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HSV-1/2 Seronegativity and HCV Seropositivity in People Living with HIV Presenting at a Tertiary Care Teaching Hospital in Awka, Anambra State, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Herpes simplex virus has public health importance as a leading cause of genital ulcers, which also facilitate human immunodeficiency virus while co-infection with hepatitis C virus and human immunodeficiency virus is common in certain populations. This study was carried out with the aim of determining the prevalence of Herpes simplex virus and hepatitis C virus in people living with HIV attending a teaching hospital in Awka, Anambra State, Nigeria. Blood samples were randomly collected from 100 HIV-infected individuals of which 42 were males and 58 were females and analysed using ELISA. Results showed an overall prevalence of HCV to be 4.0% seropositivity and HSV to be 0.0% with 100.0% seronegativity. Higher prevalence of HCV occurred in ages groups 26-35 years (4.7%) than 16-25 years (4.4%) and 36 years & above (4.0%) with a significant difference of $p < 0.05$. It showed that HCV antibody was only present among females (6.9%) and target not detected (TND) with 4.4%. Higher prevalence of HCV occurred among HIV-infected individuals having CD4 counts of >350 cells/mm3 than the <200 cells/mm3 and 200-249 cells/mm3 (0.0%). The study showed 4.4% seropositivity of HCV and 100.0% seronegativity of HSV in HIV- infected individuals with the highest prevalence of HCV recorded for age boundary 26-35 years. Thus, the increased number of HCV seropositivity among HIV-infected individuals indicates that there is a synergistic relationship between HIV and HCV infection. This study recommends that more attention should be given to the area of HIV/HCV coinfection in the management of infected patients.

Keywords: HCV; HSV; seronegativity; seropositivity; PLWHA.

1. INTRODUCTION

"Sexually transmitted infections (STIs) are emerging public health concerns" [1]. "Studies have demonstrated the bidirectional relationships between HIV and several STIs, including herpes simplex virus-2 (HSV-2), hepatitis B and C viruses, human papilloma virus, syphilis, gonorrhea, chlamydia, and trichomonas" [2]. "HIV-1 may affect the clinical presentation, treatment outcome, and progression of STIs, such as syphilis, HSV-2, and hepatitis B and C viruses. Likewise, the presence of an STI may increase both genital and plasma HIV-1 RNA levels, enhancing the transmissibility of HIV-1, with important public health implications" [2].

"Globally, infections caused by herpes simplex virus types 1 and 2 are amongst the most common human viral infections" [3]. "Herpes simplex virus (HSV) can cause genital ulcers, herpetic whitlow, and corneal blindness" [4]. "The transmission of HSV-2 is mainly through sexual means, while HSV-1 is transmitted non-sexually during infancy" [3,5]. "However, there is an increasing proportion of genital herpes infections caused by HSV-1 in the developed world" [3]. "This is probably due to changes in sexual behavior, with oral-genital sex becoming very common" [3,6]. "Both types of the virus cause sub-clinical infection and thus many of those infected are oblivious of their infection status" [3].

"HSV-2 infection is one of the most common sexually transmitted infections (STIs), with the highest burden in Africa" [1]. "Although HSV-1 is most often transmitted through nonsexual contact, recent data from some developed countries indicate that a significant proportion of first-episode genital herpes is caused by HSV-1" [7]. "Genital infection with herpes simplex virus type 2 (HSV-2) facilitates the acquisition of HIV, both mutually reinforcing infection" [8]. "In fact, HIV percutaneous transmission is substantially facilitated by the co-existing STI [1]. Prevalent STIs, particularly HSV-2 are established risk factors for HIV acquisition and transmission" [1].

"Co-infection with hepatitis C virus (HCV) and HIV is common in certain populations" [9]. "Around 130 million infections of HCV with 3% overall prevalence are there worldwide [10]. There are approximately 4–5 million persons coinfected with HIV" [10]. According to Austin et al. [11], "HCV is a leading cause of both acute and chronic hepatitis worldwide". "While HCV seropositivity rates for voluntary blood donor populations are typically less than 1%, HCV antibody prevalences ranging from 10 to 90% have been recorded in hemodialysis patients, intravenous drug abusers, and individuals with various liver disorders" [11].

"Several studies have shown that there are higher levels of HCV in the blood of HIV-infected patients coinfected with the HCV following a rapid progression to liver diseases related to the HCV and a higher risk of liver disease and cirrhosis. HCV is now considered an adaptable

infection in HIV-infected people although it is not regarded as an HIV-defining illness. A 2017 systematic review and meta-analysis of 55 prospective studies reported that the risk of HIV acquisition was almost tripled in the presence of established (prevalent) HSV and HCV infections and quintupled in the presence of recently acquired (incident) HSV and HCV infections" [12]. "HSV infection is associated with an increased risk of both HIV transmission and acquisition" [13].

"There is considerable biological and epidemiological evidence that HSV-2 infection facilitates both acquiring and transmitting HIV" [14]. "Although most research on HSV-2 and HIV has been conducted in Africa, several studies indicate positive associations between HSV-2 and HIV in the United States" [14,15]. "Because HSV-2 is transmitted sexually but not through sharing drug injection equipment, it can be used as a biomarker for sexual risk of HIV" [14,16]. According to a Greek study (Panayiotakopoulos et al.), "anti-human herpes virus 8 (HHV-8) positive patients had a tendency to have higher rates of HCV infection" [17]. In HIV-1- positive people, the initial anti-HHV-8 status is not a predictive factor. According to Panayiotakopoulos et al., "a high seroprevalence in people with HEPS may be a reflection of their risk-taking lifestyle" [17].

Seroepidemiological studies are critical to understanding the pattern and distribution of infection within populations. Based on these facts, the study is therefore, undertaken to evaluate the prevalence of HSV and HCV among HIV-infected individuals on an anti- retroviral treatment programme in a tertiary care Teaching hospital in Awka, Anambra State, Nigeria.

2. MATERIALS AND METHODS

2.1 Study Area

This study was conducted among people living with HIV attending a tertiary care Teaching Hospital in Awka, Anambra State, Nigeria.

2.2 Eligibility Criteria

Inclusion criteria included all HIV-infected individuals (age above 16 years) presenting at the HIV unit of the hospital. Non-HIV-positive patients and minors (age below 16 years) were excluded from the study.

2.3 Study Population

Plasma samples were randomly collected from 100 HIV-infected individuals of which 42 were females and 58 were males. The samples were collected from the HIV Unit of the tertiary hospital in Anambra State. Samples were collected between November 2020 and March 2022. The study age and class boundary were between 16-25, 26-35, 36-45 and 46-55 years.

2.4 Sample Collection and Preparation

Five millilitres (5ml) of blood from each patient were aseptically collected during routine investigations so that the participants were not bled twice. The samples were collected into sterile EDTA bottles and plasma samples were obtained after centrifugation. Samples were appropriately labelled and stored in two aliquots at −20°C and −80°C until analysis.

2.5 Serological Analysis

The HIV status was reconfirmed by screening their blood samples for the reality of HIV-1, 2, O and P24 HIV-1 antibodies, using Alere Determine test strips (Alere, Japan) and ELISA (factory-made by DIA.PRO Diagnostic Bioprobes Srl, Milano – Italy). Blood samples drawn from participating HIV-infected individuals were assayed for Antibodies against HCV and anti-HSV-IgG and anti-HSV-IgM using enzyme-linked immunosorbent assay (ELISA by Dia. Pro, Italy), according to manufacturer instructions. HCV infection was considered to be present in subjects who tested positive for anti-HCV. The interpretation of test results was performed according to the manufacturer's specifications.

2.6 CD4 T Cell Count Enumeration

EDTA-treated blood samples were used for CD4 T cell count using Partec CyFlow® Counter (Partec GmbH, Germany), following the instruction of the manufacturer. The specimens were analyzed on a flow cytometer for the detection of cell surface markers for CD4 cells. Results were classified based on the CDC (1997) guidelines

2.7 Data Analysis

Statistical evaluation of the data was tabulated and the total percentage (%) of HCV and HSV prevalence was calculated based on each age boundary using SPSS. Calculated percentage prevalence was recorded accordingly, the result was determined and a conclusion was drawn.

3. RESULTS

Results showed an overall prevalence of HCV to be 4.0% seropositivity and HSV to be 0.0% with 100.0% seronegativity. Results of the prevalence of HCV and HSV in HIV-infected patients, Viral load and CD4 counts are presented in Table 1. Results of the present study show that the prevalence of HCV of 4.4% (16-25 years), 4.7% (26-35 years) and 4.0% (36 years & above) with a significant difference of $p < 0.05$. It showed that HCV antibody was only present among females (6.9%) and target not detected (TND) with 4.4%. Higher prevalence of HCV occurred among HIV-infected individuals having CD4 counts of >350 cells/mm3 than the <200 cells/mm3 and 200-249 cells/mm3 (0.0%) as shown in Table 1.

4. DISCUSSION

Herpes simplex virus type 2 (HSV-2) is a public health concern, particularly in developing countries, linked to an increased risk of HIV infection and transmission [18]. Defining the Prevalence level of HIV/HCV/HSV coinfections becomes pertinent, especially among groups at high risk of the infection. Multiple infections with HCV/HSV significantly exacerbated morbidity in HIV patients. In this study, zero prevalence was reported for HIV/HSV coinfections showing 100.0% seronegativity rate among HIV-infected individuals in Awka, Anambra State, Nigeria. The zero seroprevalence of HSV-2 IgM reported in this study similar to that of Alubi et al. who reported 0.0% for HIV/HSV coinfections in Port Harcourt, Nigeria [19]. Similar to the previous study in other different countries such as Egypt, Saudi Arabia, Brazil and Turkey [20-23].

This 0.0% reported here for HSV-1 and -2 IgG and IgM antibodies is lower than the 2.8% reported by Okonko et al. in Port Harcourt, Nigeria, [24] the 6.1% reported by Muhammad et al. in Northern Nigeria [18] and the 51.1% and 2.2% reported respectively, for IgG and IgM by Okonko et al. in Port Harcourt, Nigeria [25,26]. However, it is significantly lower than the results obtained by Nag et al. among HIV/HSV-2 coinfected individuals (34.6%) in Eastern India, [27] 46.1% by Hayatudeen et al. in apparently healthy individuals in Nigeria, [28] the 20.4% by Salman et al. among children under the age of five years (20.4%) in Iraq [29] and the 99.4% in a study conducted in Port Harcourt, Nigeria [30].

The 100.0% seronegativity reported here corroborated that of Alubi et al. who reported 100.0% seronegativity rate reported for HIV/HSV coinfections in Port Harcourt, Nigeria [19]. This seronegativity rate is substantially higher than the 48.9% reported by Okonko et al. and the 0.6% reported by Okonko and Cookey, both in Port Harcourt, Nigeria [25,30]. However, it is slightly higher than the 97.8% reported by Okonko et al. in a similar study [24,26].

A previous study in Nigeria by Irena et al. reported a prevalence of HCV coinfections [31]. This result is in support of similar studies carried out by Lacazari et al., (2017) who revealed that the highest number of tested HIV-positive patients was recorded in the same age boundary (26-35 years) and revealed that this age boundary is dominated by sexually active youth [32].

Table 1. Prevalence of HCV in HIV-infected patients

Variables	No. Tested	No. Positive for HCV (%)
Age Group (years)		
16 – 25	23	1(4.3)
26 – 35	43	2(4.7)
36 & above	34	1(2.9)
Sex		
Males	42	0(0.0)
Females	58	4 (6.9)
Viral Load (copies/ml)		
TND	90	4(4.4)
< 40 and above	10	0(0.0)
CD 4 Count (cell/mm^3)		
<200	18	1(1.5)
200 - 349	20	0(0.0)
>350	62	3(4.8)
Total	**100**	**4(4.0)**

This study reported a 4.0% prevalence of HCV and this agrees favourably with that of Elenwo et al. in selected areas of Rivers State, Nigeria [33] and that of Okonko and Ernest Nwagwu in another part of Rivers State, Nigeria [34]. It is comparable to 4.3% reported by Ugwu et al. in Anambra State, Nigeria [35]. This is higher than the 0.0% reported by Alli et al. in Ibadan, Nigeria [36], Okonko et al. [37,38] and Cookey et al. [39] in Port Harcourt, Nigeria, 0.4% reported in Ilorin, Nigeria [40], 0.5% in Ibadan [41], 1.3% in Onitsha, Anambra State [42], 1.0% in Port Harcourt [43] and 2.0% reported among children in Ibadan [44]. However, Okonko et al. [41] found no HIV-HCV coinfections in their study. The 4.0% reported here is below 23.5% reported in Abeokuta, Nigeria [45,46], the 22.5% in Port Harcourt [47], the 15.0% reported in Ughelli, Delta State, Nigeria [48], 11.7% among hospitalized US veterans [11] and 5.6% in Emohua LGA, Rivers State, Nigeria [34]. In a research done in the USA and Europe, patients who were coinfected with HIV and HCV had a prevalence ranging from 25.0% to 50.0% [10,49-50]. In a different study, 74.0% of HIV-positive people had HCV [10,51]. According to a study done in Iran, 68.0% of patients had both HIV and HCV coinfection [10,52]. A comparable study with 620 HIV-positive individuals in northern India found that 1.6% of HIV-positive patients also had HCV. [10,53] These prevalence studies were typically conducted in many regions of the world, therefore variations in the prevalence might be attributed to the kinds of risk groups, variations in geographic locations, and variations in the methods of exposure [10,54-56].

In similar studies carried out by Mertz et al., older age was not found to be a risk factor for hepatitis C virus infection as it has been previously described [57]. Those who were 30 years or younger had the highest prevalence of HCV antibody but age was not statistically significant. Males had a higher rate of HCV infection in their study but gender was not a significant risk factor in the study by Mertz et al. [57] This study found higher prevalence of HCV among age group 26-35 years. This similar to the observation of Ogbodo et al. who reported higher prevalence in age group 26 years and above in Ughelli, Delta State, Nigeria [48]. Abeni et al. reported higher prevalence in age group 20-30 years in Port Harcourt, Nigeria [58]. Ugwu et al. reported higher prevalence among ages 31 and 40 years [35,42]. Udeze et al. reported higher prevalence of HCV among age groups group below 40 years [59]. Okonko et al. reported prevalence of HCV among age groups group below 30 years in Abeokuta, Nigeria [60]. Elenwo et al. reported higher prevalence in ages 21-40 years [33]. However, Sule et al. reported higher prevalence of HCV among age groups >50 years [61] Okonko et al. reported higher prevalence in 40 years and above [41,47,62]. Other studies by Okonko and Shaibu [63] and Okonko and Ernest Nwagwu [34] reported higher prevalence in <40 years and <41 years, respectively. Ogwu-Richard et al. reported higher prevalence in age group 35-44 years in Abeokuta, Nigeria [46] Ojo et al. reported higher HCV prevalence in 55 years and above [45]. Also, Udeze et al. reported higher prevalence of HCV among age groups group above 20 years in Ilorin, Nigeria [64] while in 2015, Udeze et al. reported higher prevalence of HCV among age groups group < 20 years in Ilorin, Nigeria [40].

In this study, HCV antibody was found only in females. This observation agrees favourably with previous studies in Nigeria. Ugwu et al. reported HCV prevalence only among women in Onitsha, Anambra State, Nigeria [42] Sule et al. reported higher prevalence of HCV among females than males [61]. Also, Udeze et al. [64] and Okonko et al. [62] reported higher prevalence of HCV among females than males in Ilorin and Ibadan, respectively. Ogbodo et al. reported higher prevalence in females than in males in Ughelli, Delta State, Nigeria [48]. Okonko et al. also reported higher prevalence in females than males in Port Harcourt, Nigeria [47]. Okonko and Ernest Nwagwu also reported higher prevalence in females than males [34]. However, other studies reported somewhat different in Nigeria. Udeze et al. reported higher prevalence of HCV among males than females in Ibadan [59]. Okonko et al. reported prevalence of HCV only in males in Abeokuta and Ibadan, respectively [41,60]. Also in Ibadan, Nigeria, higher prevalence of HCV was reported in male children than in female children [44]. Ojo et al. reported a higher prevalence in males than females in Abeokuta, Nigeria [45]. Udeze et al. reported higher in males in Ilorin, Nigeria [40]. Ogwu-Richard et al. reported higher prevalence in males than females in Abeokuta, Nigeria [46]. Abeni et al. also reported higher prevalence in males than females in Port Harcourt, Nigeria [58]. Also, Elenwo et al. [33] as well as Okonko and Shaibu [63] reported higher prevalence in males.

Higher seropositivity of HCV occurred among HIV-infected individuals with CD4 cell counts 350

cells/ml than other categories. This observation corroborated that of Elenwo et al., Ugwu et al. and Okonko and Shaibu who reported higher prevalence in individuals with CD4 cell count 350-499 cells/µl. [33,35,42,63] This observation also deviated from the observation of Ogwu-Richard et al. in Abeokuta, Nigeria [46]. According to certain research, persons living with HIV have greater HCV-RNA levels when their CD4 counts are below 200/mm3, in contrast to those who have higher CD4 counts [10,65].

Most studies show a correlation between HIV infection and increased risk of end-stage liver disease, greater HCV viral levels, and persistent hepatitis B virus. Following co-infection with HIV, HCV-RNA levels rise [10,65]. Also, HCV antibody was found only in individuals with target not detected (TND) viral load. This result agrees with Ugwu et al. in related studies [35,42] This is a deviation from Okonko and Shaibu who reported higher prevalence among Individuals with vial load >10,000 copies/ml in Yenagoa, Baylesa State, Nigeria [63].

Regarding the effect of STIs on HIV-1 progression, the most studied interrelationship has been with HIV-1/HSV-2 coinfection, with recent studies showing that antiherpetic medications slow the time to CD4 <200 cells/mm3 and antiretroviral therapy among coinfected patients [2]. The impact of other chronic STIs (hepatitis B and C) on HIV-1 progression requires further study, but some studies have shown increased mortality rates [2]. According to a meta-analysis, patients who had both HIV and HCV coinfection were three times more likely than those who just had HCV infection to proceed to cirrhosis or decompensated liver disease [66,67], Patients with low CD4 T lymphocyte cell counts who also have HIV coinfection are even more at risk of progression [67]. Antiretroviral therapy (ART) appears to slow the rate at which HCV disease progresses in patients who also have HIV, but multiple studies have shown that this rate still surpasses that of patients who do not have HIV [67-69].

5. CONCLUSION

The study showed 4.4% seropositivity of HCV and 100.0% seronegativity of HSV in HIV-infected individuals with the highest prevalence of HCV recorded for age boundary 26-35 years. Thus, the study found that HCV was more common in HIV-infected than HSV in HIV-infected individuals. The increased number of HCV seropositivity among HIV-infected individuals indicates that there is a synergistic relationship between HIV and HCV infection. This study recommends that more attention should be given to the area of HIV/HCV coinfection in the management of infected patients.

CONSENT AND ETHICAL APPROVAL

Written consent of each participant was obtained before sample collection and the study was approved by the Research Ethics Committee of the Chukwuemeka Odimegwu Ojukwu University Teaching Hospital (COOUTH) in Awka, Anambra State, Nigeria.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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