Epidemiology and Coinfection Analysis in HIV-Infected Individuals Presenting at a Teaching Hospital in Bayelsa State, Nigeria

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Received: 26.02.2025 **Accepted: 04.04.2025** **Published: 04.04.2025**

Abstract:
Coinfections have a major impact on viral persistence and reservoirs in some ways. Coinfections can trigger immune cell activation, creating an environment favourable for HIV-1 persistence. This study aims to analyse the coinfection profiles of persons infected with HIV presenting at a tertiary hospital in Bayelsa State, Nigeria. A cross-sectional approach was employed in the study, and the study population was drawn from persons infected with HIV undergoing clinical monitoring at the Niger Delta University Teaching Hospital (NDUTH), Bayelsa State, Nigeria. A whole blood sample was collected from 200 consented subjects. Serological analysis of cytomegalovirus ((CMV), hepatitis B core antibodies (HBc) IgM, and herpes simplex virus 1 &2 (HSV 1&2) was carried out using commercially available enzyme-linked immunoassay (ELISA) kits. CMV IgG was detected in 169 samples and CMV IgM in 130 samples, representing 84.5% of HIV patients with persistent CMV coinfection and 65.0% with recent coinfection with CMV, respectively. Also, HBV core IgM was detected in 48 (24.0%), HSV IgG in 114 (57.0%), and HSV-IgM in 79 (39.5%) of the samples tested among the study subjects. Also, 189 representing 94.5% of the samples tested, were positive for either CMV, HBV, HSV, or all three viruses. Overall, the information and findings of this study provided fresh insight and knowledge on the current circulating HIV-1 coinfections with CMV, HBV, and HSV 1&2. Clinicians can leverage these findings to provide more individualistic care to HIV patients for better health outcomes and a reduction in the rate of transmission in the general population.

Keywords: **CMV, Coinfections, HBV, HSV 1 & 2, HIV-1, IgM, IgG**

1. INTRODUCTION

HUMAN Immunodeficiency virus-1 (HIV-1) is known to be the greatest pandemic of the twenty-first century, only dwarfed by COVID-19 in 2020-2021. HIV infection has stages of progression and the last level, called full-blown acquired immunodeficiency syndrome (AIDS) is characterised by a weak immune system, increased risk of opportunistic infection, and other sequelae leading to death if not properly treated. HIV, the causative agent of AIDS is a lentivirus belonging to the family – Retroviridae, this family of viruses has a unique enzyme called reverse transcriptase enzyme enabling the virus to manifest its distinctive identity. The HIV genome has multiple open reading frames and encoding for three important structural polyproteins, Gag (group antigen), Pol (polymerase), and Env (the envelope glycoproteins), and other accessory and regulatory proteins which aid in the virus to infect it host.

HIV-1 subtypes are responsible for the global pandemic of HIV infection [1,2] and as of 2021, approximately 38.4 million people worldwide were living with HIV [3,4]. HIV-1 shows high variability due to high mutation and recombination and selective host immune response pressure[5,6]. An estimated 39 million people are currently living with HIV and it is projected that by 2050, about 46 million people will be living with HIV[7]. Of the estimated 39 million living with HIV, about 65 % reside in sub-Saharan Africa, and only half of the new HIV infections were in sub-Saharan Africa, indicating greater progress at reducing infections in sub-Saharan Africa compared with other parts of the world[8].

HIV infection affects gender and age disproportionately. Currently, an estimated 42% of the global population affected by the disease consists of women, with more than 70% of them residing in sub-Saharan Africa. In total, about 25% of all newly acquired HIV-1 infections occur in individuals who are under the age of 25,[9] and worse off with other opportunistic and viral coinfections.

Coinfections have a major impact on viral persistence and reservoirs in some ways. For example, coinfections can trigger immune cell activation, creating an environment favourable for HIV-1 persistence. The presence of coinfections influences disease progression and response to antiretroviral therapy (ART) and understanding coinfection profiles is crucial for designing effective treatment options [10,11].

HIV-infected individuals coinfected with other pathogens such as hepatitis, cytomegalovirus, and herpes simplex viruses can result in a faster progression of HIV infection to full-blown AIDS, the coinfection further compromises immune function and increased viral load.[12]

Viral hepatitis is a major public health concern, as hepatitis B virus (HBV) afflicts an estimated 350 million people, and hepatitis C virus (HCV) affects 150 million people worldwide [13-17]. Both viruses are endemic in sub-Saharan

Africa where an estimated 75 million people (over 35 million in Nigeria) live with hepatitis B and/or C viruses [15, 17, 18].

Hepatitis B virus infection is associated with significant morbidity and mortality in patients with HIV infection [17, 19,20]. Coinfection of HIV with HBV affects several patients worldwide[17, 21].

Coinfection with HBV increases the risk for hepatotoxicity of HAART and the likelihood of onset of an AIDS-defining illness, compared with infection with HIV-1 alone.[17,22-24]

The prevalence of HBV varies markedly among different HIV-infected populations, but one of the major determinants is geographical location. In areas with low HBV endemicity, such as the United States, Australia, and Europe, HBV and HIV are usually acquired in adulthood through either sexual or percutaneous transmission. HBV is 100-fold more likely to be transmitted than HIV [17], thus, HBV infection often precedes HIV infection. In these low-endemicity areas, the prevalence of HBV coinfection is 5%-7% of HIV-infected individuals but varies depending on the route of infection.

The highest prevalence of coinfection is among men who have sex with men, ranging from 9%- 17% and the lowest prevalence is from heterosexual transmission. In countries with intermediate and high HBV endemicity, the principal routes of HBV transmission are perinatal or early childhood; thus, HBV infection usually precedes HIV infection by decades. In these countries, most studies show HBV coinfection prevalence of 10%-20%, but some show prevalence rates as low as 6%. [25-28]

In countries where HBV and HIV prevalence are high, HBV coinfection occurs in 10% to 70% of HIV-infected individuals. [17,29-33] A clearer picture of HIV and HBV prevalence in Africa is important to educate the population better and control these epidemics [17].

Human cytomegalovirus (CMV) infection has become a major public health problem throughout the world since its discovery[34]. It is a common infection among HIV-infected individuals and was a leading cause of significant opportunistic infections in HIV-infected patients before the introduction of highly active antiretroviral therapy (HAART).[35-38] Its contribution to morbidity and mortality became more apparent after HAART was introduced which improved survival among HIV-infected individuals. [38]

CMV is a ubiquitous virus that infects people of all ages, genders, and races.[34] CMV viremia indicates an active infection associated with end-organ diseases (EODs), such as retinitis.[37] Following primary infection, CMV enters a latent state and reactivates when the immune status changes [39]. It is a virus of paradoxes and can be a potential killer or a silent lifelong companion.[39]

In immunocompetent individuals, CMV exists in a symbiotic equilibrium and thus disease manifestations are uncommon [40]. However, in immunocompromised persons such as patients with human immunodeficiency virus (HIV), neonates, or through iatrogenic means following organ transplantation, CMV exerts its full pathogenic potential [41]. After primary infection, CMV disperses and becomes latent in multiple organs, and due to immunosuppression as in HIV patients, CMV reactivation occurs [42]. CMV infection is thus a common opportunistic viral infection [39]. A coinfection with CMV increases morbidity and mortality in human immunodeficiency virus (HIV) disease [43].

Herpes simplex type 2 (HSV-2) is a public health concern, particularly in developing countries, and is linked to an increased risk of HIV infection and transmission [44]. HSV-2 coinfection is associated with increased genital HIV shedding, which may increase the transmissibility of HIV [45]. HSV-1 and HSV-2 are ubiquitous. They rank among the most prevalent viral STDs (sexually transmitted diseases) worldwide [46.] They are now a significant health concern, confirmed by the epidemic of genital HSV and enhanced acquisition of HIV in association with HSV infections [47-53].

Epidemiologic studies suggest synergy between HIV-1 and HSV-2 that facilitates the spread of both viruses, with HSV-2 increasing HIV-1 susceptibility and infectiousness [54] and HIV-1 infection increasing HSV-2 reactivation frequency [55]. Viral STI and genital ulcer diseases, particularly HSV-2, are also linked to increased concentrations of HIV in blood plasma and genital fluids [56]. HSV-2 is implicated as a co-factor in HIV acquisition and transmission. It may contribute significantly to HIV infections by facilitating its spread among the low-risk population within a stable sexual relationship [57].

2. MATERIALS AND METHOD

2.1. Study Design and Population.

This study was cross-sectional in design. The ethical conduct of the work was approved by the Bayelsa State Ethics Committee at NDUTH. The patient's demographic information and past medical records were obtained through the administration of standardised questionnaires. The 200 HIV-1 patients included in this study were all members of the cohort of eligible patients who were HIV-positive. On the other hand, all subjects whose data were incomplete were excluded from the study

2.2 Laboratory Analysis

Plasma was analysed for the presence of HBc IgM, CMV 1gM and IgG, HSV 1&2 IgM and IgG at the University of Port Harcourt's Virus & Genomics Research Unit of the Department of Microbiology

2.2.1. HBc IgM Serological Analysis

The HBc IgM content of plasma samples was measured using a BioRad ELISA kit. The manufacturer's instructions were followed for conducting the analysis. Interpretation was done according strict the manufacturer's instructions. The results were interpreted using the sample OD450nm to cut-off value ratio and the following values: S/CO <0.9 is considered invalid, 0.9–1.1 is considered uncertain, and >1.1 is considered valid.

2.2.2 CMV IgM and IgG Analysis

All plasma samples were analysed for the presence of CMV IgM and IgG respectively using an ELISA kit manufactured by DIA PRO. The serologic test and reading adhered to the kit manufacturer's instructions. ELISA Kit (IgG for Cytomegalovirus) manufactured by DIA.PRO Diagnostic Bioprobes Srl via G. Carducci n027 20099 Sesto San Giovanni (Milano)-Italy was used to screen for CMV Specific-IgG antibody according to the manufacturer's instructions.

2.2.3 HSV 1 & 2 IgM and IgG Analysis

All plasma samples were analysed for the presence of HSV IgM and IgG respectively using an ELISA kit manufactured by Dia. Pro. The serologic test and reading adhered to the kit manufacturer's instructions. Plasma was analysed for HSV-2 IgG antibody using the ELISA kit manufactured by Dia. Pro Diagnostic Bioprobes, Milano – Italy. ELISA tests were performed according to the manufacturer's instructions.

2.3. Data analysis

Microsoft Excel version 2021 (Microsoft, USA) was utilised to evaluate the data. The statistical significance of every analysis was determined where appropriate using the Chi-square test or Fisher's exact test at a 5% significance threshold

2.4 Ethical consideration

The study was conducted after obtaining ethical clearance from the University of Port Harcourt Research Ethics Committee.

3. RESULTS

3.1. Analysis of Study Participants' Characteristics

The age range of the 200 HIV-1 positive patients who participated in the study was 5-69 years with a mean age of 35.3 years. Table 1. indicates by age that the age group 31-40 has the highest number of HIV infections, with 65 cases. This is closely followed by the age group 41-50 with 58 infections. Also, the middle-aged groups—age groups 21-30 and 51-60 show relatively moderate frequencies of 16 and 34 infections, respectively. The youngest age group (0-10) and the elderly group (>60) have lower frequencies of 5 and 9 infections, respectively. While the age group 11-20 shows a relatively low frequency of 13 infections.

By sex (Table 1), The data indicates that the number of HIV infections is significantly higher among females (133 cases) representing 67% of the study population compared to 67 males (33%). This could suggest that females are more vulnerable or exposed to factors that increase the risk of HIV infection in this population.

As shown in Table 1, the married category has the highest number of HIV infections, with 101 cases representing 50.5% of the infected study population. Closely followed were single Individuals with 80 cases representing 40% of the infected study population. Furthermore, lower Frequencies in the widowed, separated/divorced, and undisclosed categories were observed as follows 9, 6, and 4 infections, respectively.

Based on educational background, 34.0% of the study population comprised individuals with tertiary education and this was followed by 25.0% of individuals who did not want to disclose their educational status (Table 1). As shown in Table 1, the unemployed category has the highest number of HIV infections, with 95 cases representing 48.0% of the infected study population. This was followed by students with 37 cases representing 19.0% of the infected study population. Also, civil servants with 31 cases, which represented 15.0% of the infected study population. Furthermore, lower frequencies in the self-employed, business, traders, farmers, and undisclosed categories were observed as follows 8.0%, 5.0%, 1.0%, and 1.0% infections, respectively (Table 1).

3.2. Overall Seroprevalence of Coinfections

All 200 random samples selected were reconfirmed of their HIV-positive status. Further serological analysis was conducted to detect coinfections with HBV, HSV, and CMV. The overall viral coinfection was 94.5% as 189 out of 200 study participants were either coinfected with CMV, HSV, or HBV and/or all three, and only 5.5% (11 out of 200) were not infected by either CMV, HSV, or HBV (Figure 1). Furthermore, the study showed a prevalence rate of 84.5% (n=169) for CMV, 57.0% (n=114) for HSV, and 24.0% (n=48) for HBV, respectively (Table 1).

Table 1: Prevalence of CMV IgG& IgM, HBc IgM, HSV 1&2 IgG and IgM to sociodemographic Characteristics of HIV-Infected Participants

Variables	No. Tested (%)	CMV IgG (%)	CMV IgM (%)	HBc IgM (%)	HSV IgG (%)	HSV I gM (%)
Age groups						
0-10	5(2.50)	5(100.0)	3(60.0)	1(20.00)	2(40.00)	3(60.00)
11-20	13(6.50)	9(69.23)	7(53.84)	1(7.69)	5(38.46)	4(30.77)
21-30	16(8.00)	15(93.75)	15(93.75)	5(31.25)	7(43.75)	6(37.50)
31-40	65(32.50)	55(84.62)	41(63.08)	14(21.54)	36(55.39)	32(49.23)
41-50	58(29.00)	47(81.04)	34(58.62)	16(27.58)	32(55.17)	20(34.48)
51-60	34(17.00)	30(88.24)	24 (88.24)	11(32.35)	27(79.41)	11(32.35)
Above 60	9 (4.50)	8(88.88)	6(66.67)	0(0.0)	4(44.44)	3(33.33)
Chi-square analysis		χ^2 = 5.295 p= 0.507	χ^2= 8.200 p= 0.224	χ^2= 7.168 p=0.306	χ^2=11.257 p=0.081	χ^2= 5.374 p= 0.497
Gender						
Males	67(33.50)	53(79.11)	40(59.70)	15(22.39)	45(67.16)	29(43.28)
Females	133(66.50)	116(87.22)	90(67.67)	33(24.81)	69(51.87)	51(38.34)
Chi-square analysis		χ^2 = 2.238 p=0.135	χ^2= 1.243 p= 0.265	χ^2= 0.145 p= 0.703	χ^2 =4.247 p=0.039	χ^2= 0.453 p= 0.50

Table 1 Contd.

Variables	No. Tested (%)	CMV IgG (%)	CMV IgM (%)	HBc IgM (%)	HSV IgG (%)	HSV I gM (%)
Marital status						
Singles	80(40.00)	67(83.75)	53(66.25)	19(23.75)	41(51.25)	35(43.75)
Married	101(50.50	84(83.12)	63(62.38)	25(24.75)	61(60.40)	42(41.58)
Separated/Divorced	6(3.00)	5(83.33)	4(66.67)	2(33.33)	5(83.33)	2(33.33)
Widowed	9(4.50)	9(100.00)	7(77.77)	2(22.22)	5(55.55)	2(22.22)
Undisclosed	4(2.00)	4(100.00)	3(75.00)	0(0)	2(50.00)	0(0.00)
Chi-square analysis		χ^2 = 2.56 p= 0.633	χ^2= 1.191 p=0.880	χ^2 =1.601 p= 0.809	χ^2= 3.339 p=0.503	χ^2= 4.499 p= 0.343
Education						
None	20(10.00)	18(90.0)	17(85.00)	9(45.00)	13(65.00)	9(45.00)
Primary	16(8.00)	13(81.25.0)	8(50.00)	4(25.00)	7(43.75)	9(56.25)
Secondary	46(23.00)	37(80.43)	28(80.43)	6(13.04)	24(27.22)	17(36.96)
Tertiary	68(34.00)	57(83.82)	43(63.23)	22(32.35)	40(58.82)	20(29.41)
Undisclosed	50(25.00)	44(88.00)	33 (66.00)	7 (1.4)	30(60.00)	17(34.00)
Chi-square analysis		χ^2 = 1.694 p= 0.792	χ^2= 5.503 p=0.240	χ^2=13.378 p= 0.010	χ^2 = 1.913 p = 0.752	χ^2= 4.938 p= 0.294
Occupation						
Students	37(18.50)	27(72.97)	20(54.06)	3(8.11	18(48.64)	17(45.95)
Unemployed	95(47.5)	84(88.42)	74(77.89)	28(29.47)	53(55.79)	42(44.21)
Civil servants	31(15.50)	29(93.55)	15(48.39)	8(25.81)	15(48.39)	10(32.26)
Trading/Business	27(13.5)	8(29.63)	6(22.22)	7(25.92)	5(18.52)	1(3,70)
Artisans/Farmer	6(3.00)	4(66.67)	2(33.33)	1(16.67)	4(66.67)	0(0.00)
Undisclosed	4(2.00)	3(75.00)	2(50.00)	0(0.00)	3(75.00)	1(25.00)
Chi-square analysis		χ^2 = 47.202 p=0.0001	χ^2= 32.798 p=0.0001	χ^2 = 8.327 p= 0.139	χ^2=13.629 p= 0.018	χ^2=20.462 p= 0.001
Total	**200(100.0)**	**169(84.50)**	**130(65.00)**	**48(24.00)**	**114(57.00)**	**80(40.00)**

3.3. Overall Prevalence of Cytomegalovirus IgM and IgG Antibodies

Among the 200 HIV-infected individuals investigated for possible coinfection with CMV, 169 (84.5%) were found to be seropositive for Cytomegalovirus IgG antibody and 130 (65%) for CMV IgM respectively. While there was no significant association between CMV IgG and IgM prevalence with age groups, sex, educational status, and marital status, there was a significant association between CMV IgG and IgM prevalence among participants with occupation ($\chi2$ = 47.202, p = 0.0001 for IgG and $\chi2$= 32.798, p =0.0001 for IgM, respectively (Table 1).

3.4. Overall Prevalence of HBc IgM Antibody

Among the 200 HIV-infected individuals investigated for possible coinfection with HBV, 48(24.0%) were seropositive for HBc IgM antibody. While there was no significant association between HBc IgM prevalence with age groups, sex, marital status, and occupation, there was a significant association between HBc IgM prevalence among participants with educational status ($\chi2$ = 13.378, p=0.010) as shown in Table 1.

3.5. Overall Prevalence of HSV 1&2 IgG Antibody

Among the 200 HIV-infected individuals investigated for possible coinfection with HSV 1&2, 114 (57.0%) were found to be seropositive for HSV 1& 2 IgG antibodies and 80 (40.0%) for HSV 1&1 IgM respectively. While there was no significant association between HSV 1&2 IgG and IgM prevalence with age groups, sex, educational status, and marital status, there was a significant association between HSV 1&2 IgG and IgM prevalence among participants with occupation ($\chi2$ = 13.629, p=0.018 for IgG and $\chi2$= 20.462, p=0.001 for IgM, respectively (Table 1).

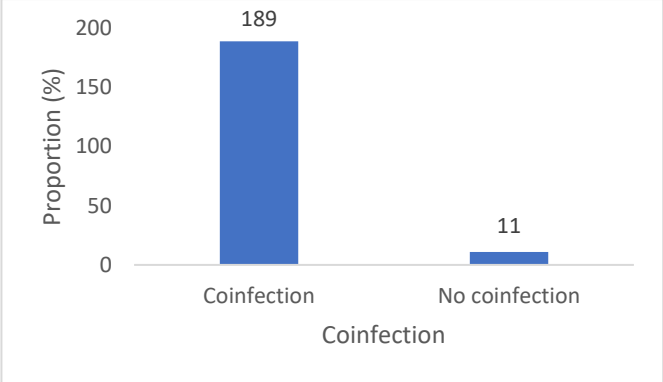

Figure 1: Proportion of study participants with coinfections

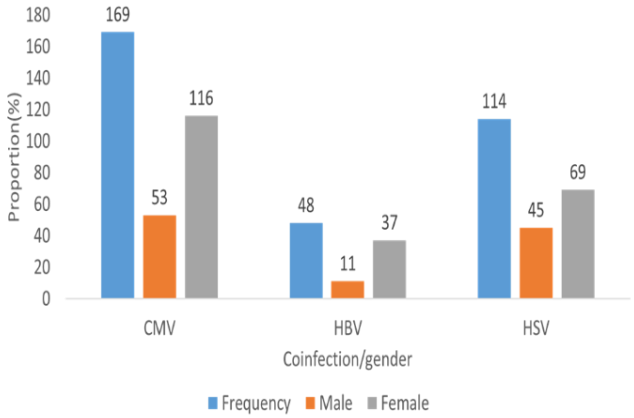

Figure 2: Distribution of HIV-1 coinfection with CMV, HBV and HSV

4. DISCUSSION

This study analysed the coexistence of hepatitis B virus, cytomegalovirus, and herpes simplex virus 1& 2 among people living with HIV-1 attending a tertiary hospital located in Bayelsa State, Nigeria. Many (67.5%) of the study participants were females while 33.3% were males. This observation agrees with [58] and [59,60] who also found most HIV-infected subjects to be females.

Females are at higher risk of HIV in developing nations, particularly in Sub-Saharan Africa, as evidenced by the larger percentage of females found in the study [60]. Also, based on the findings by the NAIIS in 2019 reported that more females (1.9%) than males (0.9%) were living with HIV in Nigeria [61].

Coinfection plays a key role in HIV disease progression, Cytomegalovirus infection is overlooked in most clinical settings, even though it can lead to more serious health conditions, particularly in immunocompromised patients. When coupled with HIV infection, it down-regulates the immune system. Assessing the coinfection's effect on the immune system becomes pertinent. This study found a high CMV IgG seroprevalence of 84.5% among HIV patients attending NDUTH which is significant and reflects the level of overall infection burden among this cohort of HIV-infected patients in Bayelsa State. This showed that the HIV patients were at high risk of CMV coinfection [62]. This observation is comparable to the findings of [63] who found 100.0% CMV seroprevalence among HIV patients in Nigeria and [64] who obtained 100.0% seroprevalence among HIV-1 infected street children at Nyumbani Children's Home in Kenya [64]. Also, it is similar to other reports from Africa; 97.2% in Benin [65], and 96.0% in Egypt [66].

This prevalence rate is slightly lower than that reported by other researchers from different parts of Nigeria. Fowotade [67] reported 93.9% seroprevalence among HIV patients in Ilorin. Umeh[68] found a seroprevalence of CMV IgG of 93.3% in Benue State. Elsewhere outside the country, a seroprevalence of 90.0%-100.0% has been reported in India [69, 70], 89.0% [34] and 77.3% by [62] in Kenya, 87.0% by [71] in the Gambia, 87.0% by [72] in Tanzania, 86.4% by [73] in South Africa, 77.3% by [62] in Kenya, and 77.2% by [74] in Sudan.

The overall prevalence of HSV among HIV-infected individuals was 57% (40% for IgM and 57% for IgG) which contrasts with coinfection rates of 2.4% found in a study of high-risk groups in India [75], 2.8% for IgM and 99.4% for IgG antibodies in a study conducted in Nigeria [76,77], 6.1% in Northern Nigeria [44] and the 2.2% reported for IgM and 51.1% reported for IgG antibodies in our previous studies in Nigeria [78].

Hepatitis B virus (HBV) coinfection in people living with HIV is a serious public health concern, as it significantly increases the risk of liver disease and accelerates HIV disease progression. In Nigeria, hepatitis coinfection is linked with increased morbidity and mortality [79]. In this study, a coinfection HBC prevalence rate of 40% was observed. This was much higher than the 3.1% prevalence reported by [80], 2.0%, and 4.1% reported by [81] and [82]. Other works also reported a lower prevalence of 6.3%, 6.7%, 7.5%, and 13.1% by [83-85], respectively.

5. CONCLUSION

The study found a high prevalence of viral coinfections among HIV-infected individuals. Cytomegalovirus (CMV) had the highest rate, with 84.5% showing persistent infections and 65% recent infections. Hepatitis B Virus (HBV) was present in 24% of participants, and Herpes Simplex Virus (HSV) affected 57% (persistent) and 39.5% (recent). Overall, 94.5% of the participants had at least one coinfection. The detection of CMV and HSV 1gM and IgG demonstrate recent and persistent infection, which could further weaken the host immunity and further act as enablers of other opportunistic infections.

Hepatitis B Virus (HBV) was present in 24% of participants. Herpes Simplex Virus (HSV) affected 57% (persistent) and 39.5% (recent). 11 study participants representing 5.5% of the 200 samples tested for coinfections were negative. It was observed that they all had low viral load and sufficient levels of CD4 cells. The study found a high prevalence of viral coinfections among HIV-infected individuals. Cytomegalovirus (CMV) had the highest rate, with 84.5% showing persistent infections and 65% recent infections. Hepatitis B Virus (HBV) was present in 24% of participants, and Herpes Simplex Virus (HSV) affected 57% (persistent) and 39.5% (recent). Overall, 94.5% of the participants had at least one coinfection.

Acknowledgements

The authors appreciate everyone who agreed to participate in the study and the administration of the Niger Delta University Teaching Hospital, Bayelsa State, Nigeria, for their approval.

Disclosure of conflict of interest

The authors claim that there are no conflicting interests.

Statement of ethical approval

All authors declare that all experiments have been examined and approved by the University of Port Harcourt Research Ethics Committee. Therefore, the study is performed following the ethical standards

Statement of informed consent

All authors declare that informed consent was obtained from all individual participants included in the study.

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