



Prevalence of Hepatitis D Virus among People Attending the Antiretroviral Clinic and the Effect on the Liver Function Enzymes

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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

Hepatitis D virus is an incomplete RNA virus requiring the assistance of the hepatitis B virus, specifically the HBsAg, to be infectious in humans. This study was designed to determine the prevalence of HDV among HIV patients and the effect on liver enzymes. The study was conducted at the Rivers state University Teaching hospital, Port Harcourt, Rivers State. Blood samples were obtained through vein puncture from 93 adults of which 41(44%) were males while 52(56%) were females between the ages 18 and 70 years attending the antiretroviral clinic and CD4+ cell count was also obtained. The samples were preserved at -20°C. Each of the samples was tested using a SWE-Care rapid strip (China) for the presence of HBsAg. HDV antibody was detected using a Dia.

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Pro ELISA kit (Italy). The AST, ALT and ALP were determined. SPSS 21 was used to analyze the data and P values were determined. From the total samples collected, 7(7.5%) of them were positive to the HBsAg test of which 3(3.2%) were males, while 4(4.3%) of them were females. Of the 7 people positive to the HBsAg, 6(6.4%) were positive to the HDV antibody with 3(3.2%) females and 3(3.2%) males. There was significant depletion of the CD4+ cells across the groups. For the liver function test, the P values were > 0.05 for AST, ALT and < 0.05 for ALP. The HDV infection from the study was not gender, nor age based and suggests a negative impact on the CD4 cells. The liver function enzyme analysis, suggest higher risk of hypertension in HIV/HBV/HDV infection.

Keywords: ALT; ALP; AST; HBsAg; HDV; HIV.

1. INTRODUCTION

According to Coghill et al. [1], Hepatitis D virus (HDV) is an incomplete RNA virus that requires the assistance of the hepatitis B virus (HBV), specifically the HBsAg, to be infectious in humans. Once chronicity is established, HDV has been described as the most severe form of viral hepatitis, with progression to cirrhosis in 10%–15% of patients within 2 years and in 70% - 80% of patients within 5–10 years. Despite this, a lack of adequate treatment options currently exists for HDV [2]. Recent data suggest that the global disease burden of the virus may be closer to 62–72 million [3]. Although once thought of as a disappearing disease, hepatitis D is now becoming recognized as a serious worldwide issue due to improvement in diagnostic testing and immigration from endemic countries [4]. According to Gunthard et al. [5], the seroprevalence of HDV among HBsAg-positive carriers has substantial variations worldwide.

Hepatitis D co-infection with HBV has been found to increase the risk for hepatitis flares and chronic hepatic complications especially in individuals with HBV/HIV co-infection. However, the impact of HDV infection on HIV/HBV co-infected individuals is not well documented, especially in Nigeria where HDV is not routinely diagnosed [5]. Thus, knowledge of HBV and HDV status among HIV-infected patients is important for adequate clinical monitoring and investigation of the prevalence and genotype distribution of HBV and HDV in HIV-positive individuals in Nigeria [3].

The Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP) and other liver enzymes are usually raised in patients infected with liver related diseases and can be a pointer to the extent of liver injury [6]. The increase in the liver enzymes, are mostly used for diagnostic purposes by Physicians [7]. Also, relationship between abnormally high levels

of liver enzyme, risks and death has in recent studies been linked together [8]. No study so far has reported the effect of HDV infection on the liver function enzymes as to know how they are affected by the infection.

CD4 cells have been found to be vital in the adaptive immune response which includes the stimulation of cytotoxic lymphocytes of which the HIV infects and kills it, thereby causing a failure of the immune system [9].

In Nigeria, especially in Port Harcourt, there are very few records of the occurrence of the triple infection of HIV/HBV/HDV since there is no routine test for the presence of HDV and the effect of the triple infection on the liver enzymes have not been studied. Also, the effect of the triple infection on CD4 cell count, needs to be studied to know the effect of HIV/HBV/HDV on it. This study was therefore designed to determine the prevalence of HDV among HIV patients and the effect on liver enzymes.

2. MATERIALS AND METHODS

2.1 Study Area

The study was conducted at the Rivers state University Teaching hospital, Port Harcourt the capital of Rivers State which is one of the southern states in Nigeria.

2.2 Study Population

Patients attending the antiretroviral clinic at the Rivers State University teaching hospital, Port Harcourt and had been on antiretroviral drugs (HAART) who gave their consent were admitted for the study.

2.3 Study Enrollment

Adults who were between the ages 18 and 70 years attending the antiretroviral clinic and were on antiretroviral drugs (HAART) for over 6

months were enrolled for the study. Relevant data were gotten from the 93 patients between the months of October and November 2022 using a modified questionnaire. The protocol used for the study was in adherence with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All study subjects gave informed consent. Any subject who did not give consent was excluded. Also patients who were infected with other viral hepatitis aside the targeted viruses, were excluded.

2.4 Sample Collection

Five milliliters of blood samples were collected through vein puncture into EDTA bottles (to prevent coagulation). The samples were centrifuged at 3000 rpm for 10 minutes to separate the plasma from the whole blood and the plasma, pipetted into another tube and labelled appropriately. These samples were preserved by refrigerating at -20°C. The CD4+ cell count which was determined using a standard laboratory procedure with the use of a flow cytometer analyzer (Version 2.4, Partec Germany) was gotten for each of the HIV positive persons.

2.5 Serological Analysis

Each of the samples was tested using a SWE-Care rapid kit strip(China) to detect the presence of the HBsAg. The detection for the HDV antibody was done using a Dia. Pro ELISA kit (Italy). The assay was performed in adherence with the manufacturer's instructions.

2.6 Liver Function Test

The Aspartate Aminotransferase (AST) and Alanine Transaminase (ALT) were determined with the Reitman and Frankel method as described by JayaPrada [10]. The AST was measured by monitoring the concentration of oxaloacetate hydrazones formed with 2,4 dinitrophenyl –hydrazine, while the ALT was measured by monitoring the concentration of pyruvate hydrazone formed with 2,4 dinitrophenyl-hydrazine. The Alkaline Phosphatase (ALP) was determined using the Kochmar and Moss methods in line with Oriakhi et al. [11] in which alkaline phosphatase acted on the buffered sodium thymolphthalein monophosphate. The addition of an alkaline reagent stopped the enzyme activity and simultaneously developed a blue chromogen which was measured photometrically.

2.7 Statistical Analysis

SPSS 21 was used to analyze the data. The P values for the gender distribution, age distribution and prevalence and the various liver enzymes was determined using the Independent T-test, while the significant difference for the C4+ Cells was determined, using the one way ANOVA test.

3. RESULTS

A total of 93 blood samples were collected from patients undergoing antiretroviral therapy, 41(44%) were males while 52(56%) were females. The patients were between the ages of 18 – 70. From the total specimen collected, 7(7.5%) of them were positive to the HBsAg test of which 3(3.2%) were males, while 4(4.3%) of them were females. The P value between the gender co-infected with HIV/HBV was 0.46. Of the 7 people who were positive to the HBsAg, 6(6.4%) were positive to the HDV antigen. The 6 patients who were detected to be HIV/HBsAg/HDV positive, were 3(3.2%) females and 3(3.2%) males and the P value between the gender was 0.76. The prevalence ages for the HIV/HBsAg/HDV, was highest among those in the age range of 36 – 40, 41 – 45 and 46 – 50 with 14% prevalence.

The mean value for CD4+4 cell count from this study, was 486 ± 43.0 cell/ml^a for HIV infected persons, 405 ± 18.71 cell/ml^b for HIV/HBV co-infected persons and 345 ± 0.0 cell/ml^c for people triple infected with HIV/ HBV /HDV.

The liver function test (AST, ALT and ALP) mean level in the patients co-infected with HIV/HbsAg was 46.00 ± 0.0 U/L, 42.75 ± 0.0 U/L, $43.33 \pm 4.0.0$ U/L and HIV/HBsAg/HDV were 11.5 ± 3.14 U/L, 9.33 ± 3.26 U/L and 43.33 ± 4.63 U/L respectively.

4. DISCUSSION

Hepatitis D has been described as the most severe form of viral hepatitis associated with a more rapid progression to cirrhosis and an increased risk of hepatocellular carcinoma and mortality compared with hepatitis B mono-infection [12]. The impact of HDV infection on HIV/HBV co-infected individuals is not well documented, especially in Nigeria where HDV is not routinely diagnosed [5] hence the reason for the study.

Table 1. Gender distribution and CD4 cell count of patients

Gender	Total tested (HIV)	Positive HIV/HBV	Percentage positive %	P value	Positive HIV/HBV/HDV	Percentage Positive %	P-value
Female	52	3	3.2	0.46	3	3.2	0.76
Male	41	4	4.3		3	3.2	
Total	93	7	7.5		6	6.4	
CD4 cell count(cell/ml)	486±43.0 ^a	405±0.0 ^b			345 ±47.3 ^c		

Table 2. Age distribution and prevalence

Age range	Total tested	Positive HIV/HBV	Percentage positive %	P value	Negative HIV/HBV	Percentage negative %	Positive HIV/HBV/HDV	Percentage Positive % to HIV/HBV /HDV	P-value
15 – 20	11	0	0	0.41	11	100	0	0	0.55
21– 25	9	1	11		8	89	1	11	
26 – 30	10	2	20		8	80	1	10	
31 – 35	9	1	11		8	89	1	11	
36 – 40	7	1	14		6	86	1	14	
41 – 45	7	1	14		6	86	1	14	
46 – 50	7	1	14		6	86	1	14	
51 – 55	12	0	0		12	100	0	0	
56-60	9	0	0		9	100	0	0	
61-65	7	0	0		7	100	0	0	
66-70	5	0	0		5	100	0	0	

Table 3. Mean values of the liver function test for the various groups

	HIV/HBV Mean value (U/L)	HIV.HBV/HDV Mean value (U/L)	Normal value (U/L)	P value
AST	45.80±4.44	46.00±0.0	40.00	0.97
ALT	45.6±3.85	42.75±0.0	55.00	0.67
ALP	33.80±4.82	43.33±0.0	35.00	0.01

From this study as shown in Table 1, 93 HIV patients were tested for the presence of HBsAg of which 7(7.5%) of them were positive to the HBsAg. The outcome from this study was higher than a previous study carried out by Baeka et al. [13] in which 5.1% was recorded and that of Okonko et al [14] in which 6.1% was recorded in the same city. This may be attributed to the increase in some social habits such as body piercing, tattoo making which has become on the increase in recent times in Port Harcourt. Also the indiscriminate blood transfusion in some sub standard hospitals which do not carry out proper blood screening before transfusion could be responsible for the increase in the co-infection of the viruses since they are both transmitted through body fluids. The global prevalence of the co-infection of HIV/HBV as recorded by Ahmadi Gharaei et al. [15] was 7.6% which was higher than that reported in this study. This may be attributed to homosexual life style permissible in many countries globally but not permitted in Nigeria and transgender women which is on the increase globally, since they both increases the spread of both HIV and HBV as reported by Adeyemi et al. [16]. The highest occurrence of the HIV/HBV co-infection, was highest among people in the age range of 26- 30 age with 2 of the 10 persons tested for the co-infection as shown in Table 2, followed by those in the age range of 21- 25 and 35 – 50 having 1 persons in each of the groups. From the analysis, the P value of the age prevalence was >0.05 which suggest that age may not be a factor in the co-infection of HIV/HBV. The male had a higher prevalence of 4.3% than the females. This may be associated with the life style more prevalent among the male such as tattooing and sharing of unsterilized barbing and shaving instruments which is very common among males.

Out of the 7 patients who were HIV/HBsAg co-infected, 6 (6.4%) tested positive to the HDV antigen. This result is within the range of result reported by Opaleye et al. [17] with a 5.6% prevalence of the HDV antigen among HIV/HBV co-infected individuals but slightly lower than the global prevalence of 7.4% recorded from the findings of Chen et al. [18]. This could be due to the higher global prevalence of HIV/HBV as reported by Ahmadi Gharaei et al. [15], since the hepatitis B surface antigen(HbsAg) is required for the defective HDV to replicate as discovered by Coghill et al. [1].

There was no significant difference between the numbers of persons infected in the various age

groups with the triple infection of HIV/HBV/HDV since the P value recorded was > 0.05 as shown in Table 2. This suggests that anybody of any age can be infected with the triple infection.

The HIV/HBV/HDV triple infection had a prevalence of 3(7.3%) of the 41 HIV positive males while the females had a prevalence of 3(5.8%) of the 52 HIV positive patients. This shows a prevalence among the males than the females. This is agreeable since the prevalence of males co-infected with HIV/HBV was higher among males than females.

CD4 cells have been found to be vital in the adaptive immune response which includes the stimulation of cytotoxic lymphocytes of which the HIV infects and kills it, thereby causing a failure of the immune system [9]. In this study, there was a significant depletion of CD4 cell count among the co-infected groups when compared with the mono infected HIV group and a significant depletion when comparing the triple infection with the co-infection in this study. The depletion in the CD4 cells among people co-infected with HIV/HBV when compared with people mono infected with HIV in this study, agrees with the findings of Rana et al. [19]. While people who were triple infected with HIV/HBV/HDV had a significantly lower CD4 cell count than those co-infected with HIV/HBV. This suggests that the triple infection has a negative effect on the restoration of the CD4 cells thereby predisposing people infected with HIV/HBV/HDV to other opportunistic infections.

Biochemical parameters in viral hepatitis infection can be used to measure the damage level and severity of the liver due to viral hepatitis [20]. Serum liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ -glutamyltransferase (GGT), are tested routinely and automatically in current clinical settings [21].

The liver function enzyme level from this study as shown in Table 3, for people co-infected with HIV/HBV, had a higher value of AST than the standard level in healthy people. While in those with the triple infection of HIV/HBV/HDV, there was a higher level of AST and ALP above the standard recommended values. There was no significant difference between the AST and ALT of both groups, while there was a significant difference of 0.01 in the ALP of the both group. According to Kwo et al. [22], the elevation in the

level of AST and ALP in an unidentifiable risk factor population, has been associated with liver related mortality. According to Katzke et al. [23], increase in the liver enzyme could be an early pointer to being at risk to other chronic disease. Therefore from these findings, people co-infected with HIV/HBV and those triple infected with HIV/HBV/HDV, are likely to be predisposed to other chronic diseases.

Increase in liver enzymes as stated by Bessone et al. [6], has been found to be common in people infected with liver disease and suggested to indicate the type of liver injury. Therefore the increase in ALP, suggest inflammation or impaired functions of the liver as stated by Salazer et al. [24]. From the study carried out by Kwo et al. [22], the rise in ALP as stated may suggest a cholestatic liver disease being predominant in the HIV/HBV/HDV infection. Also, the findings of Khalil et al. [25], showed that the increase in the level of ALP was found to be associated with both type one and type 2 hypertension. This therefore suggest that people with the triple infection of HIV/HBV/HDV are likely to be more predisposed to hypertension related issues than those co-infected with HIV/HBV and mono infected with HIV.

5. CONCLUSION

From the study carried out, the occurrence of HDV among HIV patients was associated with the presence of HBV. Also, the HDV infection from the study was not gender, nor age based. This study suggests that HDV infection has a negative impact on the restoration of the CD4 cells. The liver function enzyme analysis, suggest that the triple-infection of HIV/HBV/HDV could lead to a cholestatic liver disease due to the increase of the ALP above the standard range which also could predispose them to hypertension. Hence it is recommended that all HIV patients should undergo HBV and HDV test to be sure of their status so as to be placed on medication early in order to reduce the rate of speeding up cirrhosis thereby reducing the mortality rate.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical approval for the study was gotten from the Rivers state University teaching hospital

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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