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INVITED COMMENTARY

Hepatitis Delta Virus Infection in the United States: If You Seek, You May Find

Hamidreza Karimi-Sari[1] · **Oluwaseun Falade-Nwulia**[1]

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Hepatitis delta virus (HDV) is a defective hepatotropic pathogenic virus that requires the presence of the hepatitis B virus (HBV) to coinfect humans. Historically, HDV infection has been associated with risk factors such as injection drug use, high-risk sexual practices, or immigration from countries with a high prevalence of HBV. HDV testing guidelines have thus reflected this understanding, recommending testing in HBsAg individuals with risk factors or those with elevated transaminases despite low or undetectable HBV DNA [1]. Risk-based screening is unfortunately fraught with challenges, likely contributing to low rates of HDV screening in the US [2]. As such the burden of HDV infection is likely underestimated [2, 3].

In one study of 11,190 chronic HBV-infected patients in New York, only 12.9% were screened for HDV during 2016–2021 [2]. Another study of commercial laboratory testing of 157,333 patients with evidence of chronic HBV infection between 2016 and 2020 demonstrated follow-up HDV testing either with HDV antibody or HDV RNA in only 6.7%. Among 12,002 patients with HBV receiving care in the Veterans Health Administration between 2010 and 2020, 19.7% were evaluated for HDV using HDV antibody, HDV antigen, or HDV RNA [4]. Other data suggest that risk-based testing may not capture the full spectrum of patients with HDV infection. In a study by Nathani et al. 18% of people with HDV infection did not meet HDV risk-based American Association for the Study of Liver Diseases (AASLD) guideline screening criteria; 74% had no history of intravenous drug use, 71% were HIV negative, 68% did not have a negative HBV DNA with elevated liver enzymes, 64% were HCV negative, 51.1% were not men who have sex with men, 43% did not have high-risk sexual practices, and 18% were not from HDV endemic areas [2].

Contributors to low HDV screening rates in the US include varying guideline recommendations on who should be screened for HDV, regional differences in availability and uniformity of HDV testing, low awareness of HDV by healthcare providers, or perceived lack of benefit of screening given limited HDV treatment options [2, 4].

Low awareness of HDV, especially among primary care clinicians, may however limit the uptake of this testing. Among 1444 chronic HBV-infected patients screened for HDV, the majority were screened by gastroenterologists and hepatologists (90.2%) and fewer by infectious disease physicians (5.5%) and internal medicine physicians (2.7%). Attending physicians performed 80.5% of the screenings followed by 16.6% by advanced practice providers and 2.7% by physician trainees [2]. Efforts are needed to increase awareness of HDV infection and the negative impact of HDV/HBV coinfection on patient outcomes among a wide range of clinicians.

In the updated Chronic Liver Disease Foundation (CLDF) guidelines, universal HDV screening is recommended in all patients who are HBsAg positive. Similar to findings with the implementation of universal as opposed to risk-based testing for hepatitis C virus (HCV) infection, universal testing has the potential to increase HDV screening uptake, likely to occur through the simplification of the HDV testing decision for providers in a wide range of clinical and laboratory settings and also through reduction of the barrier to testing of stigma perceived by patients [5, 6].

In this issue of *Digestive Diseases and Sciences,* Pan et al. analyze the updated guidelines from the CLDF on testing, diagnosis, and management of HDV based on a network data review performed by an expert panel [7]. They present data on the increased risk of cirrhosis (relative risk [RR]: 2.3–2.6), hepatocellular carcinoma (RR: 1.4–9.3, liver decompensation (RR: 2.2–3.1, need for liver transplantation (RR: 1.9), and mortality (RR: 2.0–7.9) in people with

✉ Hamidreza Karimi-Sari
hkarimi1@jhmi.edu

[1] Division of Infectious Diseases, Johns Hopkins University School of Medicine, 5200 Eastern Avenue, MFL Center Tower, Baltimore, MD, USA

HBV and HDV coinfection compared with people with HBV infection alone. As recommended by the authors, initial HDV screening should be done using a total HDV antibody test. A positive HDV antibody test should then be followed by HDV RNA testing. Data suggest that HDV testing can be facilitated through reflex laboratory testing. The implementation of reflex HDV antibody testing on HBsAg-positive samples was associated with an increase in the HDV screening rate from 2 to 93% in one study [5].

There are currently no United States Food and Drug Administration (FDA)-approved treatments for HDV. PEGylated interferon alfa for at least 48 weeks used based on expert guidance for HDV treatment in patients without decompensated liver disease is associated with low rates of virologic response (23–57%) and high rates of HDV relapse after treatment discontinuation [1]. Despite these limited virologic outcomes, significant reductions in HBV DNA and normalization of alanine aminotransferase resulting from PEGylated interferon alfa are associated with improved clinical and histological outcomes [8]. Moreover, several agents including bulevirtide and lonafarnib with significantly improved adverse effect profiles are being evaluated in phase 3 clinical trials. With these emerging treatment strategies, it is time to identify individuals who have HDV infection.

Another approach to eliminating the harms of HDV is to prevent infection. The most effective approach is the use of vaccination to prevent HBV infection. In the absence of HBV infection, HDV infection cannot occur. The Advisory Committee on Immunization Practices recommends universal HBV screening of pregnant women and HBV vaccination and immunoglobin for infants born to HBsAg-positive women. The Advisory also recommends universal HBV vaccination at birth and for people 19–59 years old [9].

As we eagerly await the approval of agents effective against HDV, opportunities exist to increase awareness of HDV among clinicians and increase testing and awareness of infection among patients. Patients with HDV infection should be offered treatment or referred to specialist care for treatment either in routine practice or through clinical trials. The availability of effective HBV vaccines also provided an opportunity to prevent HDV infection through the prevention of HBV.

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