Short Communication

Hepatitis Delta Virus Infection among HIV/HBV and HBV-mono Infected Patients in Jos, Nigeria

Joseph Anejo-Okopi[1*], Jennifer Ifeoma Okpara[1], James Mogoret Dabol[1], Joshua Adetunji[1], David Adeniyi[2], David O. Amanyi[3], Otobo I. Ujah[4], Veronica David[1], Patience Omaiye[5] and Onyemocho Audu[6]

[1]Department of Microbiology, University of Jos, Jos, Nigeria; [2]APIN Public Health Initiatives, Abuja, Nigeria; [3]Department of Family Medicine, University of Jos, Jos, Nigeria; [4]Department of Obstetrics and Gynecology, Jos University Teaching Hospital, Jos, Nigeria; [5]Department of Medicine, Jos University Teaching Hospital, Jos, Nigeria, [6]Department of Epidemiology and Community Health, Benue State University, Makurdi, Nigeria.

Abstract | Globally, over 20 million of hepatitis D virus (HDV) are coinfected with Hepatitis B virus, which has an estimate of 350 million infected individuals. The study aimed to determine the prevalence of HDV infection in HBV/HIV and HBV-mono infected patients in Jos, Nigeria. This cross-sectional study was conducted on ninety (45 HBV/HBV and 45 HBV-mono) infected patients with chronic hepatitis B attending the hepatitis clinics of the two tertiary hospitals (Plateau State Teaching Hospital and HIV treatment center, at Jos University Teaching Hospital), Jos Metropolis from September to December 2018. The anti-HDV antibodies (IgM) were assayed using enzyme-linked immunosorbent assay HDV IgM ELISA Kit (MyBiosource, Inc, USA). The result was interpreted according to manufacturer's instructions. Ninety HBsAg positive patient were included (45 HBV/HIV, and 45 HBV-mono infected patients), 36 (40.0%) males, and 54 (60.0%) were females, with the overall mean age of 38.7 ±13years. However, the mean age was higher (36±13.1 years) in the HBV/HIV as compared to HBV-mono (40.6 ±12.7 years) infected patients. The mean age of patients was 36,92 ± 15,35 years. One hundred and three (63.6%) of them were males and 59 (36,4%) were females. Ten (11.1%) of patients were positive for anti-HD antibodies. the infection among the HBV/HBV was 13.3% and HBV-mono 8.9%. In the statistical analysis, the HBV-mono infected; age (p=.037), marital status (p=.001), cigarette smoking (p=.022) and condom use (p=.04) were significantly related to HDV infection. The study demonstrated high prevalence of HDV infection, which is imperative for policy makers and health care providers to strengthen the prevention measures for HDV, including the use of HBV prevention vaccine. Also, it is important to screen chronic HBV patients for HDV for early detection to avert subsequent development of end stage liver disease. Furthermore, larger studies are needed to gain better understanding of the HDV infection among chronic hepatitis B patients in endemic regions and other high-risk populations.

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***Correspondence** | Joseph Anejo-Okopi, Department of Microbiology, University of Jos, Jos, Nigeria; **Email:** josephokopi@yahoo.com
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Introduction

Hepatitis delta virus (HDV) is the smallest infectious RNA agent, that causes severe form of viral hepatitis in humans. It originates from vertebrates and the only member of the Deltaviridae family, genus Deltavirus. The genome consists of a single, minus-strand, circular RNA, approximately 1700 nucleotides

in length (Wang et al., 1986; Botelho-Souza et al., 2017). HDV is a defective RNA virus that requires the presence of the hepatitis B virus (HBV) surface antigen (HBsAg) to effectively infect the hepatocytes (Rizzetto et al., 1980). The genetic analysis of HDV isolates sowed three major genotypes, designated as I, II, and III, the prevalence of HDV infection varies global distribution depending on the prevalence of HBV infection as a risk factor (Rizzetto and Ciancio, 2012; Hung et al., 2014). Approximately 5% of HBV carriers are coinfected with HDV, leading to about 15 million persons infected with HDV globally (Rizzetto and Ciancio, 2012). The majority of HDV routes of transmission are through parenteral and sexual routes (Hughes et al., 2011), which are also shared routes for human immunodeficiency virus (HIV) transmission. Although injection drug users (IDUs) have a significantly higher prevalence of HDV infection than non-injection drug users, suggesting that HDV is more efficiently transmitted by injections of contaminated blood than by sexual intercourse (Calle Serrano et al., 2012).

The HDV infection has been considered to be one of the most important complication of HBV infection with few treatment options available (Heidrich et al., 2013). HBV/HDV coinfection have a significantly increased risk for end stage liver diseases including hepatocellular carcinoma than patients with HBV-mono infection and the general population (Ji et al., 2012; Hung et al., 2018). HDV infection occur in patients with chronic HBV infection (superinfection) but can also occur simultaneously with acute HBV infection in patients without preexisting HBV infection (coinfection), (Wedemeyer and Manns, 2010). The HDV superinfection mostly leads to rapid chronic liver disease progression resulting in hepatic failure, and death without timely medication. Although with the availability of combined antiretroviral therapy (cART), which have improved the survival of HIV-infected patients significantly, and many HIV/HBV coinfected patients may develop late liver related complications including death. However, whether the same is true for HIVHBV/HDV and HBV/HDV coinfection remains largely unclear due to paucity of data on HDV infection and disease severity. We aimed to determine the prevalence and factors associated with HDV infection among HIV/HBV-coinfected HBV-mono infected patients in Jos, Nigeria.

Materials and Methods

This was a cross-sectional and hospital-based descriptive study, carried out on 95 HBsAg positive (HIV/HBV and HBV mono-infected) patients that were recruited from Gastroenterology Unit of Plateau State Specialist Hospital and HIV treatment center of Jos University Teaching Hospital from September 2018 to December 2018. The study was among consenting adult patients aged 18-60 years attending both clinics, after obtained ethical approval from the 'Ethics Committee' boards of the hospitals. The written consent of all the participating subjects were obtained before the collection of blood samples, and those who did not give consent were excluded. The Bio data of each consenting patients were collected with a well-constructed questionnaire. Venous 4 ml blood samples were drawn from all patients into plain specimen tubes, centrifuged at 3000rpm for five minutes, the serum was separated into well labelled cryovials, and then stored at -20°C for anti-HDV (IgM) by Enzyme-Linked Immunosorbent Assay (ELISA), HDV IgM ELISA Kit (MyBiosource, Inc, San Diego, USA). The assay was carried and result interpreted according to manufacturer's instructions.

Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Sciences Software (SPSS-version 17, SPSS Inc., Chicago IL, USA). All data were presented as frequencies, the Chi-squared test was used to determine the proportion, while student T-test was used for comparison between continuous variables, and significance was at $p < 0.05$.

Results and Discussion

Ninety Hepatitis B surface antigen positive patients were included (45 HBV/HIV, and 45 HBV-mono infected patients), 36 males (40.0%), and 54 were females (60.0%), with the overall mean age of 38.7±13years. However, the mean age was higher (36±13.1) in the HBV/HIV as compared to HBV-mono (40.6±12.7) infected patients. Of the 90 patients, 10 (11.1%) were positive: 6 (13.3%) of HBV/HIV, 4(8.9%) of HBV-mono were positive for hepatitis D infection. Majority of the subjects were aged 31-40 years, followed by the 41-40 age group. Females 8(14.8%) recorded a higher prevalence compared to males 2(5.5%). Patients were within the age group 31-40 years recorded the highest prevalence of 4(13.0%), with HBV/HIV coinfected

having higher prevalence 3 (21.4). No case was reported among subjects ≥51 years. The age range for predisposition to infection with hepatitis D from this cross-sectional study was significant to age group in HBV-mono infection, p=0.034. All positive cases were found among the reproductive age. For educational status, we have more in infection (3 (9.7) among the secondary level of the HBV/HIV coinfected, while in the HBV-mono, the infection was more among the tertiary level, employment status: the infection was higher in both HBV/HIV (14.3%), HBV-mono infected (4(13.0%), the infection among the widowed was also higher HBV/HIV (33.3%), HBV-mono infected 2(28.6%), P=0.001 Table 1. In Table 2, the prevalence of hepatitis D virus in relation to risk factors such as: alcohol, consumption, smoking, use of sharp objects, tribal marks/tatoo, use of condoms, multiple sex partner, history of blood transfusion, surgery, drug use, same sex and HCV status. There was no significant association among the HBV/HIV coinfected, but higher infection was in those with no condom use (20%), and those with inconsistent use of condoms (25.0%), p=0.065, in the HBV-mono infected: smoking habit, and condom use had the p=0.022, and p=0.047 respectively, suggesting that they are risk factors for the acquisition of hepatitis D virus infection.

Hepatitis delta virus infection is a superinfection among hepatitis B virus (HBV)-infected patients, and the global prevalence of HDV vary significantly depending on the geographical location. The HDV infection contributes significantly to morbidity and mortality in chronic HBV patients and related liver diseases. Chronic HBV and HDV co-infection are associated with liver disease progression to cirrhosis and has been characterized as one of the most severe forms of viral hepatitis (Lempp and Ni, 2016). Viral infections that share same transmission route such as HIV, HCV, and HDV could influence the clinical course of HBV infection (Lempp and Ni, 2016). HDV infection requires the presence of the HBV surface antigen to assemble the complete virus, this has led to the regularly observed superinfection with HBV (Wang et al., 1986).

In this study, we observed the seroprevalence (11.1%) HDV infection among chronic HBV with HBsAg-positive patients in Jos Nigeria, which is higher compared to recent reported prevalence of 4.9% and 9.0% in western Nigeria (Opaleye et al., 2016, but lower than earlier finding of 12.5% active infection (Nwokediuko and Ijeoma, 2009). Also, a more recent study reported 83.3% of anti-HDV in Nigeria Capital city Abuja ((Ifeorah et al., 2019). However, these suggests that Nigeria is highly endemic to HDV infection, representing active infection, therefore, larger studies are needed to confirm these findings, especially with current paucity of data in the country. To the best of our knowledge, this study is the first from North-Central, Nigeria on HDV infection among HBV/HIV and HBV-mono infected patients. Interestingly, a recent large meta- analysis showed the prevalence of HDV to be 7.1% among the general population in West Africa (Stockdale et al., 2017). Other studies showed anti-HDV prevalence in HBsAg carriers in some parts of Africa: Cameroon-0.5 to 46.73% (Rodgers et al., 2017; Butler et al., 2018), and Gabon-15.6% (Stockdale et al., 2017), Burkina Faso-3.4% (Sanou et al., 2018). Recently, HDV prevalence in sub-Saharan Africa was estimated from 1.3 % to 50 %, (Andernach et al., 2014). Although, there are variations in HDV prevalence globally, which may be due to the endemicity of HBV infection, high-risk subpopulation and perhaps socioeconomic status that fuel the HDV transmission. However, studies have reported the superinfection of HDV coinfected with HBV, as a factor that worsens HBV-liver related disease including a higher likelihood of progression to hepatocellular carcinoma (Lempp and Ni, 2016). Therefore, the timely screening and diagnosis of HDV in HBV patients might identify individuals at early stage of liver disease thereby preventing the risk of cancer development. Due to this high seroprevalence among chronic HBV patients in Nigeria, providing to serologic testing may help screen the high-risk populations. Also, the large scale-up, and accessibility to HBV vaccine could help reduce the hepatitis burden, which could as well reduce HDV superinfection.

The observed higher prevalence of HDV infection in our cohort compared to HIV negative individuals, though lower than recent findings in Nigeria and neighboring Cameroon (Ifeorah et al., 2019; Butler et al., 2018) irrespective of the bias nature of the study setting and population. This suggests a significant morbidity of HBV-related liver diseases in Nigeria. In addition, although no statistical association was observed in the risk factors among the HBV/HIV, but in the HBV-mono infected, we observed significant association in the age, marital status, cigarette smoking and condom use. Although, this is not unexpected,

since these factors have shown to be risk factors for HBV infection in some recent findings (Chuang et al., 2010; Hongjaisee et al., 2020), suggesting the need for consistence use of condom, smoking control in the HBV prevention messages. For the public health purposes, education on safe sex, avoidance of smoking, as well as adherence to one sex partner should be integrated into healthcare services during hepatitis B care as it is already in existence with the HIV treatment programs, in order to reduce risk behaviors and virus transmission. Considering the population of Nigeria as the most populous black nation, and with the high prevalence of HBV, though non-homogenous, the efforts to control HBV and HDV may require more concentrated and better integration into prevention, and public health education programs.

Table 1: *HDV infection in relation to Socio-demographic factors among HBV/HIV co-infected and HBV-mono infected patients in Jos, Nigeria.*

	HBV/HIV co-infected			HBV-mono infected		
Variables	Samples No (45)	Positive No (%) 6(13.3)	P value	Samples No (45)	Positive No (%) 4(8.9)	P value
Age group (years)						
≤ 30	4	2 (50.0)	0.143	10	1(10.0)	0.034
31-40	14	3 (21.4)		17	1(5.9)	
41-50	13	1 (7.7)		9	2(22.2)	
51-60	10	0 (0.0)		9	0(0.0)	
>60	4	0 (0.0)		>60	0 (0.0)	
Sex						
Male	16	1 (6.3)	0.299	20	1(5.0)	0.412
Female	29	5 (17.2)		25	3(12.0	
Educational level						
Primary	6	1 (16.7)	0.916	3	0 (0.0)	0.422
Secondary	31	3 (9.7)		22	1 (4.5)	
Tertiary	8	2 (25.0)		20	3 (15.0)	
Employment status						
Employed	35	5(14.3)	0.969	31	4(12.9)	0.890
Unemployed	10	1(10.0)		14	0(0.0)	
Marital status						
Married	28	2(7.1)	0.062	23	2(8.7)	0.001
Single	8	1(12.5)		15	0(0.0)	
widowed	9	3(33.3)		7	2(28.6)	

The limitation of our study is the small sample size, and convenience sampling method, which could have possibly decreased the generalizability of our findings. The inability to test for HDV-RNA positive samples, therefore, can only speculate about acute, and, or chronic HDV infection of the patients. Also lack of appropriate pooled data adjustment of the risk factors to establish proper correlation effects. The study design, a cross-sectional cannot establish good causal relationship between risk factors and possible outcomes.

Table 2: *HDV infection in relation to risk Factors among HBV/HIV and HBV-mono infected patients in Jos, Nigeria.*

Variables	HBV/HIV			HBV-mono		
	Samples No	Positive No(%)	P value	Samples No	Positive No(%)	P value
Alcohol Consumption						
Yes	5	1 (20.0)	0.352	23	3 (13.0)	0.340
No	40	5 (12.5)		21	1 (4.8)	
Smoking						
Yes	2	0(0.0)	0.570	12	3 (25.0)	0.022
No	43	6 (14.0)		33	1 (3.0)	
Use of sharp objects						
Yes	2	1(50.0)	0.170	27	3 (11.1)	0.096
No	43	5 (11.6)		17	1 (5.9)	
Tribal marks/tattoos						
Yes	11	1 (9.1)	0.634	19	3 (15.8)	0.164
No	34	5 (14.7)		26	1 (3.8)	
Use of Condoms						
Yes	26	2 (7.7)	0.065	10	1 (10.0)	0.047*
No	15	3 (20.0)		18	3 (16.7)	
Sometimes	4	1 (25.0)		17	0 (0.0)	
Multiple Sex Partners						
1	30	1 (3.3)	0.060	14	3 (21.4)	0.118
2	9	3 (33.3)		17	1 (5.9)	
>2	6	2(33.3)		14	0 (0.0)	
History of Blood Transfusion						
Yes	10	1 (10.0)	0.160	9	2 (22.2)	0.124
No	35	5 (14.3)		35	2 (5.7)	
History of Surgery						
Yes	13	1 (7.7)	0.478	13	2 (15.4)	0.329
No	32	5 (15.6)		32	2 (6.3)	
Use of Hard Drugs						
Yes	1	0 (0.0)	-	2	0 (0.0)	-
No	44	6 (13.6)		43	4 (9.3)	
Same Sex Relationship						
Yes	2	0 (0.0)	-	0	0 (0.0)	-
No	43	6 (14.0)		45	4 (8.9)	
HCV Status						
Yes	5	0 (0.0)	0.552	6	1 (16.7)	0.578
No	24	3 (12.5)		39	3 (7.7)	
Don't Know	16	3 (18.8)		-	-	

Conclusions and Recommendations

This study highlights higher prevalence of HDV among the HBV/HIV than the HBV-mono infected patients, and significant association with age, marital status, cigarette smoking and inconsistent use of condom. Therefore, it is imperative that health counseling sessions among the chronic hepatitis patients should include strategies for safe sex, impact of smoking on immunity and risk of casual sex, along with sufficient condom distribution to reduce virus transmission. This finding should alert healthcare providers to define and implement clear policies based on evidence to reduce the burden of HDV infection. Such measures may include provider-initiated diagnostic tests, and provision of appropriate patient data registries. It is also important to screen chronic HBV patients for HDV for early diagnosis, and to avert liver diseases progression to hepatocellular carcinoma. Furthermore, larger surveillance and longitudinal studies are needed to gain better understanding of the HDV infection among chronic hepatitis B patients in endemic regions, and other high-risk populations, such as intravenous drug users in sub-Sahara Africa.

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Author's Contribution

JA-O, JIO and JMD: Conceptualization, design and original manuscript draft.
JIO, JMD, PO, OU, VD and DOA: Investigation and supervision.
DOA and OA: Data analysis.
JA, JIO and JMD: Resources.
JIO, PO, JMD, OU, JA, VD and DOA: Manuscript review and editing.
OA: Manuscript editing and approval.

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Conflicts of interest
The authors have declared no conflict of interest.

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