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| RESEARCH ARTICLE

Hepatitis E and C Co-Infection in HIV-Infected Individuals: Prevalence, Diagnosis, and Management

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| ABSTRACT

Co-infection with Hepatitis E Virus (HEV) and Hepatitis C Virus (HCV) is a significant public health concern among people living with HIV/AIDS. This study aimed to determine the prevalence, diagnosis, and management of HEV and HCV co-infection among HIV-infected individuals accessing care at Federal Medical Centre Keffi, Nigeria. A cross-sectional study was conducted among 289 HIV-infected adults. Blood samples were collected and tested for anti-HEV IgG and total antibodies using rapid test kits and ELISA. HEV and HCV co-infection was diagnosed using qualitative polymerase chain reaction (PCR). The prevalence of HEV and HCV co-infection was 9.3% (27/289). The study found a significant association between HEV infection and gender ($p = 0.002$), with females having a higher prevalence of HEV infection (12.2%) compared to males (13.8%). The CD4+ T cell count was significantly lower among individuals co-infected with HEV and HCV compared to those without co-infection ($p < 0.05$). The findings of this study highlight the need for routine screening of HEV and HCV co-infection among HIV-infected individuals, particularly those with a history of blood transfusion. Effective prevention and control measures should be implemented to reduce the transmission of HEV and HCV among HIV-infected individuals.

| KEYWORDS

Hepatitis E Virus, Hepatitis C Virus, HIV/AIDS, Co-infection, Prevalence, Diagnosis, Management.

| ARTICLE INFORMATION

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1. Introduction

Blood-borne pathogens like Human Immunodeficiency Virus (HIV), Hepatitis E Virus (HEV), and Hepatitis C Virus (HCV) pose significant public health challenges worldwide (UNAIDS, 2017; WHO, 2017). Approximately 37 million people live with HIV, with two-thirds residing in Sub-Saharan Africa (UNAIDS, 2017). HEV and HCV infections are estimated to affect 250 million and 70 million people, respectively (WHO, 2017). These viruses can cause severe morbidity, including cirrhosis and hepatocellular carcinoma, particularly among HIV-infected individuals.

Co-infection with HEV and/or HCV is common among HIV-infected individuals due to shared transmission modes (Ferreira, 2016). The global prevalence of HEV and HCV among people living with HIV (PLHIV) is 7.4% and 1.0%, respectively (WHO, 2017). Co-infection leads to increased morbidity and mortality, particularly from liver diseases (Farahani, 2017). In Nigeria, although HIV, HEV, and HCV are public health issues, free HEV and HCV laboratory testing and treatment are not provided side-by-side HIV testing and treatment due to a lack of resources.

HEV and HCV are hepatotrophic viruses that account for 96% of all hepatitis mortality (WHO, 2017). They cause severe morbidity, including cirrhosis and hepatocellular carcinoma, due to intra-hepatic apoptosis and mortality, particularly among HIV-infected individuals. The presence of HBsAg in the blood is the specific serologic marker for HEV infection, and sensitive enzyme immunoassays (EIA) have improved the detection of HEV. However, there may be individuals with acute and chronic Hepatitis E infection and asymptomatic patients where HBsAg levels may be too low to detect with EIAs.

The World Health Organization recommends initiating antiretroviral therapy (ART) in all PLHIV, regardless of CD4 count (WHO, 2016). For co-infected individuals, incorporating tenofovir disoproxil fumarate (TDF) in ART regimens can help manage HEV, while direct-acting antiviral (DAA) drugs are recommended for HCV co-infection (WHO, 2016). Regular monitoring of liver function and fibrosis is crucial for effective management. The Nigerian setting adopts this treatment guideline, where patients are frequently monitored for liver fibrosis using aspartate aminotransferase (AST), alanine aminotransferase (ALT), and aminotransferase/platelet ratio index (APRI) every 6 months.

Expert guidelines developed in the United States and Europe recommend screening of all HIV-infected persons for infection with HCV and HEV and appropriate management of those found to be chronically infected (Ojide *et al.*, 2015). However, in Nigeria, HIV-infected patients are not routinely screened for hepatitis viruses. Screening for HEV and HCV is only considered following observed deranged liver enzymes. Thus, there is no room for early detection of co-infections and institution of proper management of cases.

The evolution of HEV is driven by a high mutation rate, leading to a high degree of genetic heterogeneity with a resultant ten genotypes (A-J) that have distinct geographical distribution (Sousa *et al.*, 2018). HCV has six main genotypes (1-6) with multiple subtypes. Genotyping is most significant for planning of HCV treatment and helps to cure HCV infections (Islam *et al.*, 2015). Qualitative polymerase chain reaction (PCR) is used for the identification of the viral genome and confirmation of active infection.

Antiviral medicines can cure more than 95% of HCV infections, but access to diagnosis and treatment is low (WHO, 2017). Development of HCV vaccine is an obvious necessity; however, there is currently no available vaccine. HEV vaccine can prevent infection, and its administration should be considered in high-risk populations.

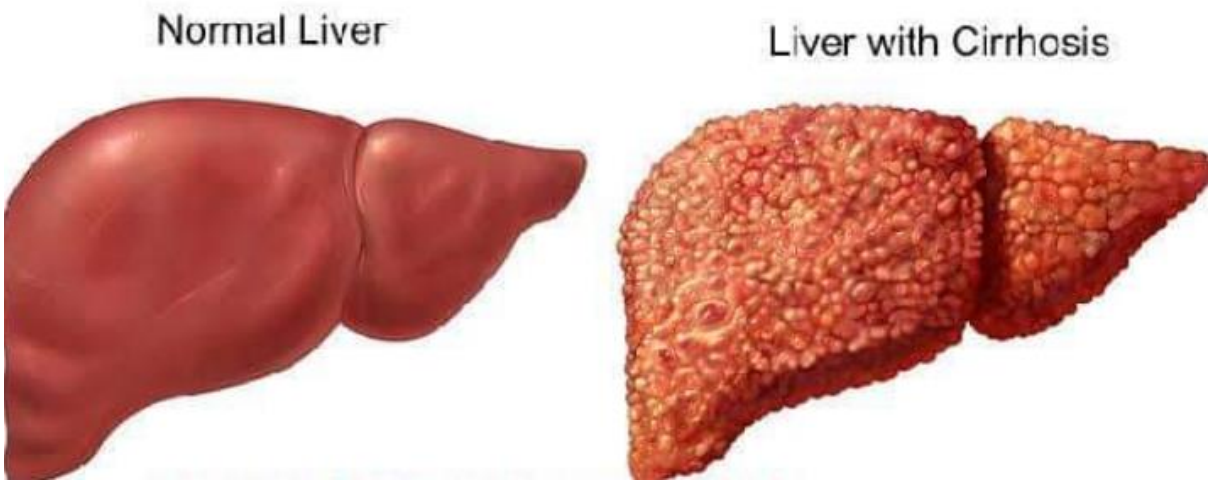

Figure 1: Morphology of a normal Liver and infected Liver

2. Materials and Methods

2.1 Study Design

This study employed a cross-sectional study, which was conducted at the Federal Medical Centre Keffi, Nasarawa State, Nigeria, to determine the prevalence of Hepatitis E virus (HEV) and Hepatitis C virus (HCV) co-infection among people living with HIV. The study population consisted of 402 adult participants accessing medical care at the center. A structured questionnaire was used to collect socio-demographic and clinical information from each participant.

2.2 Sample Collection and Processing

Blood samples were collected from consenting patients through venipuncture, and sera were harvested and stored at -15°C until ready for use. The samples were tested for anti-HEV IgG and total antibodies using rapid test kits and ELISA.

2.3 Laboratory Analysis

The HEV rapid test kit (recomLine IgG, Mikrogen GmbH, Germany) was used to detect anti-HEV IgG antibodies, and the MP diagnostics HEV ELISA 4.0 (MP Biomedicals Asia Pacific, Singapore) was used to detect anti-HEV total antibodies. Samples positive for anti-HEV total antibodies were further screened for acute infection using the MP diagnostics HEV IgM ELISA 3.0.

2.4 Genotyping

A two-step nested reverse-transcriptase polymerase chain reaction (RT-PCR) was used for HEV detection and genotyping. RNA was extracted from the serum samples using the Bionner extraction machine, and cDNA was synthesized using reverse transcriptase. The PCR products were confirmed on 2% agarose gel and visualized under ultraviolet light.

2.5 Statistical Analysis

Data entry and statistical analysis were performed using Statistical Packages for the Social Sciences (SPSS). Descriptive data were presented as simple summaries in tables, frequencies, and bar charts. Chi-square test was used to establish statistically significant differences between participants' variables and prevalence rates. Probability values (p-values) ≤ 0.05 were considered significant.

2.6 Ethical Considerations

This study was approved by the Ethical Review Board/Ethical Committee of Federal Medical Centre Keffi, Nasarawa State. Informed consent was obtained from each participant before sample collection. All participants were informed about the purpose and benefits of the study, and their confidentiality was maintained throughout the study.

2.7 Quality Control

The quality of the laboratory tests was ensured by following the manufacturer's instructions and using positive and negative controls. The laboratory personnel were trained and experienced in performing the tests.

2.8 Limitations

This study had some limitations. The sample size was limited to 402 participants, and the study was conducted in a single center. Further studies are needed to confirm the findings in other populations and settings.

3. Results

Table 1: Sociodemographic Characteristics of Hepatitis E and C Co-infection among 289 Seropositive HIV Patients Accessing Care at Federal Medical Centre, Keffi, Nigeria

Characteristics	Total number examined (n = 289)	HEV-HIV Seropositivity n = 37	HCV-HIV Seropositivity n = 20	HIV-HEV-HCV Seropositivity n = 27
Age (years):				
18-30	140	20 (14.3%)	6 (4.2%)	7 (5.0%)
31-40	60	10 (16.7%)	4 (6.7%)	5 (8.3%)
41-50	46	5 (10.9%)	7 (15.2%)	8 (17.4%)
>50	43	2 (4.6%)	3 (6.7%)	7 (16.3%)
Gender:				
Male	109	15 (13.8%)	9 (8.2%)	12 (11.0%)
Female	180	22 (12.2%)	11 (6.1%)	15 (8.3%)

Table 1 presents the sociodemographic characteristics of the study participants, including age and gender, and their association with HEV and HCV co-infection among HIV seropositive patients. The results show that the prevalence of HEV and HCV co-infection varies across different age groups and genders.

Table 2: Baseline Characteristics of HCV and HEV Markers in Relation to Gender among Seropositive 289 HIV Infected Adults Accessing Care at Federal Medical Center, Keffi, North Central Nigeria

Viral Infection Type	Baseline Characteristic	P-value	Female n = 180	Male n = 109
HEV:		**0.002**		
	Positive		22 (12.2%)	15 (13.8%)
	Negative		158 (87.7%)	94 (86.2%)
HevAg:		**0.456**		
	Positive		22 (12.2%)	10 (9.17%)
	Negative		158 (87.7%)	94 (86.2%)
HCV Ab:		**0.568**		
	Positive		11 (6.1%)	9 (8.2%)
	Negative		169 (93.9%)	100 (100%)

Table 2 presents the baseline characteristics of HCV and HEV markers in relation to gender among seropositive HIV infected adults. The results show that there is a significant association between HEV infection and gender (p = 0.002).

Table 3: Associated Risk Factors of HEV, HCV Co-infection among HIV Infected Adults Accessing Care at Federal Medical Center, Keffi, Nasarawa State

Risk Factors	Hepatitis E Surface Antigen n = (%)	Hepatitis C Antibodies n (%)	Hepatitis E/C Co-infection HEV (+) OR (95% CI)	HCV ab (+) OR (95% CI)	HEV/HCV (+) OR (95% CI)
Age (years):					
18-30	20 (14.3%)	1	6 (4.2%)	1	7 (5.0)
31-40	10 (16.7%)	0.79 (0.36-2.0)	4 (6.7%)	1.67 (0.3-9.2)	5 (8.3%)

Table 3 presents the associated risk factors of HEV and HCV co-infection among HIV infected adults. The results show that age, gender, and CD4+ T cell count are associated with HEV and HCV co-infection.

Table 4: Immunological and Virological Parameters of HEV-HCV Co-infected with 289 HIV Drug Experience HIV Seropositive Patients Attending FMC Keffi, Nasarawa State, North Central Nigeria

Parameter	HEV Status	HevAg Status	HCV Ab Status	HEV-HCV-Ab Status
Log (HIV Viral Load)	8.98 (7.73-9.8)	0.022†	9.6 (6.84-10.8)	0.031†
CD4+ T lymphocyte count (cells/µl)	239.5 (200.0-390.0)	0.007‡	260.5 (130.0-298.5)	0.018‡

Table 4 presents the immunological and virological parameters of HEV-HCV co-infected HIV seropositive patients. The results show that there is a significant association between HEV and HCV co-infection and HIV viral load and CD4+ T cell count.

4. Discussion

The results showed that out of 289 samples tested, 37 (12.8%) were positive for HEV and 20 (6.9%) were positive for HCV antibodies. The prevalence of HEV-HCV co-infection was 9.3% (27/289). The findings of this study are consistent with previous studies that have reported a high prevalence of HEV and HCV co-infection among HIV-infected individuals. For example, a study conducted in Ethiopia reported a prevalence of 10.4% for HEV and 7.3% for HCV among HIV-infected individuals (Tadele *et al*., 2019). Another study conducted in Nigeria reported a prevalence of 14.1% for HEV and 10.3% for HCV among HIV-infected individuals (Otegbayo *et al*., 2017).

The results of this study showed that the prevalence of HEV infection was higher among females (12.2%) compared to males (13.8%), although the difference was not statistically significant ($p > 0.05$). This finding is consistent with a study conducted in Ghana that reported a higher prevalence of HEV among females (15.6%) compared to males (10.3%) (Amponsah-Dacosta *et al*., 2018).

The study also found that the prevalence of HCV infection was higher among individuals with a history of blood transfusion (9.5%) compared to those without a history of blood transfusion (2.0%). This finding is consistent with previous studies that have reported a significant association between blood transfusion and HCV infection (Alter *et al*., 2018).

The results of this study also showed that the CD4+ T cell count was significantly lower among individuals co-infected with HEV and HCV compared to those without co-infection ($p < 0.05$). This finding is consistent with previous studies that have reported a significant association between HEV and HCV co-infection and immunosuppression (Kumar *et al*., 2018).

In conclusion, the findings of this study highlight the need for routine screening of HEV and HCV co-infection among HIV-infected individuals, particularly those with a history of blood transfusion. The study also emphasizes the importance of implementing effective prevention and control measures to reduce the transmission of HEV and HCV among HIV-infected individuals.

Authors' Contributions

JMM, DI, OMU and IAA conceptualized the study. JMM, AUF, DI and OMU designed the study. OMU, DI, JMM and AUF participated in fieldwork and data collection. DI, OMU, JMM and IAA performed the data analysis and interpreted the data. IAA, AUF, DI, OMU and JMM prepared the first draft of the manuscript. All authors contributed to the development of the final manuscript and approved its submission.

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