# Prevalence and Characteristics of Hepatitis Delta Virus Infection in a Tertiary Hospital Setting in Cameroon

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***Background/Aims:*** **Hepatitis B virus (HBV) and hepatitis D virus (HDV) coinfection is associated with more severe liver disease than HBV alone. More knowledge on the epidemiology and clinical impact of HDV-infected individuals is needed in Cameroon. We aimed at determining the frequency of anti-HDV antibody testing in hepatitis B surface antigen (HBsAg) positive patients, the proportion of anti-HDV positivity, and the characteristics of anti-HDV positive compared to anti-HDV negative patients in a tertiary hospital setting in Cameroon.** ***Methods:*** **A cross-sectional study was conducted. Clinical records of chronic HBV-infected patients attending the gastroenterology unit at the Douala General Hospital from 2010 to 2014 were reviewed.** ***Results:*** **Of 365 files of HBsAg-positive patients defined as chronic HBV infection, 80.5% (294) were tested for anti-HDV antibodies, among whom 10.5% (31/294) were positive. Median aspartate aminotransferase ($P < 0.0001$), alanine aminotransferase ($P < 0.0001$), and gamma glutaryl transpeptidase ($P < 0.0001$) were significantly higher while platelets count ($P < 0.002$) and prothrombin time ($P < 0.0001$) were significantly lower in anti-HDV positive compared to anti-HDV negative patients. Liver necroinflammation ($P < 0.0001$), fibrosis score ($P < 0.0001$), and decompensated cirrhosis ($P < 0.0001$) were also significantly associated with anti-HDV positivity.** ***Conclusion:*** **The proportion of anti-HDV antibody positivity remains high in this setting and was significantly associated with more severe liver disease compared to those who were anti-HDV negative. More studies are needed to evaluate rates of HDV testing in other centers in Cameroon and the subregion. Preventive strategies for HBV prevention, which also apply to HDV, must still be reinforced by healthcare providers and policy makers. (J Clin Exp Hepatol 2017;7:334–339)**



Worldwide, there are an estimated 350 million people considered to have chronic hepatitis B (HBV) infection, of whom 5% (15–20 million) have serologic evidence of exposure to the hepatitis D virus (HDV).[1,2] The West and Central African regions are among the geographical regions with intermediate to high prevalence of both viruses.[3]

HDV is a small defective RNA virus that requires HBV for its transmission.[3] Transmission routes for HDV are similar to those of HBV namely blood borne, sexual, and perinatal, the latter being least common. HDV infection can thus be transmitted either simultaneously with HBV infection (coinfection) or to individuals who are already chronic HBV carriers (superinfection).[6] HDV in association with HBV produces significantly more severe illness than HBV alone[7] progressing more rapidly to cirrhosis with hepatic decompensation and hepatocellular carcinoma while persisting HDV replication is considered the most important predictor of mortality.[1,8–10]

A changing trend in the epidemiology of HDV has been observed, with a global decline in prevalence.[2,11] Consistent declines in prevalence of HDV have been reported following multicenter studies in former highly endemic countries such as Italy, Spain, Turkey, and Taiwan.[12–15] This decreasing trend is the result of global HBV vaccination and other active preventive measures.[16] There is no evidence in the medical literature of a similar trend in sub-Saharan Africa where HDV remains a major health problem as HBV is still uncontrolled.[17] Although significant morbidity is attributed to HDV, there is a paucity of clinical data in Cameroon. The prevalence of HDV in hepatitis B surface antigen (HBsAg)-positive patients from previous studies in Cameroon ranged from 6.5% to 17.6%.[18–20] Published data on the impact of HDV is even

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*Abbreviations:* AFP: alpha-fetoproteins; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ELISA: enzyme-linked immunosorbent assay; GGT: gamma glutaryl transpeptidase; HBeAg: hepatitis B e antigen; HBe ab: hepatitis B e antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus; HIV: human immunodeficiency virus; PT: prothrombin time
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scarcer especially as screening for anti-HDV is not routine in HBsAg-positive patients. To make matters worse, generic Nucleotide Analogues for treatment of chronic HBV are readily available since 2015 whereas monitoring of treatment for viral suppression may not be adequately done in this low-income setting. Xiridou modeled the transmission dynamics of HBV taking into account HDV coinfection and showed that in populations in which HDV is endemic, control programs that ignore its presence may show overoptimistic results and lead to an underestimation of the HBV epidemic, as HBV control is dependent on the reproduction number of dual HBV/HDV coinfection.[21] Hepatitis D therefore plays an important role in the spread and control of HBV. Augmenting the existing HBV monitoring programs with monitoring of HDV could boost the accuracy of the surveillance of HBV prevalence and the efficacy of control programs. Also, a systematic approach to routinely screen for HDV will lead to more appropriate management. Increased knowledge on the epidemiology and clinical impact of HDV-infected individuals will have significant public health and policy implications. In view of the above, we aimed at determining the frequency of anti-HDV antibody testing in HBsAg positive patients, the proportion of anti-HDV positivity, and subsequently the characteristics of anti-HDV positive compared to anti-HDV negative patients in a tertiary hospital setting in Cameroon.

## METHODOLOGY

### Study Design and Setting

This was a cross-sectional study carried out in the Douala General Hospital, which is a tertiary health facility in the largest city and economic capital of Cameroon with an estimated population of over 3 million inhabitants. This hospital has a capacity of 320 beds and harbors all the major medical and surgical specialties, among which the gastroenterology unit is where most patients with liver diseases are referred to for management. There is a fully functional laboratory (subjected to periodic quality control and validation) where baseline tests relevant to viral hepatitis diagnosis and management are done.

### Patients

A thorough clinical case note review was performed on the files of all chronic HBV patients who attended the Gastroenterology outpatient clinic between the 1st of January 2010 and 31st December 2014. Included in this study were adults aged 18 and above with chronic HBV infection (defined as evidence of persistence of a positive HBsAg test for more than 6 months) and those with more than one clinic attendance. Excluded were patients with incomplete files and hepatitis C (HCV) and human immunodeficiency virus (HIV) coinfections.

### Data Collection

A structured pretested questionnaire designed to gather sociodemographic, clinical, and laboratory data was completed for each patient file. Sociodemographic characteristics included age, sex, marital status, and insurance details. Symptoms and signs associated with chronic HBV infection (pedal edema, ascites, splenomegaly, hepatomegaly, and jaundice) and laboratory data (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutaryl transpeptidase (GGT), serum albumin, prothrombin time (PT), and alpha-fetoproteins (AFP)) were as well included. Included also were questions pertaining to data on hepatitis B viral markers (HBsAg), hepatitis B e antigen (HBeAg), anti-HBe antibody, quantitative HBV-DNA, hepatitis D markers (anti-HDV antibody, HDV-RNA), Liver Fibrosis Score, and abdominal ultrasound.

Participants described as 'insured' were those who had full or partial compensation for medical expenses.

The diagnosis of liver cirrhosis and hepatocellular carcinoma (HCC) were made following clinical, laboratory, and radiological assessments by the resident gastroenterologists and recorded in the patients' files.

The criteria for decompensated cirrhosis were clinical evidence of the following: bleeding esophageal varices, ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy.[2]

HCC was diagnosed based on the following criteria: a positive lesion detected by an abdominal ultrasonography or computed tomography and a serum alpha-fetoprotein level of 400 ng/mL or greater.[22]

### Laboratory Testing

Routine hematology and biochemistry were carried out by standard automated laboratory methods in the Douala General Hospital Laboratory. An abnormal ALT/AST level was defined as values greater than 40 IU/L.[23] A solid-phase enzyme-linked immunosorbent assay for the qualitative detection of HBsAg, HBeAg, anti-HBe, and anti-HCV antibody was used (*RecombiLISA* ELISA, CTK Biotech, San Diego, California, USA). Anti-HDV was detected by ELISA, anti-HDV kit Adaltis, Rome, Italy.

Quantitative determination of HBV DNA was by real-time PCR using COBAS AmpliPrep/COBAS TaqMan HBV Test, version 2.0 Roche Diagnostics, Mannheim, Germany. HDV RNA quantification was performed with a single-step quantitative reverse transcriptase polymerase chain reaction (RT-PCR), Roche, LightMix kit, Meylan, France.

FibroTest/ActiTest (BioPredictive, Paris, France), a non-invasive commercial biomarker of fibrosis, was used and converted to the METAVIR score to categorize fibrosis in chronic hepatitis B according to a 5-stage classification: F0 (no fibrosis), F1 (portal and periportal fibrosis without septa), F2 (portal and periportal fibrosis with rare septa), F3 (numerous septa without cirrhosis), and F4 (cirrhosis).

The METAVIR score also categorized activity according to a 4-grade classification: A0 (no activity), A1 (minimal activity), A2 (moderate activity), and A3 (severe activity).

ETHICS: Ethical approval was obtained from the Douala General Hospital Ethics committee for research.

### Statistics

Variables were described as mean (±standard deviation) or median (interquartile range) if quantitative or as count (percentage) if categorical. We used the Student t test to compare means between groups and the Wilcoxon rank sum test to compare medians between groups. Association between categorical variables was assessed using the $\chi^2$ test or the Fisher's exact test where necessary. The threshold for significance was set at the level of 5% and analyses were done using STATA 13.

## RESULTS

We reviewed 365 files of HbsAg-positive patients defined as chronic HBV infection and 80.5% (294) of them were tested for anti-HDV antibodies. The general characteristics of the study population are described in Table 1. The mean age of the total population was 34(±10) years and 71.2% (211/294) were below 39 years. Males were in the majority (75.1%).

The proportion of HBV patients with anti-HDV positivity was 10.5% (31/294) (95% CI 7.5–14.6%), and only 2 of them were positive for HBeAg.

In Table 2, we compared the sociodemographic, clinical, laboratory, viral, and histological characteristics between anti-HDV antibody positive and negative subjects. Anti-HDV-positive patients were significantly younger compared to anti-HDV-negative patients (35 ± 10 vs 30 ± 11,

**Table 1 General Characteristics of the Study Population.**

| Characteristics | Total (*N*) | Count (*n*) | Percentage (*n*/*N* %) |
|---|---|---|---|
| Age, tertiles | 294 | | |
| <30 | | 104 | 35.4 |
| 30–38 | | 107 | 36.4 |
| >38 | | 83 | 28.2 |
| Gender | 294 | | |
| Female | | 73 | 24.8 |
| Male | | 221 | 75.1 |
| Marital status | 294 | | |
| Not in couple | | 135 | 45.9 |
| In couple | | 159 | 54.1 |
| Residence | 293 | | |
| Rural | | 15 | 5.1 |
| Urban | | 278 | 94.9 |
| Insurance, yes | 294 | 21 | 7.1 |
| HBeAg positive | 294 | 2 | 0.7 |
| Anti-HDV antibody positive | 294 | 31 | 10.5 |
| Fibrosis stage | 274 | | |
| <F2 | | 201 | 73.4 |
| ≥F2 | | 73 | 26.6 |
| Necroinflammation grade | 274 | | |
| <A2 | | 218 | 79.6 |
| ≥A2 | | 56 | 20.4 |
| Hepatocellular carcinoma | 294 | 8 | 2.7 |
| Median platelets $\times 10^3$/L | 294 | 186 (152–227) | |
| Median AST (IU/L) | 294 | 28.9 (20–43) | |
| Median ALT (IU/L) | 294 | 26 (20–47.3) | |
| Median GGT (IU/L) | 268 | 29 (20–42) | |
| Median PT (%) | 283 | 92 (80–100) | |
| Median HBV DNA (IU/mL) | 293 | 518 (55–3843) | |
| Median HDV RNA (copies/mL) | 12 | $212 \times 10^4$ ($2.7 \times 10^4$–$787 \times 10^4$) | |

HDV: hepatitis delta virus; HBV: hepatitis B virus; HBeAg: hepatitis B e antigen; HBe ab: hepatitis B e antibody; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutaryl transpeptidase; PT: prothrombin time.

**Table 2 Sociodemographic, Laboratory, Clinical, and Histological Characteristics of HbsAg-Positive Patients by Their Anti-HDV Status.**

| Characteristics | Total (HBsAg positive) | Anti-HDV negative | Anti-HDV positive | *P* value |
|---|---|---|---|---|
| Age (years) | 34 (±10) | 35 (±10) | 30 (±11) | 0.008 |
| Gender | | | | |
| Female | 73 (24.8) | 66 (25.1) | 7 (22.6) | |
| Male | 221 (75.1) | 197 (74.9) | 24 (77.4) | 0.76 |
| Marital status | | | | |
| Not in couple | 135 (45.9) | 119 (45.3) | 16 (51.6) | |
| In couple | 159 (54.1) | 144 (54.7) | 15 (48.4) | 0.50 |
| Residence | | | | |
| Rural | 15 (5.1) | 15 (5.7) | 0 (0.0) | |
| Urban | 278 (94.9) | 247 (94.3) | 31 (100.0) | 0.38 |
| Insurance | | | | |
| Yes | 21 (7.1) | 17 (6.5) | 4 (12.9) | |
| No | 273 (92.9) | 246 (93.5) | 27 (87.1) | 0.26 |
| Platelets $\times 10^9$/L | 186 (152–227) | 189 (157–229) | 155 (72–194) | 0.002 |
| AST (IU/L) | 28.9 (20–43) | 28 (19–38) | 109 (78–159) | <0.0001 |
| ALT (IU/L) | 26 (20–47.3) | 25 (19–41) | 109 (52–160) | <0.0001 |
| PT (%) | 92 (80–100) | 95 (84–100) | 76 (55–86) | <0.0001 |
| GGT (IU/L) | 29 (20–42) | 26 (19–36) | 67 (41–112) | <0.0001 |
| HBV DNA (UI/mL) | 434 (41–3843) | 518 (55–3843) | 66 (24–11342) | 0.29 |
| Fibrosis stage | | | | |
| F0 | 127 (46.4) | 125 (51.0) | 2 (6.9) | |
| F1 | 74 (27.0) | 72 (29.4) | 2 (6.9) | |
| F2 | 27 (9.9) | 23 (9.4) | 4 (13.8) | <0.0001 |
| F3 | 32 (11.7) | 17 (6.9) | 15 (51.7) | |
| F4 | 14 (5.1) | 8 (3.3) | 6 (20.7) | |
| Necroinflammation grade | | | | |
| A0 | 164 (59.9) | 161 (65.7) | 3 (10.3) | |
| A1 | 54 (19.7) | 53 (21.6) | 1 (3.5) | <0.0001 |
| A2 | 29 (10.6) | 18 (7.4) | 11 (37.9) | |
| A3 | 27 (9.9) | 13 (5.3) | 14 (48.3) | |
| Decompensated cirrhosis | | | | |
| No | 276 (93.9) | 257 (97.7) | 19 (61.3) | |
| Yes | 18 (6.1) | 6 (2.3) | 12 (38.7) | <0.0001 |
| Hepatocellular carcinoma | | | | |
| No | 286 (97.3) | 254 (97.7) | 29 (93.6) | |
| Yes | 8 (2.7) | 6 (2.3) | 2 (6.5) | 0.20 |

HDV: hepatitis delta virus; HBV: hepatitis B virus; HBeAg: hepatitis B e antigen; HBe ab: hepatitis B e antibody; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutaryl transpeptidase; PT: prothrombin time.



$P < 0.008$). Median AST, ALT, platelets count, and GGT were significantly higher, while median PT was significantly lower in anti-HDV antibody positive than negative patients. Median HBV DNA was lower in anti-HDV-positive patients ($P = 0.29$), though not statistically significant (Table 2).

Out of the 294 HBV patients, 274 had done noninvasive tests for liver fibrosis and inflammation (Table 1). Anti-HDV-positive patients had higher liver fibrosis and neuroinflammatory scores ($P < 0.0001$). Decompensated liver cirrhosis too was associated with anti-HDV positivity ($P < 0.0001$) (Table 2).

## DISCUSSION

In this cross-sectional study, we investigated the frequency of anti-HDV testing in HBsAg-positive patients, the

proportion of anti-HDV antibody positivity in eligible study participants, and then compared characteristics between those who were anti-HDV positive and negative. We found out that 80.5% of HBsAg-positive patients were tested for anti-HDV antibody. Of those tested, 10.5% were anti-HDV antibody positive, who were shown to be significantly associated with more severe liver disease (elevated transaminases, increased necroinflammation, fibrosis, and decompensated cirrhosis) than anti-HDV antibody negative subjects.

With 80.5% of HBsAg-positive patients tested for anti-HDV, this was much higher than in most of the literature, be it in Europe or America. In a 13-year prospective multicenter study in Greece, anti-HDV testing varied from 57% of HbsAg-positive patients when tested prior to 2003 and 35.3% thereafter in 2013.[24] Similarly, in a study involving four tertiary hospitals in London, in one of the centers, only 40% of HBV patients were tested for anti-HDV on the request of a clinician. In the second center, in contrast, there was a reflex laboratory algorithm, which understandably achieved anti-HDV testing on almost all first HbsAg-positive samples.[25] Testing for anti-HDV is inappropriately low in the United States. In a retrospective study of all veterans who tested positive for HBsAg from 1999 to 2013, only 8.5% were tested for anti-HDV.[26] Low testing rates generally reflect relative inexperience with HDV in general[27] or infrequent referral to the appropriate specialist and poor access to HDV testing modalities. Prompt referrals to a gastroenterologist/hepatologist have been shown to be more strongly associated with testing than visits to other specialists such as internists and infectious disease specialists.[26] In this study setting, all study participants were reviewed by one of the three resident gastroenterologists, and thus the high proportion of testing for anti-HDV. However, anti-HDV testing is recommended for all HBV-infected patients.[23]

The frequency of anti-HDV positivity in this study was 10.5%. From three previous studies on the prevalence of anti-HDV prevalence in Cameroon, the only comparable study to ours had a higher anti-HDV positivity of 17.6% of HBsAg-positive subjects.[20] The second study had a very small sample size (6.5% anti-HDV positivity from 31 HBsAg-positive patients).[18] Lastly, in the most cited of these Cameroonian studies, there was a high prevalence of 27.3% of anti-HDV positivity. Study participants were made up of mainly a high-risk group,[19] which consisted of sex workers, patients with febrile jaundice, and multiple transfused sickle cell anemia patients. This could be understandable because at that time HDV testing was conducted mainly in chronic HBV patients from high-risk groups and in those with advanced liver disease[28] and was therefore unrepresentative of the global HBsAg-positive population. This therefore shows that studies on the prevalence of anti-HDV positivity in HBsAg-positive patients can produce relatively different outcomes, which may result from the disparity in the centers, the number of study participants, and disparity in patient groups. This was clearly exemplified in a study on the characterization of HDV in sub-Saharan Africa[29] involving patients from Burkina Faso, Nigeria, Chad, and Central African Republic. Anti-HDV antibody prevalence varied widely ranging from 0% to 27.3%. Study participants were a mixed group of asymptomatic carriers, pregnant women, HIV-positive patients, liver patients, and children.

Consistent with previous studies, our data confirmed that anti-HDV-positive patients had more severe disease, especially as regard to liver chemistries, liver function, and fibrosis stage, compared to anti-HDV-negative patients. These patients had significantly higher levels of ALT, AST, and GGT with median values 3–4 times above HDV-negative patients as was also found by other authors.[27,30] Platelet counts were lower and PTs prolonged.[11,17,27,30] Similarly, histologically anti-HDV-positive patients were clearly shown to have more advanced necroinflammation and fibrosis stage as was the clinical presentation of decompensated cirrhosis.[27] The risk of developing cirrhosis is known to be three times higher in HDV-infected patients compared with HBV alone.[31] This study did not corroborate other studies that showed the association between HCC and HBV/HDV coinfection.[32] This was probably due to the small number of patients who presented with HCC in this cross-sectional study.

There were a number of limitations to this study, notably its retrospective nature over a five-year period in which laboratory assays and clinical diagnosis might have not been consistent, thus increasing possibilities of measurement errors and misclassification, as well as missing data. This study was done in a single, tertiary center, which may have patients who are not representative of the HBV patients in the general population. Only 38% of anti-HDV-positive patients were tested for HDV-RNA; this could provide more information, especially as high levels are known to predict risk of disease progression and cirrhosis.[10] Almost 20% of HBsAg-positive patients were excluded from the study because of lack of testing for anti-HDV antibodies. Despite these limitations, this is the first documented data in Cameroon with such a large number of patients.

## CONCLUSION

Four out of five HBsAg-positive patients receiving care in a tertiary hospital settings' gastroenterology clinic were tested for anti-HDV antibodies. The proportion of anti-HDV antibody positivity remains high in this setting. We have clearly shown from this study that anti-HDV positivity was significantly associated with more severe liver disease compared to those who were anti-HDV negative. More studies are needed to evaluate rates of HDV testing in other

centers in Cameroon and the subregion. Clinicians who provide care to HBV-infected patients should be aware of the severity of liver disease in anti-HDV-positive patients. Preventive strategies for HBV prevention, which also apply to HDV, must still be reinforced by healthcare providers and policy makers.

## AUTHORS' CONTRIBUTION

HNL, DNN, CO, and GNA conceived the study. SAFBE, AM, OSD, and RK collected the data. HNL, OSD, GNA, and RK, analyzed the data and drafted the manuscript. HNL, CO, RK, DNN, SAFBE, AM, OSD, and GNA proofread and corrected the manuscript. All authors agreed with the final manuscript to be submitted for publication.

## CONFLICTS OF INTEREST

The authors have none to declare.

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