Determinants of Hepatitis D in Sub-Saharan Africa: Trends and Challenges (Systematic Review)

Isaac Boamah1,2
1University of Ghana Medical School, P.O. BOX 4236 ACCRA
2Livingstone International University of Tourism Excellence & Business Management (LIUTEBM) Ibex Hill, Lusaka, Republic of Zambia

ABSTRACT

Hepatitis D, also referred to as hepatitis D virus, or hepatitis delta virus (HDV) is considered to be a subviral satellite because it can propagate only in the presence of the hepatitis B virus (HBV) (WHO, 2020). There are uncertainties about the epidemic patterns of HDV infection and its contribution to the burden of liver disease. Hepatitis D virus (HDV) is a defective virus that completes its life cycle only with hepatitis B virus (HBV). The HBV with HDV super-infection has been considered as one of the most severe forms of the chronic viral hepatitis (Chen et al, 2019). However, there is a scarcity of data on the Sub-Saharan Africa burden of HDV infection. We estimated the Determinants of Hepatitis D in Sub-Saharan Africa: Trends and Challenges.

Keywords: HBV, HDV, Infection, Sub-Saharan Africa.

1 Introduction

Hepatitis D virus (HDV) is a defective single-stranded RNA virus of the Deltaviridae family. It is an incomplete RNA virus that needs the hepatitis B surface antigen to transmit its genome from cell to cell. It therefore only occurs in people who are positive for the hepatitis B surface antigen. The mean incubation period varies from 60 to 90 days, but it can vary as widely as 30 to 180 days. The mode of transmission of HDV is similar to that of HBV. HDV infection can occur either as a co-infection with HBV or as a super infection in those with chronic HBV. HBV / HDV Co-infection leads to severe acute disease, indistinguishable from acute HBV and with a relatively low risk of chronicity. Super-infection usually develops as acute exacerbation of chronic hepatitis with a high risk of progression to chronic liver disease. Diagnosis of Acute HDV Infection Positive HDV Ag and HDV-RNA (PCR) confirm a diagnosis of acute HDV infection. The anti-HDV (IgM class) appears 30–40 days after the first symptoms. Management is conservative and supportive (GHG, 2012).

In acute hepatitis, simultaneous infection with HBV and HDV can lead to a mild-to-severe hepatitis with signs and symptoms indistinguishable from those of other types of acute viral hepatitis infections. These features typically appear 3–7 weeks after initial infection and include fever, fatigue, and loss of appetite, nausea, vomiting, dark urine, pale-coloured stools, jaundice (yellow eyes) and even fulminant hepatitis. However, recovery is usually complete, development of fulminant hepatitis is infrequent, and chronic hepatitis D is rare (less than 5% of acute hepatitis). In a super infection, HDV can infect a person already chronically infected with HBV. The super infection of HDV on chronic hepatitis B accelerates progression to a more severe disease in all ages and in 70–90% of persons. HDV super infection accelerates progression to cirrhosis almost a decade earlier than HBV mono-infected persons. Patients with HDV induced cirrhosis are at an increased risk of hepatocellular carcinoma (HCC); however, the mechanism in which HDV causes more severe hepatitis and a faster progression of fibrosis than HBV alone remains unclear (WHO, 2022).

Sub-Saharan Africa has four geographic regions: West Africa, Middle Africa, East Africa, and Southern Africa. The medical burden of HDV remains high in low and low-to-middle-income countries of Africa, Asia and Oceania, where the prevalence of HBsAg carriers is often in excess of 5% in the population. The impact of HBV vaccination is still low: in Africa, only 11 countries had introduced HBV birth vaccine coverage by 2017 (WHO, 2020).

2 Literature

Hepatitis delta virus (HDV) is a small, defective RNA virus that can infect only individuals who have hepatitis B virus (HBV); worldwide more than 15 million people are co-infected. There are eight reported genotypes of HDV with unexplained variations in their geographical distribution and pathogenicity. The hepatitis D virion is composed
of a coat of HBV envelope proteins surrounding the nucleocapsid, which consists of a single-stranded, circular RNA genome complexed with delta antigen, the viral protein. HDV is clinically important because although it suppresses HBV replication, it causes severe liver disease with rapid progression to cirrhosis and hepatic decompensation. The range of clinical presentation is wide, varying from mild disease to fulminant liver failure. The prevalence of HDV is declining in some endemic areas but increasing in northern and central Europe because of immigration. Treatment of HDV is with pegylated interferon alfa; however, response rates are poor. Increased understanding of the molecular virology of HDV will identify novel therapeutic targets for this most severe form of chronic viral hepatitis (Hughes, 2011).

HDV is a satellite RNA virus that depends on HBV for propagation. It uses the HBsAg as a viral envelope and shares the same hepatocytic receptor for viral entry. HDV is among the smallest of viruses capable of causing human disease, yet HBV co-infection with HDV is the most severe form of viral hepatitis. HDV transmission follows 2 patterns. Infection occurring simultaneously with HBV can cause extensive hepatic necrosis and manifest as a severe or even fulminant hepatitis with a high case fatality rate. With recovery, simultaneous infection in adults usually results in clearance of both viruses. Super-infection of persons with chronic HBV infection typically results in HDV persistence, leading to accelerated progression to cirrhosis and an increased risk of HCC relative to chronic HBV infection alone. Due to variation in awareness and incomplete testing among HBsAg-positive people, issues with standardisation of confirmatory molecular diagnostic techniques, and a historical lack of effective treatment options, HDV ascertainment has been suboptimal, even in high-income settings. HDV may therefore have an under-recognised role in the causation of liver disease and liver-related deaths (Stockdale et al, 2020). In a study published in the Journal of Hepatology in 2020, conducted in collaboration with WHO, it was estimated that hepatitis D virus (HDV) affects nearly 5% of people globally who have a chronic infection with hepatitis B virus (HBV) and that HDV co-infection could explain about 1 in 5 cases of liver disease and liver cancer in people with HBV infection. The study identified several geographical hotspots of high prevalence of HDV infection including Mongolia, the Republic of Moldova, and countries in western and central Africa (WHO, 2022).

There are eight known hepatitis D virus genotypes, which differ in geographical distribution and presumably in natural course and disease severity. Genotype 1 is predominantly found in Europe, genotypes 2 and 4 in Asia, genotype 3 in South America, and genotypes 5–8 in Africa (Stockdale et al, 2020). In over 90% of people, chronic hepatitis B virus infection can be controlled long term with oral nucleoside analogues, which inhibit the viral polymerase. However, they do not affect chronic hepatitis D virus infection. Specific therapies for hepatitis D virus infection are not yet available; standard of care for chronic infection is 48 weeks of pegylated interferon alfa, which is associated with clearance of hepatitis D virus RNA in around 25% of patients (with the caveat that long-term relapses are likely to occur) (Stockdale et al, 2020). Various therapeutic targets in hepatitis D virus infection, including prenylation, viral entry, and HBsAg secretion, are under investigation, but these drugs all are in early clinical development. Regulatory authorities such as the European Medicines Agency classify hepatitis D virus infection as an orphan disease and have given orphan drug status to novel therapies (Manns, 2017).

Understanding of the global epidemiology of hepatitis D virus infection is still poor, with many knowledge gaps. The virus was first discovered in Italy by Mario Rizzetto, and was described in 1977 as the third of the five major hepatotropic viruses. A substantial proportion of the population with hepatitis B virus infection resides in Africa. However, data for hepatitis D virus epidemiology are scarce for sub-Saharan Africa, where the prevalence of HBsAg exceeds 8%. Hepatitis D virus might represent an important additive cause of chronic liver disease in this region. Particularly severe forms of hepatitis D virus infection were reported in the Amazon Basin, where the combination of hepatitis D virus genotype 3 with hepatitis B virus genotype F is prevalent. The natural course of hepatitis D virus infection and disease phenotype depend on host, virus, and environmental factors (Manns, 2017). In The Lancet Global Health, Alexander Stockdale and colleagues did a systematic review and meta-analysis to assess anti-hepatitis D virus seroprevalence in HBsAg-positive patients in sub-Saharan Africa. This publication contributes substantially to knowledge about localised clustering of hepatitis D virus endemicity across sub-Saharan Africa, with high prevalence particularly in central Africa, but also in West Africa. By contrast, prevalence was very low in east and southern Africa. These data strongly support the hypothesis that hepatitis D virus infection significantly contributes to morbidity and mortality of chronic hepatitis B virus in central and western Africa. Another finding of this study is that, apart from anti-hepatitis D virus antibody testing by commercially available ELISAs, diagnostics (eg, determination of viral replication, genotyping by PCR) are limited or not widely available in most of these regions. In the 30 studies retrieved, HCV RNA testing was reported for only 16 anti-HDV positive populations, a total of 324 patients. This Article also includes new data from two HIV-positive cohorts in Ghana and Malawi, and
draws attention to the importance of hepatitis B virus, hepatitis D virus, and HIV co-infection as a life-threatening combination.

Estimating HDV prevalence and the relative contribution of HDV towards liver disease, including among general populations and specific population groups, is critical to guide clinical care and policy formulation and inform effective public health interventions and development of new medicines. Yet, obtaining accurate estimates of HDV epidemiology is challenging for several reasons. Firstly, at the population level, large sample sizes are required to identify HBsAg-positive individuals prior to testing for HDV. In settings with low prevalence of HBV infection, sufficiently large surveys may not be feasible. Secondly, heterogeneity in HDV estimates might be expected because of variable and potentially evolving epidemic patterns, as well as variations in methodology. Thirdly, the selection criteria for HBsAg and subsequent HDV testing may lead to non-representative sampling. Therefore, careful assessment of potential biases and assessment of representativeness is required to synthesise epidemiological estimates of HDV prevalence (Stockdale et al, 2020).

Further studies of the prevalence, natural history, health burden, and mode of transmission of hepatitis D virus infection in Africa are urgently needed. Screening every patient infected with hepatitis B virus in sub-Saharan Africa is essential. Additionally, access not only to anti-hepatitis D virus antibody testing but also to RNA and genotype testing needs to become available throughout the region. Data for the natural history of hepatitis D virus are absent for sub-Saharan populations (and thus for genotypes 3–8). The Hepatitis Delta International Network published their registry data for 1576 patients from many centres in Europe, Asia, North America, and South America this year (Manns, 2017).

The routes of HDV transmission, like HBV, occur through broken skin (via injection, tattooing etc.) or through contact with infected blood or blood products. Transmission from mother to child is possible but rare. Vaccination against HBV prevents HDV coinfection and hence expansion of childhood HBV immunization programmes has resulted in a decline in hepatitis D incidence worldwide. Chronic HBV carriers are at risk of infection with HDV. People who are not immune to HBV (either by natural disease or immunization with the hepatitis B vaccine) are at risk of infection with HBV, which puts them at risk of HDV infection. Those who are more likely to have HBV and HDV co-infection include indigenous people, people who inject drugs and people with hepatitis C virus or HIV infection. The risk of co-infection also appears to be potentially higher in recipients of haemodialysis, men who have sex with men and commercial sex workers (WHO, 2022).

Pegylated interferon alpha is the generally recommended treatment for hepatitis D virus infection. Treatment should last for at least 48 weeks irrespective of the patient’s response. The virus tends to give a low rate of response to the treatment; however, the treatment is associated with a lower likelihood of disease progression. This treatment is associated with significant side effects and should not be given to patients with decompensated cirrhosis, active psychiatric conditions and autoimmune diseases. More efforts are needed to reduce the global burden of chronic hepatitis B and develop medicines that are safe and effective against hepatitis D and are affordable enough to be deployed on a large scale to those who are most in need (WHO, 2022).

3 Method

A search of PubMed, Embase, Scopus, Science Direct, Web of Science, and Google Scholar identified 3,104 articles published between 1st January 1998 and 16th January 2023, after removal of duplicate citations. The search strategy included synonyms of hepatitis D and terms describing HDV epidemiology, signs and symptoms, diagnosis, treatments, trends and challenges. Following a review of abstracts, 93 articles were selected for review of full text. We identified 43 reports for review in the grey literature. We included studies with a minimum sample size of 50 patients. Between 16th and 17th January 2023, we also performed searches of the grey literature within the Global Health Data Exchange database, international health surveillance programmes, and official national health surveillance websites and reviewed surveys, censuses, vital statistics, and reports not already included in previously identified scientific publications. We additionally searched world atlas (Sub-Saharan Africa - WorldAtlas) and the World Health Organization (Hepatitis D (who.int)) to retrieve HDV trends and challenges.

4 Results and discussion

Trends

Rates of HDV have not been reported for several countries and no longitudinal trend has been described. In Africa, a 2017 meta-analysis determined that the pooled seroprevalence of HDV in general and in liver disease populations was, respectively, 25.6% and 37.7% in Central Africa and 7.33% and 9.5% in Western Africa. It was
only 0.05% in the general population of Eastern and Southern Africa but information from these macro-areas is scarce. Recent surveys have confirmed a hyper-endemic pattern of HDV infection in poor countries of the equatorial belt. HDV seroprevalence in Cameroon was 10.6% in 1,621 unselected HBSAg-positive individuals in 2011 and 46.7% in 1,928 HBSAg-positive hospital patients in 2010 to 2016, while it was 27.7% in 303 HBSAg carriers between 2005 and 2008 in Gabon. In both countries there were large regional variations. In the Central African Republic, 50% of patients with chronic HBSAg-positive hepatitis and hepatocellular carcinoma (HCC) were anti-HD positive between 1998 and 2010 and, in the Democratic Republic of Congo, 26.1% of HBsAg-positive patients with jaundice were seropositive in 2017 (Rizzetto et al, 2021).

From a total of 2717 initially identified studies, only 182 articles from 61 countries and regions met the final inclusion criteria. The overall prevalence of HDV was 0.98% (95% CI 0.61 to 1.42). In HBsAg-positive population, HDV pooled prevalence was 14.57% (95% CI 12.93 to 16.27). Seroprevalence was 10.58% (95% CI 9.14 to 12.11) in mixed population without risk factors of intravenous drug use (IVDU) and high-risk sexual behaviour (HRSB). It was 37.57% (95% CI 29.30 to 46.20) in the IVDU population and 17.01% (95% CI 10.69 to 24.34) in HRSB population (Chen et al, 2019).

A study of 282 studies, comprising 376 population samples from 95 countries, which together tested 120,293 HBsAg-positive people for anti-HDV. The estimated anti-HDV prevalence was 4.5% (95% CI 3.6–5.7) among all HBsAg-positive people and 16.4% (14.6–18.6) among those attending hepatology clinics. Worldwide, 0.16% (0.11–0.25) of the general population, totaling 12.0 (8.7–18.7) million people, were estimated to be anti-HDV positive. Prevalence among HBsAg-positive people was highest in Mongolia, the Republic of Moldova and countries in Western and Middle Africa, and was higher in injecting drug users, haemodialysis recipients, men who have sex with men, commercial sex workers, and those with HCV or HIV. Among HBsAg-positive people, preliminary PAF estimates of HDV were 18% (10–26) for cirrhosis and 20% (8–33) for HCC (Stockdale et al, 2020).

The overall prevalence rates of HDV infection (HBsAg positive) in the general populations examined in the Northern Africa region ranged from 1.2 to 8.9%. The lowest rate was reported in Libya, followed by Tunisia, Algeria, and Morocco. The highest rates were reported in Mauritania, Sudan, and Egypt. The prevalence rate of HDV among liver disease and hemodialysis patients ranged from 19% to 27.2% with an estimated seroprevalence of 20.7% (95% CI: 9.87–44.53). Significant variability in HDV seroprevalence was noticed among the countries in the region, particularly among liver disease patients. In studies specially those reported from Egypt, Tunisia, Sudan, and Mauritania, in which patients with confirmed liver disease were compared with the general population (asymptomatic and without evidence of hepatic diseases), the presence of antihepatitis D virus among patients with liver diseases and HBsAg positive was statistically significant (P< 0.001) (Daw et al, 2018).

Demographic factors such as sex and age, which may influence the prevalence of HDV in North Africa, were analyzed in this review. HDV prevalence was reported consistent at all ages among adults of 18-45 years, but no specific age trend and no significant association with sex were observed. This is in agreement with a recent prospective multicenter study conducted in Taiwan indicating that there is a significantly increasing trend in HDV prevalence with age in people who are not intravenous drug users. Blood donors and pregnant women have shown prevalence rates of infection similar to those of the general population. Furthermore, no study compared the prevalence of HDV in urban and rural regions in North Africa despite the great diversity in the level of urbanization in these countries. A recent study on HCV in this region showed that the prevalence of HCV in rural areas is higher than in urban cities, particularly in Egypt and Sudan (Daw et al, 2018).

In another study by Daw et al, 2018 the risk factors for HDV infection in North Africa have not been studied and we did not identify any study showing an association between hepatitis D virus seroprevalence and HIV, HCV coinfection, intravenous drug use, and other HDV risk factors. However, North Africa has been considered a leading hub of drug trafficking and an area of high prevalence of HCV and HIV. A large cohort study carried out in Libya in 2014 showed a major increase in the acquisition of HIV, HBV (plus or minus HDV), and HCV, particularly among intravenous drug users. This is in agreement with a recent hepatitis delta outbreak reported in ongoing epidemics of injection drug use in Eastern Europe and Russia. Interestingly, new incident cases of HDV in Taiwan are no longer among intravenous drug users but among HIV-positive homosexual men, often presenting with liver flare-ups and syphilis independently of the use of successful antiretroviral therapy (Chen et al, 2021).

**Challenges**

There are significant data gaps, most strikingly in North America and Latin America, Southern Africa and most of Asia, where more data are required to obtain accurate estimates of anti-HDV prevalence. Several issues exist for the correct diagnosis of HDV, ultimately affecting its true prevalence. Ideally, HDV diagnosis should be made...
with the identification of both HDV antibody and RNA, to distinguish between the chronic and previous infections, and to monitor treatment response. Most antibody tests are ELISA kits, but the accuracy of internal and commercial quantitative analysis of HDV RNA varies significantly, and sometimes HDV RNA cannot be detected in HDV RNA-positive samples (Chen et al, 2021).

Bremer et al. found that automated nucleic acid isolation led to viral load underestimation by comparing manual and four automated HDV RNA extraction methods (AmpliPrep, MagNA Pure, QIAcube QBK and QIAcube VRK). Moreover, the secondary structure and different HDV genotypes should be considered when designing primers and probes. Besides, the choice of quality control products will also affect the accurate quantification of HDV RNA. The ideal viral nucleic acid quality control products cannot not only be used for the quality control of nucleic acid detection process, but also an important material basis for the evaluation of detection procedures and the comparison of results between different laboratories.

At present, the quality control products of RNA viruses are mostly bare RNA fragments or whole virus particles. Bare RNA fragments, as quality controls, are easily degraded by RNase in the environment and cannot effectively react with to the nucleic acid extraction process. Traditional RNA preservatives such as alcohols and guanidine can lead to RNA degradation. RNAlater is a good RNA stabilizer, but has different effects on enveloped and non-enveloped viruses. For example, at room temperature, after long term storage of RNAlater, the cellular infectivity of non-enveloped enterovirus remained high, but the cellular infectivity of enveloped vesicular stomatitis virus decreased (Chen et al, 2021). The whole virus particles, especially the inactivated virus particles, have safety risks as quality control materials. Although inactivated drugs can reduce infectivity, there is still a risk of incomplete inactivation, and virus inactivation reagents (such as formaldehyde) will destroy viral nucleic acid, affecting the extraction of its nucleic acid. The ideal RNA quality control products should be stored for a long time without degradation or loss of copy number. Armored RNA technology can overcome RNA instability and has been widely used in the research of RNA viral nucleic acid quality control products. Pasloske et al. invented armored RNA by building the quality controls for HIV.

The principle of this technology is the use of genetic engineering methods to clone a sequence containing phage coat protein gene and target fragment into the expression vector. The vector transcribed the cloned fragment into recombinant RNA and assembled it into spherical RNA–protein complex, namely RNA virus-like particles, using the shell protein synthesized from the shell protein gene on the vector, thus preventing the RNA degradation (Chen et al, 2021).

According to Rizzetto et al, The information on HDV from other countries in Africa comes from a single or few regional studies. These studies are limited by geographic distribution, as such; accurate country-specific prevalence estimates remain elusive, as slight variations in studies can significantly change national prevalence figures. The distribution of HDV reported in Oceania is also limited and irregular; anti-HD and serum HDV RNA were found in 55.7% and in 37%, respectively, of 54 HBsAg-positive patients in Kiribati, Western Pacific, but in no patients from Tonga, Fiji and Vanuatu.

HBV replication was presumably suppressed by anti-retrovirals and HDV infection was independently associated with mortality and liver-related events, including HCC. A recent systematic review and meta-analysis of CHD has also shown that the disease is associated with an increased risk of HCC compared to HBV monoinfection, with a pooled odds ratio (OR) of 1.28 (95% CI 1.05–1.57; F2 = 67.0%). In a sensitivity analysis limited to prospective studies, the OR was 2.77 (95% CI 1.79–4.28; F2 = 0%), suggesting that the overall rating may have been underestimated by study heterogeneity. Furthermore, the risk was higher in HIV-coinfected populations (pooled OR 7.13; 95% CI 2.83–17.92; p <0.001, F2 = 0%) and in studies from Asia, albeit with substantial heterogeneity (pooled OR 1.44; 95% CI 1.04–2.00; p = 0.03; F2 = 68.5%). Although an association between higher HCC risk and particular HDV genotypes was not reported, this cannot be ruled out based on the selective geographical distribution of some genotypes, in particular genotype 2 which is localised mostly in the Far East (Rizzetto et al, 2021).

5 Conclusion
An estimated 12 million people worldwide have experienced HDV infection, with higher prevalence in certain geographic areas and populations. HDV is a significant contributor to HBV-associated liver disease. More quality data are needed to improve the precision of burden estimates. Our study highlights the need for increased focus on the routine HDV screening and rigorous implementation of HBV vaccine programme. While WHO does not have specific recommendations on hepatitis D, prevention of HBV transmission through hepatitis B immunization, including a timely birth dose, additional antiviral prophylaxis for eligible pregnant women, blood safety, and safe
injection practices in health care settings and harm reduction services with clean needles and syringes are effective in preventing HDV transmission. Hepatitis B immunization does not provide protection against HDV for those already infected with HBV.

Public health agencies may want to report on HDV infection and implement activities to mitigate the risk of HDV acquisition according to their local epidemic. In addition to the adoption of routine testing for all HBsAg-positive people, the addition of anti-HDV/HDV RNA testing (including the use of dry blood spots) as part of representative population surveys such as demographic health surveys, would be useful in areas with sparse data.

Hepatitis D is widely distributed but neglected disease. A better description of the role that HDV plays in causing liver disease, better efforts to improve epidemiological data collection, ascertainment of temporal trends and identification of locally important risk factors would inform development of new medicines and help in mounting an effective public health response (Stockdale, 2020).

Stockdale and colleagues’ Article not only fills a major gap in knowledge about the epidemiology of hepatitis D virus infection in sub-Saharan Africa, it also highlights the need to include African populations in future trials of drugs for hepatitis D virus infection, which seems to be a topic of interest in the pharmaceutical industry at present, given that hepatitis B virus infection can be controlled and hepatitis C virus infection can be cured. The pharmaceutical industry should be encouraged to include African centres at a very early stage in their clinical development programmes for novel hepatitis D virus therapies, rather than waiting until the drugs have been developed and approved elsewhere. Finally, promotion and support of vaccination against hepatitis B virus infection are more important than ever, given the continued absence of vaccines against hepatitis D virus infection to protect chronic hepatitis B virus carriers against superinfection.

Reference

7. Hepatitis D (who.int)