Original Article

Hepatitis Delta Virus Surveillance Practice among Clinicians in Nigeria: A Cross-Sectional Survey

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ABSTRACT

Background: The near total absence of routine Hepatitis Delta Virus (HDV) screening in many countries in sub-Saharan Africa is a major challenge to understanding the burden of HDV in the region. **Aim:** To evaluate Hepatitis Delta Virus screening practices and associated factors among clinicians in Nigeria. **Methods:** A cross-sectional study was conducted in June–July 2022, in which a self-administered questionnaire that inquired about HDV awareness, screening practices, and treatment options was shared electronically with consenting clinicians practicing in Nigeria. At the end of the survey, data was analyzed using descriptive and inferential statistics. The level of significance was set at 0.05. **Results:** At the end of the survey, 210 of the 213 responses retrieved from respondents were analyzed. The respondent's mean age was 38.60 ± 7.27 years with a male-to-female ratio of 1:2.5. They comprised 13.8% gastroenterologists and 86.2% respondents in other areas of clinical medicine. The study showed that 89.5% of the respondents knew that HDV infection occurs only in hepatitis B virus (HBV)-infected individuals. Most (91.4%) respondents do not screen for HDV in chronic HBV patients, mainly due to the non-availability of screening tools and lack of awareness of any screening test for HDV. Research interest was reported as the reason for screening among clinicians who had ever screened for HDV. Pegylated interferon was the main regimen used for treatment by 87.5% of respondents. About 2% did not know treatment options for HDV. A significant association between knowledge of HDV infection and area of specialty, as well as the nature of medical practice was noted (P = 0.008 and 0.013, respectively). **Conclusion:** The study showed a high level of awareness of HDV dependency on HBV, for natural infection to occur. However, it documented very minimal HDV screening in clinical settings and factors affecting screening among clinicians.

Keywords: *Awareness, clinicians, HDV, Nigeria, screening*

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Introduction

Hepatitis Delta Virus (HDV) is a defective virus that requires hepatitis B virus envelope protein (HBsAg) for its assembly and propagation.[1] Although the smallest agent known to cause human disease, HDV accounts for the most severe forms of viral hepatitis.[2] HDV infection worsens hepatitis B virus (HBV) infection (while often inhibiting HBV-DNA replication), resulting in acute hepatic decompensation more frequently and faster progression to cirrhosis and hepatocellular carcinoma (HCC).[3] Because of HDV dependency on HBV, successful implementation of universal HBV vaccination is important for HDV prevention and control. Most countries in sub Saharan Africa, including Nigeria, are hyperendemic for HBV, yet there is suboptimal universal HBV vaccination and birth dose coverage in the region.[4-6] Consequently, HDV may be a yet unidentified healthcare problem in Nigeria.

According to the World Health Organization (WHO), the global burden of HDV infection remains unclear.[7] Globally in 2022, about 254 million people were living with Chronic Hepatitis B (CHB), and an estimated 5% of this number have HDV infection,[8] implying that approximately 12.7 million individuals are infected with HDV worldwide. However, the true global HDV estimates continued to be a matter of debate, as systematic reviews and meta-analyses aimed at assessing HDV global burden have varied outcomes.[2,9,10] This portrays the challenges in obtaining reliable HDV epidemiological data. Nigeria is an HBV hyperendemic region, with HBsAg carrier rate ranging from 5.9% to 12.9% according to a recent systematic review.[11] Hence, the country has a substantial pool of persons at risk of HDV infection, yet HDV epidemiological data is scarce.

Hepatitis Delta Virus screening guidelines differ among countries.[12-15] The Asian Pacific Association for the Study of the Liver (APASL) and their European counterparts, the European Association for the Study of the Liver (EASL) recommend HDV screening for all HBV-infected persons at least once.[12,16] Additionally, EASL recommends anti-HDV re-testing in HBV surface antigen (HBsAg)-positive individuals whenever there is a clinical indication, e.g., in cases of acute decompensation of chronic liver disease or aminotransferase flares.[16] Similarly, the American Association for the Study of Liver Diseases (AASLD) recommends testing individuals with HBV who are at particular risk for HDV.[12] The World Gastroenterology Organization (WGO) recommends HDV screening in CHB if Alanine Transaminase (ALT) is elevated with little or no HBV viral replication.[13] Presently in Nigeria, the Society for Gastroenterology and Hepatology in Nigeria (SOGHIN) guidelines recommend anti-HDV screening for all HBsAg-positive individuals, although it noted the reality of anti-HDV not being routinely available in clinical settings in Nigeria.[14]

In Nigeria, there is limited data regarding HDV spread, and the HDV burden remains unclear. Available studies in Nigeria showed prevalence rates ranging from 2% to 18% among different population groups in particular regions with no data on some other regions.[17-23] Although, HBV screening is done routinely in clinical settings in Nigeria; however, it is not the case for HDV co/superinfection, even in individuals with HBV-related advanced hepatic fibrosis, cirrhosis, or hepatocellular cancer (HCC).[14] In the country, HDV surveillance is suboptimal due to the non-implementation of existing screening protocols in clinical settings. Nigeria may not be alone in the neglect of HDV surveillance, as studies have reported sub-optimal screening evidenced by a complete lack of data on national HDV prevalence in many countries.[2,9,10] Consequently, with diminished clinical and research interest, HDV infection has become a neglected healthcare problem in many countries. We conducted a questionnaire-based survey among clinicians in Nigeria to evaluate HDV awareness and screening practice, and elucidate factors influencing HDV surveillance in clinical settings in Nigeria.

Methods

Study design and population

The study was a descriptive cross-sectional questionnaire-based survey. It focused on consenting clinicians practicing in health facilities in Nigeria. Inclusion criteria included being a medical doctor who had practiced for at least one year in any private or public health facility in Nigeria and giving informed consent to participate in the study. Non-consenting medical doctors were excluded. Study participants were recruited between June and July 2022.

Sample size and sampling technique

The estimated sample size was computed at 95% confidence level, 5% margin of error, and anticipated response of 50% using the Epi Info software version 7, which yielded a calculated sample size of 342. However, only 213 respondents completed the online survey over 2 months of data collection (June 02- July 31, 2022). The study participants were recruited via convenience sampling using a snowballing method on social media platforms (WhatsApp) and e-mail to share the online survey link.

Survey instrument

A 20-question questionnaire divided into three sub-sections (demographics, work, and HDV awareness/survey practices/treatment modalities) composed mostly of multiple-choice questions, with a few freestyle answers for age, area of medical specialty, and HDV treatment modalities. The demographic sub-section inquired about basic information such as gender, age, country of undergraduate medical training, and nature of postgraduate medical training. The occupation sub-section inquired about specialty, type of healthcare settings, position and years of medical practices, and average number of HBV patients (including HBV-related HCC and cirrhosis) seen per month. The last section explored HDV awareness, screening practices, and treatment modalities employed by the respondents. The instrument designed as a Google form was set to allow only one submission per respondent, without the option to allow response editing after submission.

Procedure for data collection

Data was collected using an anonymous self-administered questionnaire distributed via email and WhatsApp group chat of relevant doctors' fora. The instrument was pre-tested for clarity and feasibility by distributing to clinicians who are members of the Enlightenment Initiative on Viral Hepatitis (EIVH) https://eivh.org/. The EIVH was founded in 2020 and consists of members including gastroenterologists, infectious disease experts, researchers, pharmacists, and nurses, among others, spread across four out of the six geopolitical zones in Nigeria. After pre-testing of the questionnaires, which yielded a Cronbach-alpha reliability coefficient of 0.82, the survey was distributed to clinician members of EIHV who subsequently shared within their professional networks and contacts resulting in snowball sampling. Snowball sampling used here refers to chain referral sampling in which first-stage distributors (members of EIHV) shared the survey with their professional networks, as well as personally reaching out to these contacts to share among relevant networks.

Ethical consideration

This study was a part of a larger study on virological profiles and serum biomarkers of HBV-induced HCC with ethical approval obtained in the years 2021 and 2022 from the Institutional Review Board committee of participating institutions, including University of Abuja teaching hospital (UATH/HREC/PR/2021), University College Hospital Ibadan (001/6/UI/EC/20/20516), Aminu Kano Teaching Hospital Kano (NHREC/20/01/2020/AKTH/EC/3070), Federal Teaching Hospital Katsina (FMCNHREC. REG. N003/082012), and Federal Teaching Hospital Ido-Ekiti (ERC/2022/0812/833A). Informed consent was obtained from the respondents by their choice of the "I agree option" to the statement on consent located on the first page of the survey instrument, which followed the introductory paragraph describing the study aims. Clicking accept automatically means consent is given, leading to access to the subsequent subsection of the instrument. Conversely, if "do not agree" was chosen the data collection process automatically terminates after appreciating the respondent for their time. To ensure the confidentiality of the information provided by the participants, no identifying information was collected, password-protected and encrypted laptops were used for the study, and only research team members had access to the primary study data.

Data analysis

Copies of the questionnaire were checked for completeness, and a serial number was given to each completed questionnaire for easy identification and recall. A coding guide was developed based on the variables and responses teased out from the questionnaires. This coding code was used to aid data entry into a computer. The IBM SPSS software (version 20.3) was used to facilitate data analysis. Descriptive statistics including mean, frequency distribution, percentages, and charts were used to present univariate data. Chi-square statistics and Fisher's Exact Test were used to test the association between dependent and independent variables at a level of significance set at 0.05.

Results

A total of 213 responses were retrieved at the end of the survey. Responses were checked for completeness, and improperly/partially filled responses were removed from the analysis. Altogether, only 210 responses were analyzed. The mean age of the respondents was 38.60 + 7.25 years with a male-to-female ratio of 1:2.5. While 13.8% of the respondents were gastroenterologists, the remaining others belonged to other areas of clinical medicine. Most (72.4%) of the respondents worked in public tertiary hospitals, and about 52.9% had more than 10 years of working experience [Table 1].

Overall, 89.5% of respondents knew HDV as a virus that requires hepatitis B virus (HBV) for its replication and occurs only in persons with HBV infection. Among those who answered the question about modalities for HDV screening, 11.0% Indicated that they do not know HDV screening methods. Response regarding available treatment options for HDV reported Peg-IFN as an option in 53.5% of respondents, while 16.1% reported conventional HBV treatment to be adequate for HDV [Table 2]. However, 23.2% of the respondents

Table 1: Socio-demographic characteristics of participants

Characteristics	Frequency	*n*=210 Percent (%)
Sex		
Female	59	28.1
Male	151	71.9
Age (years) (mean age 38.60 ± 7.25 years, range=22–71 year		
< 29	23	11.0
30–39	102	48.6
40–49	70	33.3
>50	15	7.1
Level of care/facility		
Primary Health Care Centre	6	2.9
Secondary Health Care Centre	38	18.1
Tertiary Health Care Centre	166	79.0
Nature of Practice		
Public Hospital	152	72.4
Private Hospital	19	9.0
Public and Private Hospital	39	18.6
Position		
Medical Officers	48	22.9
Residents	20	25.2
Specialist/ Consultants	142	52.9
Area of Specialty in Medicine		
General Practice	42	20.0
Family Medicine	25	11.9
Gastroenterology	31	14.8
Other internal Medicine*	52	24.8
Others[#]	60	28.6
Respondents' length of years in practice (years)		
< 5	46	21.9
5–10	53	25.2
>10	111	52.9
Highest Postgraduate Training		
None	17	8.1
Master's degree (M.Sc./ MPH)**	15	7.1
Residency	175	83.3
Doctoral Degree	3	1.4

had no idea of any treatment for HDV [Table 2]. Among clinicians who had managed HDV, Peg-IFN (87.5%) was the predominant treatment of choice [Table 2].

Of all the respondents, 91.4% have never screened for HDV in CHB patients, even among those with HBV-related HCC (83.3% of the gastroenterologists) [Table 3]. Among the few (8.6%) that screened their CHB patients for HDV, it was mainly done for research interests [Table 3]. The reasons for non-HDV screening among respondents included non-availability of screening tests (58.7%), not aware of any screening test for HDV (36.5%), HDV screening not a routine

Table 2: Knowledge relating to HDV infection, screening, and treatment

	Frequency	Percent (%)
[#]Know about HDV infection (*n*=210)		
Yes	188	89.5
No	22	10.5
How HDV Screening is done β (n=163)*		
HDV Ab	65	40.0
HDV RNA	47	28.8
HDV Ag	32	19.6
HDV Ag and HDV RNA	1	0.6
Don't know	18	11.0
What are the treatment options for HDV *(n=198)		
Pegylated interferon	106	53.5
Myrcludex	2	1.0
Supportive care	12	6.1
Treatment of HBV will take care of HDV	32	16.2
No idea	46	23.2

[#]Participants were asked if they knew that HDV infection can only occur in individuals with HBV

practice in their facility (2.7%), and referral of patients (2.1%) [Table 3]. Overall, 95.2% of respondents have never managed HDV infection [Table 3]. Practicing either in private or public hospitals was significantly associated with knowledge of HDV infection compared to those who practiced both in private and public hospitals (P = 0.013). Knowledge of HDV infection was distributed among respondents as follows; internal medicine specialty other than gastroenterology (98.3%), gastroenterology and hepatology (96.8%), general practice (89.5%), family practice (84.0%), and other specialties (70.9%) [Table 4]. Overall, there was a significant association between the area of specialty and knowledge of HDV infection (P = 0.008). However, no significant association was found between knowledge of HDV infection and other socio-demographic variables, such as sex, years of experience, and level of care of practice.

Discussions

Nigeria is an HBV hyperendemic region.[11] Thus, it has a large pool of individuals at risk of HDV infection. However, due to suboptimal HDV surveillance in most sub-Saharan African nations, including Nigeria,[24] HDV may be an unrecognized health concern. Our finding revealed that, majority of the clinicians were knowledgeable about the fact that HDV is only seen in HBV-infected persons. The high level of HDV awareness regarding the dependency of HDV on HBV among the respondents was anticipated since the respondents were

Table 3: Screening practices and experience relating to HDV management

Average number of HBV seen in a month	Frequency	Percent (%)
None	54	25.7
1–5	85	40.5
6–10	26	12.4
>10	45	21.4
Practice of conducting screening for HBV patients		
Always	8	3.8
Sometimes	10	4.8
Never	192	91.4
*Reasons for not conducting HDV screening in HBV patients (*n*=189)		
No Screening test available at the health centre	111	58.9
Not aware of any screening test for HDV	69	36.5
Not routinely done	5	2.7
Patients usually referred	4	2.1
*Reasons for conducting HDV screening (*n*=16)		
Research purpose alone	11	68.8
Clinical practice alone	0	0
For Research purpose and Clinical Practice	5	31.2
Practice of Conducting HDV screening for patients with HBV$^{\beta}$ * induced HCC (*n*=31)		
Always	0	0
Sometimes	5	16.1
Never	26	83.9
Reasons for not conducting HDV screening in HBV induced HCC patients $^{\beta}$* (*n*=25)		
No Screening test available at health centre	19	76.0
Not aware of any screening test for HDV	2	8.0
Not routinely done	2	8.0
Don't think it is necessary	1	4.0
Not commonly seen/Never seen such case	1	4.0
Ever-managed HDV infection		
Yes	10	4.8
No	200	95.2
*Management regimen used (*n*=8)		
Pegylated interferon	7	87.5
Treatment of HBV with nucleotides analogues	1	12.5

$^{\beta}$responses provided by gastroenterologist only. *Nonresponses were excluded

all clinicians who had gone through years of rigorous medical training with additional sub-specialization (in some cases). This finding is in contrast with limited knowledge of HDV shown in HDV-infected patients and caregivers.[25] In contrast to high-level knowledge of HDV infection, most (45.5%) of the respondents had limited knowledge regarding correct treatment options for HDV infection. This trend was not surprising as many of the participating clinicians had never managed HDV infection, and therefore may not find updating knowledge on HDV management relevant to their clinical practice. Myrcludex B/Bulevirtide was only recently approved conditionally for use in patients with detectable HDV RNA and compensated liver disease by the European Medical Agency.[26]

This study showed that over ninety percent of clinicians who participated in the study do not screen for HDV in CHB patients including those with HBV-related cirrhosis and HCC. Regretfully, some (23.2) of the respondents were unaware of any screening test for HDV. Total absence and/or sub-optimal HDV screening practices have been reported even in developed countries, even with established HDV screening guidelines.[25,27-30] This suggests that the lack of HDV screening in clinical settings is not peculiar to Nigeria but may rather reflect a global pattern compounded by prior unavailability of simple and improved diagnostics for screening and establishment of a standard HDV-RNA quantification laboratory. Major reasons for HDV screening inertia in our study participants included HDV screening not being a routine practice in their respective healthcare facility, and lack of availability of screening tests, among others. The SOGHIN 2021 clinical practice guidelines on viral hepatitis management in Nigeria recommended anti-HDV screening in all CHB, however,

Table 4: Association between respondents' selected characteristics and knowledge of HDV infection N=210

Variables	Know about HDV infection			χ^2	*P*
	Yes (%)	No (%)	Total		
Sex					
Male	52 (88.1)	7 (11.9)	59 (100.0)	0.169	0.802
Female	136 (90.1)	15 (9.9)	151 (100.0)		
Years of practice					
≤5 years	41 (89.1)	5 (10.9)	46 (100.0)	0.125	1.000
5 – 10 years	99 (89.2)	12 (10.8)	111 (100.0)		
>10 years	48 (90.6))	5 (9.4)	53 (100.0)		
Level of care of practice					
Primary Health Care	6 (100.0)	0 (100.0)	6 (100.0)	1.51$^{\pi}$	0.373
Secondary Health Care	32 (84.2)	6 (15.8)	38 (100.0)		
Tertiary Health Care	150 (90.4)	16 (9.6)	166 (100.0)		
Nature of practice					
Public hospital	141 (92.2)	12 (7.8)	153 (100.0)	7.31$^{\pi}$	0.013*
Private Hospital	18 (94.7)	1 (5.3)	19 (100.0)		
Public and private hospital	29 (76.3)	9 (23.7)	38 (100.0)		
Area of specialty					
Family Medicine	21 (84.0)	4 (16.0)	25 (100.0)	13.77$^{\pi}$	0.008*
General Practice	34 (89.5)	4 (10.5)	38 (100.0)		
Gastroenterology	30 (96.8)	1 (3.2)	31 (100.0)		
Other internal medicine$^{\beta}$	57 (98.3)	1 (1.7%)	58 (100.0)		
Others$^{\beta\beta}$	46 (70.9)	12 (20.7)	58 (100.0)		

π- Fisher's exact was used. *- P-value <0.05. $^{\pi}$Other areas of internal medicine. $^{\pi\pi}$Others – other areas of medicine

the guideline noted possible unavailability of the test routinely.[14] Therefore, the reported unavailability of screening test platforms and HDV not being a routine test in most health facilities agrees with the observation raised in the SOGHIN guideline regarding the unavailability of HDV screening in routine practice in Nigeria. Practically non-existing HDV screening in CHB in clinical settings in Nigeria as shown in this study poses a challenge to obtaining reliable epidemiological and clinically relevant data regarding HDV spread and burden in the country. Consequently, understanding the actual burden of HDV in the country remains elusive, and may hinder evidence-based public health measures against viral hepatitis in general. Recent advances in HDV research have led to a better understanding of HDV pathogenesis, with consequent increased available treatment options at various stages of development and clinical trials.[31] There are also improved methods for diagnosis and opportunities for the deployment of rapid test kits for HDV screening.[32-34] Thus, leveraging already existing studies with sample pools on different HBV-positive cohorts will be useful in providing rapid data on HDV in Nigeria.

Practicing in areas of medicine not regularly involved in the management of viral hepatitis patients may account for the significant association between knowledge of HDV infection and the area of specialty found in this study. Similarly, another study documented low HDV awareness and knowledge among primary care physicians.[30] The study,[30] suggested low HDV awareness among primary care physicians as a key factor in limited HDV screening test uptake. Significantly lower rates (76.3%) of HDV knowledge among dual practitioners, in comparison to those who practiced in either private (94.7%) or public (92.2%) health institutions, will require further studies to elucidate the implication of this finding and the likely impact of nature of practice on clinician knowledge of neglected diseases such as HDV. Other studies have documented the pros and cons of dual practice with respect to economics and service delivery.[35-37] But there is limited data on the impact of the nature of practice on knowledge of less frequently screened- for medical conditions such as HDV.

Due to the diverse nature of our respondents in terms of clinical practices, the study outcomes may be less representative of the total population of clinicians, such as gastroenterologists, infectious disease experts, etc., who may be more involved in the management of viral hepatitis in Nigeria. Though the study was conducted among clinicians across various parts of the country, the result cannot be generalized due to the small sample

size. The poor response rate to the online survey is a major limitation.

In conclusion, the study documents limited HDV screening in clinical settings in Nigeria and highlights factors that influence screening, such as unavailability of testing facilities, lack of screening test awareness, etc., HDV awareness creation and larger nationwide studies will be necessary to provide more insight on HDV screening and associated factors among clinicians in Nigeria. Such studies will generate needed data to guide policy and drive evidence-based practice.

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Conflicts of interest

There are no conflicts of interest.

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