

Prevalence and Risk Factors for Herpes Simplex Virus Type 2 Infections Among HIV Infected Individuals in Lagos.

Philip Olayiwola Oshun¹, Bamidele Mutiu², Ibidunni Bode-Sojobi¹

¹Department of Medical Microbiology and Parasitology, College of Medicine, University of Lagos. ²Department of Medical Microbiology and Parasitology, Senior Lecturer, Lagos State University, College of Medicine, Ikeja Lagos.

¹Department of Medical Microbiology and Parasitology, Senior Lecturer, College of Medicine, University of Lagos, Idi-Araba Lagos.

Abstract

Background: Out of the 1.4 million new HIV infections acquired sexually in 2016 among individuals aged 15–49 years, 420 000 were attributable to HSV-2 infection. This study aimed to determine the prevalence of HSV – 2 infections and associated risk factors among HIV infected individuals in Lagos. **Methods:** A cross-sectional study was conducted to determine the prevalence of and risk factors for HSV – 2 infections in randomly selected HIV infected individuals at an HIV clinic. Blood samples were collected and tested for HSV – 2 IgG antibodies with an enzyme linked immunosorbent assay (IBL International, Germany). **Result:** Three hundred and sixty-three HIV infected participants were recruited into the study of which 259 (71.3%) were females and 104 (31.3%) were males. The mean age was 41.7±9.5 years. The prevalence of HSV – 2 in HIV infected participants was 84% (95% CI 80 – 88%). The prevalence of HSV – 2 was significantly higher in those older than 40 years with an adjusted odds ratio of 1.88 (95% CI [1.04 – 3.79], p=0.036) and those with a duration of HIV greater than 2 years with an adjusted odds ratio 2.5 (95% CI [1.3 – 4.85], p=0.007). **Conclusion:** The prevalence of HSV – 2 in HIV infected individuals was very high. Older age and longer duration of HIV infection were the significant risk factors for HSV – 2 infections. Routine screening of HIV infected patients for HSV – 2 infections in HIV clinics should be practiced. Strategies for prevention and control of HSV – 2 infections should be introduced.

Keywords: HSV – 2, HIV, Prevalence, Risk Factors

INTRODUCTION

Sexually transmitted infections are a major public health problem worldwide affecting the quality of life and causing serious morbidity and mortality.¹ Genital herpes (GH) is one of the most common sexually transmitted infections (STI) and Herpes simplex virus type 2 (HSV-2) is the most common cause of GH. An estimated 491 million people aged 15–49 (13%) worldwide have herpes simplex virus type 2 (HSV-2) infection, the main cause of genital herpes.¹ In 2016, about 5% of the world's population (187 million) aged 15–49 years had at least one episode of HSV-related

Correspondence:

Dr Philip O. Oshun FMCPATH,
Senior Lecturer and Clinical Microbiologist,
Department of Medical Microbiology and Parasitology,
College of Medicine, University of Lagos.
Sampydee@yahoo.com, 08023299445.

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genital ulcer disease globally. ^[2] Of these, 178 million had HSV-2 infection. ²

According to recent global estimates in 2021, 38.4 million people were living with human immunodeficiency virus (HIV) with 1.5 million new infections and 650,000 people died of AIDS related illness. ³ The prevalence of HIV in Nigeria is 1.4% with 1.9 million people living with HIV. In 2020, there were 86,000 new infections and 49,000 ADIS related deaths. ⁴ Out of the 1.4 million new HIV infections acquired sexually in 2016 among individuals aged 15–49 years, 420 000 were attributable to HSV-2 infection. ^[5] The proportion of new sexually acquired HIV infections in 2016 that were attributable to HSV-2 infection was 29.6%. ⁵ The contribution of HSV-2 to HIV was largest for the WHO African region, women, and individuals aged 25–49 years. ⁵

There is a strong association between infection with HSV-2 and HIV infection. HSV-2 leads to inflammation and small breaks in the genital and anal skin that can make it easier for HIV to cause infection. Both viruses increase transmissibility of the other and HSV-2 disease can become severe among those with HIV-related immunosuppression. ^{6,7} A 2017 systematic review and meta-analysis of 55 prospective studies stated that the risk of HIV acquisition was at least increased 3 times in the presence of established HSV-2 infection and increased 5 times in the presence of recently acquired HSV-2 infection after controlling for sexual behaviour and other factors. ⁸ HSV-2 lesions contain substantial numbers of CD4+ lymphocytes, which are target cells for HIV. Laboratory studies have shown that these CD4+ lymphocytes are likely to facilitate the acquisition of HIV in HIV-negative, HSV-2-positive individuals when they are exposed to HIV. ⁹

When there is co-infection of HSV and HIV, there is a double negative effect. Genital HSV-2 reactivation has been shown to increase HIV viral load, risk of HIV transmission, and disease progression. ^{6, 10} Those with multiple partners and unprotected sex are at higher risk of co-infection. The HSV-2 affects 50 – 90% of HIV-infected persons, with the highest infection rate among heterosexuals in sub-Saharan Africa and men who have sex with men in the Americas. ¹¹ In Nigeria, studies have reported a seroprevalence of HSV-2 in HIV infected persons of 70% in Abeokuta, and a prevalence of 87% was reported in patients attending a sexually transmitted disease clinic in Jos. ^{12, 13}

Routine screening and testing for HSV-2 are not offered in HIV clinics across Nigeria. This may lead to unrecognized HSV-2 infection and perhaps treatment with HSV-2 suppressive therapy which may

slow down HIV disease progression in those who are not eligible for ART. There is little or no data on the prevalence of HSV-2 infection in people living with HIV/AIDS within Nigeria. This study aimed to determine the prevalence and risk factors of HSV-2 infection in HIV infected patients.

METHODS

Study Setting

This study was conducted at the Lagos University Teaching Hospital (LUTH) HIV clinic. This clinic has been operational since 2004. It implements free treatment of HIV/AIDS with antiretroviral drugs with support from the President’s Emergency Plan for AIDS Relief (PEPFAR) according to national guidelines. There is on-site HIV screening, counselling, provision of medications, follow-up, monitoring, and evaluation of all patient activities. Over 20,000 adults and 1,200 children have been enrolled in the treatment programme. The clinic has a dedicated laboratory that offers viral load and CD4+ cell count. The diagnosis of HIV was done by the HIV clinic using the serial HIV testing algorithm. The study population consisted of adult HIV-positive patients attending the LUTH APIN HIV clinic. The inclusion criteria were HIV-infected patients aged ≥ 18 years who gave informed consent to participate in the study.

Study Design

This was a cross-sectional study to determine the prevalence of herpes simplex virus 2 infection in HIV positive patients from April to August 2016. Participants were chosen by simple random sampling on each clinic day. A list of all patients who had clinic appointments on each day was compiled and a simple random sample of 5 patients were chosen using a computer-generated list of random numbers with Microsoft Excel software. Each participant was tested for HSV-2 IgG antibodies.

Data Collection

Demographic clinical and laboratory data were collected from the participants using a structured questionnaire. Data on the risk factors, multiple sexual partners, smoking, alcohol use, sexual orientation, use of condoms, and intravenous drug use. The CD4 count, HIV viral load, and antiretroviral therapy were retrieved from the case notes of the patients.

Sample Collection and HSV – 2 Antibody Testing

Five millilitres of blood was collected into a plain bottle. Blood was allowed to clot and then spun in a centrifuge for 20 minutes at 2000 revolutions per minute. A sterile pipette was used to transfer plasma into a plain sterile cryo-tube. Plasma was stored at -20°C until testing.

Processing of specimens was performed at the medical microbiology laboratory LUTH. Serum was tested by enzyme immunosorbent assay (ELISA) for IgG antibodies to HSV-2 using the Herpes simplex virus 2 IgG ELISA (IBL International, Germany) according to the manufacturer’s instruction.

Ethical Approval

Ethical approval was obtained from the Lagos University Teaching Hospital Health Research and Ethics Committee – ADM/DCST/HREC/409. An informed consent form was signed by those who agreed to participate in the study.

Data Analysis

Prevalence data and 95% confidence intervals (CI) were calculated. Categorical variables were compared using the Chi-square test while continuous variables were compared using the student’s t-test to evaluate the association between the presence of HIV/HSV co-infection and associated risk factors. Multivariate logistic regression was done for variables with p-value < 0.05 the chi-squared test or t – test to determine the independent risk factors. A p – value, of <0.05 was considered to be statistically significant.

We used the STROBE cross sectional checklist when writing our report ¹⁴.

RESULTS

Socio-Demographic and Clinical Characteristics of the Study Participants

Three hundred and sixty-three HIV infected participants were recruited into the study of which 259 (71.3%) were females and 104 (31.3%) were males. The age of the participants ranged from 18 – 73 years with a mean age of 41.7±9.5 years while the median age was 41 years. Most of the participants were married (257, 70.8%), while 12.7% were single. About 46.8% of them had secondary education, while 30.9% of them had tertiary education (table 1). The mean age at first sexual intercourse was 20.8 ±4.3 years. Most of the participants (210, 58.7%) had one sexual partner and 20.7% had three or more sexual partners. The predominant sexual orientation was heterosexual (96.3%). Few participants smoked (4.4%), consumed alcohol (21%), were involved in intravenous drug abuse (24%), had a history of genital ulcer (16.3%), and history of sexually transmitted infections. The use of antiretroviral therapy was reported by 95.6% of participants (see Table 1). The mean duration of antiretroviral therapy was 6.6 ± 3.8 years. The median

CD4 count was 488 cells/mm³ (IQR: 348 – 649). The mean log₁₀HIV viral load was 2.5±1.5 log copies/ml.

Table 1: Prevalence of HSV – 2 Infection in Relation to Socio-demographic Characteristics in HIV-I-infected Participants in LUTH

Variable	Number (%) tested	Number (%) positive	Odds ratio	P value
Gender				
Female	259 (71.3)	220 (84.9)	1.26 (0.69 – 2.30)	0.55
Male	104 (28.7)	85 (81.7)	1	
Age group				
<= 40	180 (49.6)	143 (79.4)	1	
> 40	183 (50.4)	162 (88.5)	2 (1.12 – 3.61)	0.02
Marital status				0
Single	46 (12.7)	33 (71.7)	1	
Married	257 (70.8)	218 (84.8)	2.20 (1.06 – 4.56)	0.05
Widowed	41 (11.3)	38 (92.7)	5.0 (1.31 – 19.04)	0.01
Divorced	8 (2.2)	6 (75)	1.18 (0.17 – 6.63)	1
Separated	11 (3.0)	10 (90.9)	3.94 (0.46 – 36.94)	0.26
Education				0.22
None	16 (4.5)	15 (93.8)	1	
Primary education	64 (17.8)	54 (84.4)	0.35 (0.07 – 2.95)	0.44
Secondary education	168 (46.8)	145 (86.3)	0.42 (0.01 – 3.01)	0.7
Tertiary education	111 (30.9)	87 (78.4)	0.24 (0.01 – 1.74)	0.19
ART				
Yes	347 (95.6)	293 (84.4)	1.81(0.56 – 5.82)	0.48
No	16 (4.4)	12 (75)	1	
Duration of HIV				
≤ 2 years	56 (15.6)	40 (71.4)	2.56 (1.31 – 4.98)	0.005
> 2 years	303 (84.4)	262 (86.5)	1	
Duration of ART				
≤ 2 years	52 (15.2)	38 (73.1)	1	0.04
> 2 years	289 (84.8)	248 (85.8)	2.22 (1.11 – 4.43)	
CD4 count (cells/mm³)				
< 350	92 (25.3)	72 (78.3)	0.59 (0.32 – 1.07)	0.11
≥ 350	271 (74.7)	233 (85.9)	1	
Viral load (copies/ml)				
<= 200	279 (77.1)	238 (85.3)	1.5 (0.80 – 2.80)	0.28
> 200	83 (22.9)	66 (79.5)	1	

Prevalence of HSV – 2

In this study, the prevalence of HSV – 2 in HIV infected participants was 84% (n=305, 95% CI 80 – 88%). The prevalence of HSV – 2 infections in females was 84.9% (n=220, 95% CI: 81 – 89%), while it was 81.7% (95% CI 74.3 – 89.2%) in males. The mean age of participants who tested positive for anti – HSV – 2 was 42.1 ± 9.2 years.

Risk Factors for HSV – 2 Infections

In the bivariate analysis, HSV – 2 was significantly associated with age (p= 0.02). The prevalence of HSV –

2 was significantly higher in those older than 40 years. The prevalence of HSV – 2 increased with age. The prevalence of HSV – 2 was significantly higher in those with a duration of HIV greater than 2 years (86.5%) compared with those 2 years or less (71.4%), $p=0.005$. The prevalence of HSV – 2 was significantly higher in those with a shorter duration of antiretroviral therapy $p=0.04$ (table 2).

Table 2: Prevalence of HSV – 2 Infection in Relation to Its Risk Factors in HIV Infected Individuals in Lagos

Variable	Number (%) tested	Number (%) positive	Odds ratio	P value
Age at first sexual intercourse				
≤20	181 (53.1)	151 (83.4)	1	
>20	160 (46.9)	136 (84.2)	1.12 (0.63 – 2.02)	0.80
Sexual partners				
None	41 (11.5)	31 (75.6)	1	
1	210 (58.7)	179 (85.2)	1.86 (0.83 – 4.18)	0.16
2	33 (9.2)	28 (84.8)	1.81 (0.55 – 5.93)	0.48
3 or more	74 (20.7)	64 (86.5)	2.06 (0.78 – 4.48)	0.22
Sexual orientation				
Heterosexual	334 (96.3)	279 (83.5)	0.39 (0.05 – 3.04)	0.48
Homosexual	13 (3.7)	12 (92.3)	1	
Condom use				
Yes	199 (55.4)	168 (84.4)	1.10 (0.63 – 1.93)	0.74
No	160 (44.6)	133 (83.1)	1	
Smoking				
Yes	16 (4.4)	13 (81.3)	0.82 (0.23 – 2.98)	0.76
No	345 (95.6)	290 (84.1)	1	
Alcohol use				
Yes	76 (21)	65 (85.5)	1.16 (0.57 – 2.37)	0.68
No	286 (79)	239 (83.6)	1	
IVDrug abuse				
Yes	86 (24)	71 (82.6)	0.86 (0.45 – 1.65)	0.66
No	272 (76)	230 (84.6)	1	

Table 3: Multivariate Logistic Regression of Risk Factors for HSV – 2 Infections

	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)	p value
Age group			
≤40	1	1	0.036
>40	2 (1.12 – 3.61)	1.88 (1.04 – 3.79)	
Duration of HIV			
≤2 years	1	1	0.007
>2 years	2.56 (1.31 – 4.98)	2.5 (1.3 – 4.85)	
Duration of ART			
≤2 years	1		
>2 years	2.22 (1.11 – 4.43)	1.81 (0.87 – 3.74)	0.16

In further analysis, variables with p values <0.05 from the bivariate analysis were included in the multivariate logistic regression. The variables included age group and duration of HIV infection. From the multivariate analysis, age group and duration of HIV infection were significantly associated with the prevalence of HSV – 2. Those older than 40 years had a higher prevalence with an adjusted odds ratio of 1.88 (95% CI [1.04 – 3.79], $p=0.036$). Those who had HIV infection for more than 2 years had a higher prevalence of HSV – 2 with an adjusted odds ratio of 2.5 (95% CI [1.3 – 4.85], $p=0.007$) Table 3.

DISCUSSION

The prevalence of HSV – 2 infections in HIV infected patients was estimated in a population of adults consisting predominantly of females. The prevalence of HSV – 2 in HIV positive patients in this study was 84%. This prevalence is very high, demonstrating a high burden of genital herpes among HIV infected patients. The implication is that there should be routine screening of HIV infected patients in this clinic to identify those with HSV -2 infections and provide antiviral therapy. This high prevalence has been reported in parts of Nigeria including a prevalence of 70% in Abeokuta, and 87% among patients attending the sexually transmitted disease clinic in Jos.^[12, 13] In Africa the prevalence of HSV -2 is higher than in most other continents.¹ In a systematic review and meta – analysis of HSV – 2 in sub-Saharan Africa, the pooled prevalence of HSV – 2 among HIV infected individuals was 71.3%.¹⁴ It is higher than many reports of HSV prevalence of 36.4% from Gwagwalada, 56.2% from Abakaliki and 26.6% from Kenya.^{15 – 17} The differences in sample size, socio-demographic factors, risk behaviours and types of exposure may account for the variation in the prevalence rates. The high prevalence rate in this study underlines the important relationship between HIV and HSV – 2 infections. This relationship has implications for the management of HSV – 2 infections in HIV infected individuals and the prevention of both HSV – 2 infections and HIV.

Consistent with other studies, the prevalence of HSV – 2 increased with age.^{1, 14, 17, 18} The prevalence was higher in those older than 40 years. This may be due to the increased number of sexual partners and increased years of sexual activity with age. Infection with HSV – 2 is lifelong and therefore it may be expected to find an increasing prevalence of HSV – 2 with increasing age. The association of duration of HIV more than 2 years with a higher prevalence of HSV – 2 may be because HIV infected individuals are now living longer and can maintain sexually active lives while taking their antiretroviral therapy. This was also found in a study in the USA where duration since HIV diagnosis greater than 2.3 years was significantly associated with the prevalence of HSV – 2.¹⁹

Women are at greater risk of both HSV – 2 and HIV. In most studies, the prevalence of HSV – 2 is higher in women than in men.^{14, 17, 19} Women living in the WHO Africa Region have the highest HSV-2 prevalence and exposure to HIV – putting them at the greatest risk of HIV infection, with negative implications for their health and well-being. Even though the prevalence of HSV – 2 was higher in females in this study, it was not statistically significant. History of multiple sexual partners is a major risk factor for both HSV-2 and HIV.¹⁷ However, in this

study, no significant association was found between multiple sexual partners and HSV -2 prevalence.

The study has some limitations. Firstly, this is a seroprevalence study so a diagnosis of infection (genital herpes) could not be confirmed, and IgM antibodies were not tested. Secondly, it is not a hospital-based study, so it might not reflect the prevalence at the level of the community.

CONCLUSION

In conclusion, the prevalence of HSV – 2 in this study was very high at 84%. -The prevalence of HSV – 2 is significantly higher in those older than 40 years and those with a duration of HIV greater than 2 years. Routine screening of HIV infected patients for HSV – 2 infections in HIV clinics should be practised. Strategies for prevention and control of HSV – 2 infections should be introduced. New interventions such as HSV – 2 vaccines, topical microbicides and new antiviral therapy are needed in the prevention of HSV -2 infections which may indirectly help in the reduction of HIV acquisition and transmission.

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