1.10 were EQUIVOCAL.

**HIV testing**

HIV is the cause of HIV infection/AIDS and two strains of the virus (HIV-1 and HIV-2) are known to exist. The presence of infection with the virus elicits antibodies to either HIV-1 or HIV-2.

Testing for the antibodies to HIV is done in series using two different kits - Determine and Chembio HIV 1/2 STAT-PAK assays. Both are single use immunochromatographic tests for the qualitative detection of antibodies to HIV 1/2.

**CD4 count**

For monitoring the immunological response, the CD4 count was measured using the Cytflow technique with an instrument known as the Partec-Cytflow counter (Partec Germany).

**Statistical analysis**

Data obtained was analyzed using the SPSS version 16.0 statistical software. Frequency tables were used where appropriate to present the various data obtained. Student T test was used for the comparison of means and chi square for the comparison of proportions. This study was carried out at 5% level of significance (95% confidence interval), therefore p values <0.05 were considered significant. The results obtained from this study helped to determine the seroprevalence of HSV-2 in HIV infected individuals and to determine the difference in prevalence of HSV-2 between HIV positive and HIV negative persons.
RESULTS

Two of the 4 patients (50%) in the age group 11-20 years were positive for HSV-2 antibodies and the same number were seronegative. Seventy one (71) patients of the total 174 were in the age group 31-40 years with 52 (73.2%) of them being sero-positive for HSV-2 antibodies while 19 (26.8%) were sero-negative. All the patients (4) in the age group 61-70 years were positive for HSV antibodies. From age groups 21-30 years through 61-70 years there was an increase in the relative percentage of patients who were seropositive for HSV-2 antibodies and a decrease in the percentage of patients who were seronegative. p<0.05 (0.002) shows a statistical significance in the association between age groups and HSV status with the relative percentage in seropositivity rising with increasing age of the patients (table 1).

Seventy-one (78%) of the 91 females involved in this study were positive for HSV-2 antibodies while 47 (56.6%) of the 83 males were positive for HSV-2 antibodies. The mean age for the HSV-2 positive patients was 40.24 years compared to 32.98 years for the HSV-2 negative patients. p<0.05 shows a statistical significance in the association between age, sex and HSV status (table 1).

The prevalence of HSV-2 antibodies in HIV positive subjects was 92.4% compared to 40.2% in HIV negative subjects. Forty-nine (59.8%) of the 82 HIV negative subjects were negative for HSV-2 antibodies however p<0.05 shows there is statistical significance in the association between HSV sero-positivity and HIV status (table 2).

Fifty-three (63.9%) of the male subjects were married while 66 (72.5%) of the female subjects were married representing the most in both categories.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HSV+ (%)</th>
<th>HSV- (%)</th>
<th>Total (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>2(50.0)</td>
<td>2(50.0)</td>
<td>4(100)</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>18(42.9)</td>
<td>24(57.1)</td>
<td>32(100)</td>
<td></td>
</tr>
<tr>
<td>31-40</td>
<td>52(73.2)</td>
<td>19(26.8)</td>
<td>71(100)</td>
<td>0.002</td>
</tr>
<tr>
<td>41-50</td>
<td>27(77.1)</td>
<td>8(22.9)</td>
<td>35(100)</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>15(83.3)</td>
<td>3(16.7)</td>
<td>18(100)</td>
<td></td>
</tr>
<tr>
<td>61-70</td>
<td>4(100)</td>
<td>0(0)</td>
<td>4(100)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>118</td>
<td>56</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47(56.6)</td>
<td>36(43.4)</td>
<td>83(100)</td>
<td>0.003</td>
</tr>
<tr>
<td>Female</td>
<td>71(78.0)</td>
<td>20(22.0)</td>
<td>91(100)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>40.24±10.24</td>
<td>32.98±9.54</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>
Thirty-seven (37) of the married male subjects were positive for HSV-2 antibodies while 56 of the married female subjects were positive for HSV-2 antibodies. HSV-2 sero-positivity was most among the subjects that were married and $p<0.05$ (0.004 and 0.001 for males and females respectively) shows a statistical significance in the association between gender, marital status and HSV status (table 3).

Fifty-eight (69.9%) of the males in this study had positive history of multiple sexual exposure and 42(50.6%) of them were positive for HSV-2 antibodies which almost tripled those who were negative for HSV-2 antibodies. Five males (6% of males in the study) who were positive for HSV-2 antibodies had no history of exposure to multiple sexual partners.

Twenty-three (25.3%) of 91 females in this study who were positive for HSV-2 antibodies had positive history of exposure to multiple sexual partners which more than tripled those who were negative however 48 females (52.7% of females in the study) who were positive for HSV-2 antibodies had no history of exposure to multiple sexual partners.

There was no statistical significance in the association between gender, exposure to multiple sexual partners and HSV-2 sero-positivity for females while there is statistical significance in the association for males ($p<0.05$) (table 4).

### Table 2: Prevalence of HSV-2 antibodies among HIV+ and HIV- subjects

<table>
<thead>
<tr>
<th>HSV status</th>
<th>HIV+ (%)</th>
<th>HIV- (%)</th>
<th>Total</th>
<th>$\chi^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV+</td>
<td>85(92.4%)</td>
<td>33(40.2%)</td>
<td>118</td>
<td>54.019</td>
<td>0.000</td>
</tr>
<tr>
<td>HSV-</td>
<td>7(7.6%)</td>
<td>49(59.8%)</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>92(100%)</td>
<td>82(100%)</td>
<td>174</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Association between gender, marital status (MST) and HSV status

<table>
<thead>
<tr>
<th>Gender</th>
<th>Marital status</th>
<th>HSV+ (%)</th>
<th>HSV- (%)</th>
<th>Total (%)</th>
<th>$\chi^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Divorced</td>
<td>0(0)</td>
<td>1(1.2)</td>
<td>1(1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Married</td>
<td>37(44.6%)</td>
<td>16(19.3%)</td>
<td>53(63.9%)</td>
<td>10.847</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Single</td>
<td>0(12.0%)</td>
<td>19(22.9%)</td>
<td>29(34.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>7(56.6%)</td>
<td>36(43.4%)</td>
<td></td>
<td>83(100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Divorced</td>
<td>2(2.2%)</td>
<td>0(0)</td>
<td>2(2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Married</td>
<td>56(61.5%)</td>
<td>10(11.0%)</td>
<td>66(72.5%)</td>
<td>15.600</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Single</td>
<td>8(8.8%)</td>
<td>10(11.0%)</td>
<td>18(19.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Widow</td>
<td>5(5.5%)</td>
<td>0(0)</td>
<td>5(5.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>71(78.0%)</td>
<td>20(22.0%)</td>
<td></td>
<td>91(100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Association between gender, multiple sexual exposures (MSE) and HSV status

<table>
<thead>
<tr>
<th>GENDER</th>
<th>MSE</th>
<th>HSV+ (%)</th>
<th>HSV- (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>42(50.6)</td>
<td>16(19.3)</td>
<td>58(69.9)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5(6.0)</td>
<td>20(24.1)</td>
<td>25(30.1)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>57(66.6)</td>
<td>36(43.4)</td>
<td>93(100)</td>
<td></td>
</tr>
</tbody>
</table>

\[
\chi^2 = 19.541, \quad p-value = 0.000
\]

<table>
<thead>
<tr>
<th>GENDER</th>
<th>MSE</th>
<th>HSV+ (%)</th>
<th>HSV- (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Yes</td>
<td>23(25.3)</td>
<td>7(7.7)</td>
<td>30(33.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>48(52.7)</td>
<td>13(14.3)</td>
<td>61(67.0)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>71(78.0)</td>
<td>20(22.0)</td>
<td>91(100)</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

This study showed a statistically significant relationship between HIV status and HSV status. The prevalence of HSV-2 antibodies in HIV infected persons was 92.4% while the prevalence in HIV negative subjects was 40.2%. Seroprevalence of HSV-2 antibodies in HIV infected persons at 92.4% compared favourably with findings of prevalence rates between 50-90% in published data of HSV-2 infection in HIV infected populations from different parts of the world.\(^{[13]}\)

The higher prevalence in this study could be explained by the burden of HIV infection in Nigeria and sub-Saharan Africa in general. Seroprevalence of HSV-2 in HIV negative subjects at 40.2% also compared favourably with reported findings in Central African Republic, The Gambia, Tanzania, Uganda, South Africa and Zimbabwe with prevalence rates between 10-50% in men and 30-80% in women.\(^{[8]}\)

The prevalence of HSV in HIV negative subjects has geographical variations with the highest prevalence rates noted in Ethiopia, Tanzania and Uganda.\(^{[8]}\) Similarly, prevalence of HSV in HIV negative subjects was noted to be considerably higher in some other developing countries outside of sub-Saharan Africa (Colombia, Brazil and Haiti).\(^{[8]}\) This may reflect the high prevalence in this study as it was carried out in Nigeria, regarded as a developing nation. The difference in HSV prevalence in HIV positive and HIV negative subjects in this study was statistically significant.

Age and sex had been noted to be independent predictors of HSV infection. Like most sexually transmitted infections, genital herpes parallels the onset of sexual activity, with rates rising in adolescence and peaking in 20-29-year olds.\(^{[38]}\)

Results from this study showed that the most of HSV-2 positive subjects were in the age group 31-40 years. The age group noted in this study was higher than the peak age of sexual activity noted in previous research\(^{[38]}\) however this study was not a follow up study therefore the possibility that most of the patients may have acquired the infection before this study was carried out cannot be ruled out, more so the acquisition and development of antibodies to HSV-2 infection persists throughout life. In
addition to this varying finding, a larger sample size was used in the previous study\textsuperscript{39} reported and this was done in a developed country where the onset of sexual activity had been reported to be earlier than those in developing countries. This study used a smaller sample size and it was carried out in a population where early presentation to health facilities for health related problems is usually a challenge and therefore delayed.

In another prospective (follow up) study\textsuperscript{39} in rural Tanzania, a strong association between HIV seroconversion and HSV seropositivity at baseline was found among younger men aged 15-24 years than among those aged 25 years and above. The observed difference in the age range for acquisition of HSV infection was due to follow up in the study done in rural Tanzania.

Gender was found to be a statistically significant predictor of HSV infection (p<0.05) in this study. More females (71) than males (47) were found to be positive for HSV-2 antibodies. This compared with findings from previous studies\textsuperscript{10,11} where on the average, women were about 45% more likely than men to be infected with HSV-2, potential explanations being that there is a higher transmission from men to women\textsuperscript{10} and the likelihood of women choosing sexual partners who are older than themselves\textsuperscript{11} and who therefore have an increased risk of HSV-2 infection.

This study also showed interplay between gender, marital status and positive history of multiple sexual exposures as predictors of acquisition of HSV infection. HSV-2 infection is a sexually transmitted infection therefore exposure to multiple sexual partners is a risk factor for acquisition of the virus. In this study, a slightly higher number of subjects (88) had positive history of multiple sexual partners/exposure with a significant number (65) being positive for HSV-2 antibodies however a significant number (53) of the subjects who did not have positive multiple sexual exposure history were also positive for HSV-2 antibodies. p>0.05 showed there was no statistical significance in the association between multiple sexual exposure history and HSV status. This finding is comparable to a study in the U.S.\textsuperscript{39} where relationship status (increased number of sex partners) irrespective of gender was found to be an independent predictor of HSV-2 seroprevalence however female sex more than the males had increased prevalence even in the absence of multiple partners. The U.S. study was population based and had a much larger sample size.

Fifty-eight (69.9%) of 83 males who had multiple sexual partners/exposure history were positive for HSV-2 antibodies. Twenty-five (30.1%) of the males did not have multiple sexual partners/exposure history and 5 (6.0%) were positive for HSV-2 antibodies. p<0.05 showed that there was statistical significance in the association between males who have had multiple sexual partners/exposure and HSV-2 seropositivity. It was also noted in this study that a significant proportion of married men amongst the males and married women amongst the females were positive for HSV-2 antibodies. This reflected in the high prevalence of HSV-2 infection amongst married males (44.6%) and females (61.5%).

In contradistinction to the finding of high seropositivity for HSV-2 antibodies in males who had multiple sexual exposures, a significant proportion of females who did not have positive history of multiple sexual partners/exposure were positive for HSV-2 antibodies. Ninety-one (91) females were involved in this study and 61 of them did not have positive history of multiple sexual partners/exposure however 48 (52.7%) of them were positive for HSV-2 antibodies. Married females constituted a significant number among the females. p>0.05 showed there was no statistical significance in the association between multiple sexual partners/exposure history and HSV status for females.

The possible explanation to these findings could be that their (male) spouses may have been the source of the infection or infection may have been acquired before the institution of marriage. A study\textsuperscript{39} for HSV-2 transmission involving 144 heterosexual couples showed that transmission occurred in 14 (9.7%) couples including 11 (16.9%) of 65 couples with male and 3 (3.8%) of 79 with female source partners (p<0.05) with annual rate of acquisition noticed to be higher (31.8%) in susceptible female partners.
concluded that the risk of acquisition of HSV was higher in women than men.

The finding of significantly higher HSV-2 infections in females (including married females) compared with findings in studies done all over the world where HSV prevalence rates were consistently higher in women than men in all the regions of the world.

CONCLUSION

The prevalence of HSV-2 antibodies in HIV infected persons (92.4%) in this study is significantly higher than that in HIV negative persons (40.2%). Subjects in the age group 31-40 years constituted the most with positive HSV status and there was also an increase in the relative percentage of patients who were positive for HSV-2 antibodies with increasing age. There appears to be a complex interplay between gender, marital status and positive multiple sexual partners/exposure history with the acquisition of HSV infection in this study. A significant proportion of married males and females were positive for HSV-2 antibodies. Notably a significant proportion of males who were positive for HSV-2 antibodies had positive multiple sexual partners/exposure history however this study also showed that a significant proportion of females who did not have positive history of multiple sexual partners/exposure were also positive for HSV-2 antibodies with the married females constituting a significant percentage of the females.

HSV testing is not commonly done in Nigeria except for research purposes. This study highlighted the need for HSV type specific testing to be offered especially to all HIV positive patients. HSV 2 antibody testing is invaluable to the patients who return antibody positive as it will help them to be more observant for symptoms suggestive, particularly, of genital herpes and therefore facilitate early presentation to the hospital for evaluation and treatment. In addition, testing of all at risk population will offer epidemiological data for possible institution of interventional strategies. This is now more important in view of the frequently asymptomatic nature of the infection. Persons at risk for sexual acquisition of HIV infection (e.g. serodiscordant partners) will also benefit from HSV-2 testing in order to significantly reduce the risk of HIV acquisition.

REFERENCES


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