

# Multisociety consensus recommendations on hepatitis delta virus infection

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## Abstract

Hepatitis D virus (HDV) prevalence data and country-specific HDV guidelines are not widely available in the Gulf Cooperation Council (GCC) states. We developed consensus recommendations to guide healthcare professionals, policymakers, and researchers in improving HDV management and patient health outcomes in three GCC states: Kuwait, Saudi Arabia, and the United Arab Emirates. A consensus panel comprising hepatology experts (n = 6) from the three GCC societies was formed. The panel identified two broader areas related to clinical practice (screening and diagnosis, and treatment and management), addressed critical questions, and developed draft recommendations in February 2024. The strength of the final set of recommendations was subjected to consensus voting in March 2024. A majority was defined *a priori* with a two-thirds vote (67%). The paper outlines those recommendations alongside showcasing the current epidemiology of HDV in the GCC states, emphasizing the variability in prevalence, demographic patterns, and region-specific risk factors. It also highlights the current state of screening and diagnosis practices, identifying key obstacles, such as access to advanced screening protocols and diagnostic tools. Furthermore, HDV treatment landscape and preventative strategies are outlined, focusing on vaccination, public health initiatives, and the crucial role of public awareness and education. Ethical and sociocultural considerations are discussed, underscoring the importance of culturally sensitive healthcare practices. These recommendations present a comprehensive overview of the challenges and strategies for managing HDV in these states. Policy recommendations are provided to support HDV management, including standardizing care protocols and promoting public health measures.

**Keywords:** Hepatitis D virus, Kuwait, Saudi Arabia, UAE, screening, practice guidelines, consensus, epidemiology, treatment

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## INTRODUCTION

The hepatitis delta virus (HDV), an incomplete virus requiring hepatitis B virus (HBV) coinfection for its replication, presents a significant etiological factor in hepatic morbidity and mortality.<sup>[1]</sup> Recognized as the most virulent among the hepatitis viruses, HDV induces both acute and chronic hepatic disorders. In the acute phase, HDV infection may cause fulminant hepatic failure. Chronic liver disease is typified by an accelerated progression toward hepatic cirrhosis, decompensated liver disease, and hepatocellular carcinoma (HCC).<sup>[2]</sup> The global prevalence of HDV in the general population was estimated to be 0.16% in a recent meta-analysis,<sup>[3]</sup> corresponding to approximately 12 million infections worldwide. Globally, the prevalence of HDV represents a public health challenge. A 2013 systematic review estimated 15–37% HDV infection among HBV carriers in the Eastern Mediterranean region.<sup>[4]</sup> However, a 2023 scoping review found that HDV prevalence data and country-specific HDV guidelines are not widely available in the Gulf Cooperation Council (GCC) states and precise prevalence of HDV is not known.<sup>[5]</sup> In Saudi Arabia, a single-center study found an HDV seroprevalence of 7.7% in HBV-positive patients, with 30.7% testing positive for HDV RNA.<sup>[6]</sup>

The GCC states, characterized by their distinct sociocultural and economic landscapes, present unique challenges in managing HDV, such as ensuring equitable healthcare services across diverse populations with varying healthcare needs and preferences.<sup>[7]</sup> As a result, this position statement and recommendations of the Saudi Society for the Study of Liver Disease and Transplantation (SASLT), Kuwait Gastroenterology Association (KGA), and The Emirates Gastroenterology and Hepatology Society (TEGHS) set out to accomplish the following key objectives:

- 1. Highlight current HDV epidemiological trends in the region:** to help understand prevalence, incidence, and demographic distribution, as this is crucial for tailoring targeted interventions to prevent, manage, and control HDV.
- 2. Identify HDV management challenges and opportunities in the region:** to aid in delineating existing disease prevention, diagnosis, and treatment obstacles and prospects, considering the healthcare landscape and cultural contexts.
- 3. Provide evidence-based regional HDV management recommendations:** to propose comprehensive guidelines for effective disease management based on the latest research and best practices, focusing on adapting these to the context of these GCC states.

With these objectives, we strive to shed light on the under-recognized issue that HDV represents in these GCC states and catalyze a concerted effort to improve patient health outcomes and public health practices in this region.

## HEPATITIS DELTA VIRUS EPIDEMIOLOGICAL TRENDS IN THE REGION

Understanding the disease epidemiology in the region is pivotal for tailoring public health strategies and healthcare interventions.<sup>[5,8]</sup> Prevalence and incidence rates vary across the different countries, potentially reflecting differences in public health policies, healthcare access, and population screening practices. A recent review with data on Jeddah, Saudi Arabia, found a 7.7% (n = 42) HDV seroprevalence among 182 hepatitis B surface antigen (HBsAg)-positive patients, with 30.7% (n = 165) testing positive for HDV RNA.<sup>[6]</sup> In patients with drug dependence from Saudi Arabia, the overall prevalence of anti-HDV among HBsAg-positive patients was 13.6%.<sup>[9]</sup> The anti-HDV prevalence in Kuwait was 31% in carriers of HBsAg.<sup>[10]</sup> In a Qatari study, of 2,348 HBsAg-positive patients, 125 (5.3%) were positive for HDV.<sup>[11]</sup> Still, a recent review reported that recent HDV prevalence data on the majority of GCC are unavailable, highlighting the specific need for HDV screening among the population in the GCC states.<sup>[12,13]</sup>

While comprehensive region-wide data may be lacking, available studies suggest a noteworthy presence of HDV in the GCC states.<sup>[14]</sup> The epidemiological landscape of HDV in this region, marked by its unique demographic and sociocultural contexts, underscores the need for region-specific approaches in tackling this health issue.<sup>[5]</sup> Enhanced surveillance, targeted research, and culturally sensitive public health interventions are essential to better understand and address the disease burden in this region.

## CONSENSUS PANEL

The consensus panel comprised hepatology experts (n = 6) representing the three societies: SASLT, KGA, and TEGHS. The panel identified two broader areas related to clinical practice in the region: (1) screening and diagnosis and (2) treatment and management. The panel addressed three critical questions in both areas and developed draft recommendations based on literature evidence, patient preferences, and patient values in February 2024. The strength of the final set of recommendations was subjected to consensus voting using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method ('strong' or 'weak') in March 2024. A majority was defined *a priori* with a two-thirds vote (67%).

## SCREENING FOR AND DIAGNOSIS OF THE HEPATITIS D VIRUS IN THE REGION

### Who should be screened?

Effective screening and diagnosis are critical in managing and controlling HDV infection. Disease screening in the GCC states largely follows international guidelines, such as those issued by the European Association for the Study of the Liver (EASL),<sup>[15]</sup> which advocates for HDV testing in all HBsAg-positive individuals. However, the guidelines proposed by the American Association for the Study of Liver Diseases (AASLD) diverge, suggesting a risk-based approach for HDV screening in patients with an HBV infection, specifically targeting patients with HBV infection, who may be at higher risk for HDV coinfection, based on various factors, such as demographics, clinical history, and epidemiological considerations.<sup>[16]</sup> This difference in approach underscores the need for healthcare providers in the GCC states to carefully consider and adapt international guidelines to suit the regional context and healthcare infrastructure while ensuring effective screening and diagnosis of HDV infection. Recent empirical data indicate that such a risk-based screening strategy may fail to identify a substantial fraction of HDV cases.<sup>[17]</sup> Furthermore, it has been observed that anti-HDV testing is infrequently conducted among HBsAg-positive carriers,<sup>[18]</sup> even in regions where universal screening is recommended, highlighting a significant gap in adherence to guidelines in practice.

Increasing awareness among healthcare professionals about the importance of screening for HDV in patients with HBV, particularly among high-risk groups, is crucial.<sup>[19]</sup> These high-risk groups include individuals with chronic HBV infection or hepatitis C (HCV) infection,<sup>[20]</sup> people who inject drugs, people with multiple sexual partners, men who have sex with men, individuals from endemic regions with high HDV prevalence, household contacts of HDV-infected individuals, and healthcare workers.<sup>[17,21]</sup> By targeting these high-risk groups for screening, healthcare professionals can improve early detection and management of HDV infection, ultimately reducing the burden of liver disease and associated complications. HDV screening practices in the GCC states vary, often due to differences in healthcare infrastructure and resource allocation. For this reason, variations in healthcare policies and priorities among GCC states can further contribute to differences in HDV screening practices. These disparities highlight the importance of tailored approaches to screening and diagnosis that consider the unique context of each country while striving for equitable access to testing and care for all individuals at risk of HDV infection.<sup>[22]</sup>

### Recommendations

1. Every HBsAg-positive patient should be screened for HDV antibodies (strong consensus).
2. Increase awareness among healthcare professionals about the importance of screening for HDV in patients with HBV, particularly among high-risk groups (strong consensus).
3. Develop and implement standardized and validated HDV screening protocols across the region to ensure consistency in disease detection and management (strong consensus).
4. Incorporate HDV screening into existing national hepatitis B and C screening programs to streamline the process and maximize resource utilization (strong consensus).

### How should screening be performed?

In patients presenting with acute or chronic HDV infection, the identification of specific HBV and HDV markers is essential for accurate diagnosis and management.<sup>[21]</sup> HDV infection may occur as a combined simultaneous coinfection with HBV, leading to acute HBV and HDV, or as a superinfection in individuals with chronic HBsAg positivity.<sup>[23]</sup> The diagnosis of acute HBV/HDV simultaneous coinfection relies on the detection of acute HBV infection markers [HBsAg, immunoglobulin (Ig) M and G antibodies to hepatitis B core antigen (anti-HBc IgM and IgG)] and acute HDV infection markers (anti-HDV IgM and IgG and serum HDV RNA).<sup>[24,25]</sup> The hallmark of HBV/HDV simultaneous coinfection is the presence of anti-HDV IgM in conjunction with elevated anti-HBc IgM levels.<sup>[26]</sup> The SASLT practice guidelines highlight the need for targeted HBV/HDV recommendations.<sup>[27]</sup>

Acute HDV infection resulting from acute HBV coinfection typically resolves spontaneously, progressing to chronicity in only a small fraction of cases.<sup>[26]</sup> In contrast, HDV superinfection in individuals with chronic hepatitis B (CHB) often leads to severe acute hepatitis, evolving into chronic hepatitis D (CHD) in a majority of cases.<sup>[28]</sup> Distinguishing superinfection from coinfection can be challenging, especially if prior HBsAg status is unknown,<sup>[29]</sup> with low or absent anti-HBc IgM levels potentially suggesting superinfection. During HDV superinfection, HBV replication may be suppressed.<sup>[29]</sup> CHD is diagnosed through elevated anti-HDV IgG levels, often with concurrent anti-HDV IgM and serum HDV RNA. Given the significant impact of active HBV infection on HDV infection outcomes and disease progression in CHD, thorough HBV characterization is recommended, including HBeAg/anti-HBe status

and serum HBV DNA quantification.<sup>[29]</sup> Fluctuations in HDV RNA and HBV DNA levels have been observed in longitudinal studies, particularly in HBeAg-positive patients, necessitating retesting of HBeAg status and HBV DNA during follow-up, especially in cases of major liver disease profile changes or HDV RNA clearance.<sup>[30]</sup> Serum HBsAg levels in patients with untreated CHD have shown more variability compared to patients with only CHB.<sup>[31]</sup> A considerable association between HDV RNA and quantitative HBsAg serum levels has been noted. However, the implications of HBsAg serum levels and their fluctuations over time for prognosis and clinical outcomes in patients with CHD remain to be fully understood.<sup>[31]</sup> The significance of new HBV markers, such as HBV core-related antigen and HBV RNA, in managing CHD is still emerging. Initial studies suggest their potential in better understanding the interaction between HBV and HDV through the natural disease course and therapeutic process.<sup>[32,33]</sup> Further research is necessary to evaluate the cost-benefit of incorporating these markers in the clinical management of patients with CHD in the Gulf states.

As for tools, anti-HDV serological assays are the primary diagnostic instruments used in the region, followed by molecular testing for HDV RNA to confirm and assess viremia. However, it is important to note that the availability of reliable serological assays remains a substantial challenge afflicting centers across the Middle East. Variability in the performance and reliability of different assays further complicates diagnostic efforts, necessitating careful consideration of assay selection and interpretation.<sup>[34]</sup> Furthermore, while molecular testing for HDV RNA is utilized to confirm viremia, challenges persist regarding the availability and standardization of these assays. The lack of standardized protocols and reference materials for HDV RNA testing poses hurdles in ensuring consistent and accurate results across laboratories.<sup>[35]</sup> Additionally, issues related to the cost, accessibility, and technical expertise required for molecular testing further contribute to the diagnostic complexities associated with HDV infection in the region.<sup>[36]</sup> Since the availability of disease diagnostic tools varies across the GCC states, efforts should be made to increase this, as well as the affordability of comprehensive diagnostic testing, including serological assays and molecular techniques, in all countries. Moreover, point-of-care testing and mobile health technologies could be introduced to reach remote or underserved areas. Accurate and timely diagnosis of HDV is essential for effective patient management and for controlling the spread of the virus.<sup>[37]</sup> The region can make significant strides in the struggle against HDV by improving screening practices.

### Recommendations

1. In patients with acute hepatitis, the detection of IgM anti-HBc is pivotal for differentiating those with HBV/HDV simultaneous coinfection from HBsAg-positive individuals with HDV superinfection (strong consensus).
2. HBV e antigen (HBeAg)/anti-hepatitis B e-antigen (anti-HBe) status and HBV DNA levels should be evaluated, as active HBV infection can exacerbate the severity of HDV (strong consensus).

### Should a liver biopsy or noninvasive tests be used in patients with a hepatitis D virus infection?

Histological examination is the gold standard for the most precise characterization of liver disease, offering categorical grading and staging of necroinflammation and fibrosis.<sup>[38]</sup> However, techniques such as HDV antigen immunohistochemistry and HDV RNA detection, which are used for assessing HDV infection burden, are not routinely performed in most pathology laboratories. In patients with CHD, liver biopsy is indicated when it can influence clinical or therapeutic decisions, particularly when imaging and blood tests yield conflicting results or ascertain the impact of HDV in the context of multiple liver disease cofactors.<sup>[39]</sup> A liver biopsy is crucial in clinical trials to correlate serum markers of virological and biochemical responses with liver disease grading and staging and intrahepatic HDV expression and to rule out drug toxicity. However, for diagnosing cirrhosis, a liver biopsy is not mandatory when imaging techniques (e.g., ultrasound, computed tomography, magnetic resonance imaging) show characteristic cirrhotic features.<sup>[40]</sup> For monitoring CHD progression, a liver biopsy is less suitable. In contrast, noninvasive tests (NITs) like liver stiffness measurements (e.g., transient elastography, shear wave elastography) and fibrosis scores [e.g., aspartate aminotransferase to platelet ratio index (APRI), fibrosis-4 index] are more informative.<sup>[41]</sup> Yet, in CHD settings, the validity of NITs remains less established due to limited large-scale validations. Their combined use with indirect markers of liver inflammation or techniques influenced by inflammation may lead to overestimating fibrosis in CHD, which is characterized by significant hepatic inflammation. Misclassification of cirrhosis has been reported in studies using these scores.<sup>[42]</sup> The diagnostic performance of fibrosis scores has generally been lower than transient elastography. However, specific scores like the Göteborg University Cirrhosis Index, Lok indexes, and APRI have shown high accuracy in identifying cirrhosis.<sup>[42]</sup> While transient elastography and specific scores show promise in CHD staging and treatment efficacy monitoring, further studies are needed for their validation.

**Recommendations**

1. A liver biopsy may be performed in patients with HDV to assess the grading and staging of liver disease (weak consensus).
2. The data on the application of NITs in patients with CHD are currently limited, and their correlation with liver histology is not adequately established (strong consensus).

**TREATMENT AND MANAGEMENT OF HEPATITIS D VIRUS IN THE REGION**

The management of CHD is complex, given the aggressive nature of the virus and the limited efficacy of current treatment options. This section provides an overview of the treatment landscape in the GCC states, discusses challenges around treatment access and adherence, and offers recommendations for optimizing treatment protocols and patient management.

**Who should be treated?**

The primary treatment for HDV has traditionally been pegylated interferon-alpha (PEG-IFN $\alpha$ ), aiming to suppress viral replication. However, response rates are variable and often suboptimal. Newer treatment options, such as bulevirtide,<sup>[43]</sup> are approved in some countries, such as Russia, while there is conditional approval in the European Union. Liver transplantation remains a viable option for patients with HDV-related liver failure, but access to this treatment is limited due to resource availability and donor shortages.

CHD infection is a progressive condition where spontaneous remission remains an uncommon clinical outcome.<sup>[44]</sup> Studies show the gradual progression of liver pathology in patients with minimal but persistent hepatic necrosis, even in the absence of a history of significant hepatic impairment, highlighting this aspect of CHD.<sup>[45]</sup>

Central to the progression of CHD infection is the persistence of viral replication, a factor that significantly influences the course of the disease.<sup>[46]</sup> The suppression of this replication, achieved through antiviral therapy, has been consistently associated with clinical improvement.<sup>[44]</sup> It is, however, crucial to underscore that the initiation of antiviral therapy in patients with CHD infection should be a decision grounded on an individualized patient evaluation.

The response to standard or PEG-IFN $\alpha$  treatment, especially in the context of cirrhosis, has been the subject of considerable investigation. Data from studies such as the Hep-Net–International Delta Hepatitis Intervention Trial (HIDIT)-1<sup>[47]</sup>

and HIDIT-2<sup>[48]</sup> suggest that cirrhosis does not markedly impact the response to PEG-IFN $\alpha$  treatment. Notwithstanding these observations, the overall response rate to PEG-IFN $\alpha$  hovers around 29%, with a relapse rate of approximately 50% during extended 24-week follow-up periods.<sup>[49]</sup>

Emerging therapeutic modalities like bulevirtide are promising in managing CHD infection. Bulevirtide inhibits the entry of HBV and HDV into hepatocytes by binding to and inactivating the sodium taurocholate cotransporting polypeptide, a key receptor for these viruses on the liver cell membrane. Preliminary data suggest that the efficacy of such new treatments is not significantly modulated by the presence of cirrhosis at baseline.<sup>[43]</sup>

In the context of CHD infection-associated decompensated cirrhosis, the therapeutic landscape remains unfulfilled, with no licensed treatments currently available. For such patients, liver transplantation emerges as the optimal intervention.<sup>[50]</sup> In scenarios where transplantation is unfeasible, a strategy centered on best-supportive care is recommended.

**Recommendations**

1. All patients with CHD infection should be considered for antiviral therapy (strong consensus).
2. Appropriate agencies may improve the availability and affordability of current and emerging treatment options, including participation in international clinical trials in the region (strong consensus).

**Which virologic markers should be monitored during treatment?**

The primary objective of treatment for CHD is to mitigate the progression of chronic liver disease, thus reducing the incidence of cirrhosis, hepatic decompensation, HCC, and liver-related mortality.<sup>[51]</sup> In trials for CHD, virologic and biochemical endpoints, individually or combined, are employed as surrogate markers to gauge treatment efficacy.<sup>[52]</sup> However, long-term evidence correlating these endpoints with clinical benefits is currently limited to PEG-IFN $\alpha$  treatment,<sup>[53]</sup> with ongoing studies for bulevirtide.<sup>[51]</sup>

Existing data on PEG-IFN $\alpha$  in CHD, despite limitations due to study design and variations in diagnostic assays for HDV RNA monitoring,<sup>[54]</sup> indicate that survival improves with the loss of HBsAg<sup>[55]</sup> and that decreased liver-related complications are associated with serum HDV RNA clearance at 24 weeks post-treatment or thereafter.<sup>[44]</sup> This suggests that achieving low HDV RNA levels (below 1000 IU/mL) might be linked with favorable CHD outcomes.<sup>[51]</sup> Data also suggest that combined alanine aminotransferase normalization and significant

reduction (over 2 log) of HDV RNA during PEG-IFN $\alpha$  treatment, and beyond, improve long-term clinical outcomes.<sup>[53]</sup> HDV treatment has witnessed a significant milestone with the publication of the bulevirtide phase 3 clinical trial results.<sup>[43]</sup> This trial evaluated the efficacy and safety of bulevirtide. It involved administering bulevirtide at a dose of 100 mg subcutaneously once daily for 24 weeks to patients with chronic HDV infection ( $n = 280$ ). The results demonstrated a remarkable virological response (71% and 76%, 2-mg and 10-mg groups, respectively), with a substantial reduction in HDV RNA levels observed in a majority of participants. Additionally, bulevirtide treatment was well tolerated, with a favorable safety profile observed throughout the study period, and was safe in patients with significant portal hypertension.<sup>[56]</sup> These findings represent a significant advancement in HDV therapy, particularly considering that they were not available at the time of the formulation of earlier guidelines, such as those by EASL.

The United States Food and Drug Administration, EASL and AASLD have synthesized specific clinical trial endpoints for CHD treatment, aimed at maintenance and finite treatment strategies.<sup>[52]</sup> Although robust validation is lacking in clinical practice, these endpoints can be reasonably applied in real-life management of patients with CHD.

### Hepatitis D virus RNA

Monitoring HDV replication is crucial during treatment; thus, viral load should be assessed regularly using standardized, validated, and real-time molecular assays.<sup>[51]</sup> Biannual testing is recommended for monitoring response to therapy and its maintenance during extended treatment. Post treatment, regular HDV RNA testing at different intervals is advised, depending on the treatment type: 6 and 12 months after the end of PEG-IFN $\alpha$  treatment and yearly thereafter due to potential late relapses.<sup>[57]</sup> After discontinuing bulevirtide monotherapy due to safety reasons, therapeutic failure, lack of response, or long-term HDV RNA suppression, earlier and more frequent testing is recommended due to the risk of viral replication rebound.<sup>[58]</sup> Specifically, we suggest follow-up testing within a variable timeframe of 1–3 months to closely monitor HDV RNA levels after treatment cessation. This frequent monitoring may be crucial for detecting any resurgence in viral replication promptly and guiding subsequent treatment decisions. Additionally, assessing other markers of liver function and disease progression, such as liver enzyme levels and clinical symptoms, may also be warranted during this post-treatment monitoring period to comprehensively evaluate the patient's response to therapy discontinuation.<sup>[58]</sup>

### Hepatitis B virus DNA

HBV replication may impact disease progression in CHD. For patients not on nucleos(t)ide analogs, monitoring HBV DNA every 6 months is advisable as dominance patterns between HBV and HDV can shift over time and during PEG-IFN $\alpha$  treatment.<sup>[59]</sup> During bulevirtide therapy, slight reductions in HBV DNA levels have been observed without evidence of HBV reactivation.<sup>[43]</sup> Consequently, after discontinuing bulevirtide, more frequent monitoring of HBV DNA is recommended in patients not receiving nucleos(t)ide analog treatment.

### Hepatitis B surface antigen

A key goal of PEG-IFN $\alpha$ -based treatment is the loss of HBsAg.<sup>[60]</sup> Testing for HBsAg during and after PEG-IFN $\alpha$  is essential as it may decline or disappear years post treatment.<sup>[61]</sup> In the context of bulevirtide treatment, HBsAg levels generally do not change significantly<sup>[58]</sup>; thus, regular monitoring during bulevirtide monotherapy is not essential. However, annual testing might still be considered due to reported cases of spontaneous HBsAg decline.<sup>[62]</sup>

#### Recommendations

1. PEG-IFN- $\alpha$ -based finite therapy should be considered the standard therapy for CHD (weak consensus).
2. The assessment of virological response during and after therapy for CHD is crucial (strong consensus).
3. HDV RNA levels should be assessed every 6 months during treatment and as clinically indicated (strong consensus).
4. For patients on PEG-IFN- $\alpha$ -based finite therapy, HDV RNA testing should be performed at the treatment completion, after 6 and 12 months, and then annually (strong consensus).
5. For patients with no or compensated cirrhosis, bulevirtide treatment can be recommended after standard therapies fail or if it is not tolerated (strong consensus).
6. In the event of discontinuing bulevirtide, HDV RNA should be assessed during bulevirtide discontinuation, followed by 1, 3, 6, and 12 months, and then annually to monitor for viral replication relapse (strong consensus).
7. Annual testing of HBsAg is advised during and following therapy (strong consensus).
8. HBV DNA levels should be assessed every 6 months in all patients undergoing treatment without nucleos(t)ide analog (strong consensus).
9. Frequent HBV DNA testing may be necessary following bulevirtide discontinuation (strong consensus).

### Should screening for hepatocellular carcinoma be performed?

In patients with CHD and advanced fibrosis (i.e., bridging fibrosis, meta-analysis of histological data in viral hepatitis (METAVIR) F3, or Ishak stage 4 or 5) or cirrhosis (METAVIR F4, Ishak stage 6), HCC surveillance via ultrasound every 6 months is imperative, irrespective of anti-HDV therapy.<sup>[63]</sup> Given the absence of definitive thresholds for NITs to detect advanced fibrosis or cirrhosis in patients with CHD, the initiation of HCC surveillance should be based on radiology findings, clinical assessments, or other indicators of advanced liver disease like ascites or hepatic encephalopathy.<sup>[64]</sup> Notably, patients with CHD have a heightened risk of HCC development compared to patients with HBV monoinfection. A systematic review (n = 98,289 from 93 eligible studies) corroborated this increased risk by reporting a higher incidence of HCC in individuals coinfecting with HBV/HDV (odds ratio 1.28; 95% confidence interval 1.05–1.57) compared with HBV monoinfection.<sup>[63]</sup>

SASLT and EASL guidelines on HCC management recommend surveillance for noncirrhotic patients with advanced fibrosis, irrespective of liver disease etiology, and for noncirrhotic patients with CHB and a PAGE-B score > 10, based on individual risk assessment.<sup>[65,66]</sup> Given the lack of comprehensive data on the incidence rate of HCC in patients with noncirrhotic CHD, surveillance is prudent in cases with bridging fibrosis, particularly when additional HCC risk factors are present (e.g., HCC history in the family, comorbidities like obesity, consumption of alcohol and/or tobacco, aflatoxin exposure, presence of HIV and/or HCV coinfection).<sup>[67]</sup>

The effect of HDV viremia on HCC risk remains unclear. Some studies report a nonsignificant increase in HCC cases with HDV viremia,<sup>[19]</sup> while others indicate a significant contribution of HDV RNA positivity to HCC development.<sup>[68]</sup> Thus, surveillance for HCC should be continued for patients with CHD and advanced fibrosis/cirrhosis who were positive or negative for HDV RNA.

The purpose of HCC surveillance is to detect early and enable curative therapies or liver transplantation. Biannual ultrasound surveillance is strongly advocated in SASLT and EASL guidelines.<sup>[65,66]</sup> The use of serum alpha-fetoprotein alongside ultrasound can enhance early-stage HCC detection rates in cirrhotic patients, though it does increase false-positive rates.<sup>[69]</sup>

#### Recommendation

1. As for other chronic liver diseases, HCC screening should be performed every 6 months for CHD with advanced fibrosis/cirrhosis, irrespective of therapy initiation (strong consensus).

### PREVENTION AND POLICY STRATEGIES

Effective prevention strategies are vital in reducing the burden of HDV infection in the GCC states. While there is no specific vaccine for HDV, vaccination against HBV is critical as HDV requires HBV for its replication.<sup>[70]</sup> Strengthening HBV vaccination and treatment programs is essential; particularly, targeting high-risk populations that are hard to reach (e.g., people who inject drugs with decentralized care via mobile units) and ensuring complete vaccination schedules are essential. One example would be integrating HDV prevention strategies like education into campaigns to prevent and treat other conditions (e.g., during HBV vaccination) to maximize each patient encounter with the healthcare system.<sup>[71]</sup> It is crucial to increase public awareness about HDV, its transmission routes, and prevention methods, especially in high-risk regions. This involves educational campaigns that are culturally sensitive and accessible to all segments of the population, for example, through community engagement programs. Progress in managing HDV in the GCC states is closely tied to ongoing research, as shown by the many ongoing research initiatives, including this set of consensus recommendations in the Gulf states.

### CONCLUSION

HDV represents a significant health challenge within the GCC states, necessitating a comprehensive and multi-faceted approach. Through this consensus statement, we shed light on the various aspects of HDV management in the region, encompassing epidemiology, diagnosis, treatment, prevention, and policy recommendations. Our collective efforts must be directed toward enhancing the understanding of the impact of HDV, improving diagnostic and treatment strategies, and reinforcing prevention methods. This involves a collaborative approach that leverages the strengths of healthcare systems, embraces the diversity of the population, and addresses the unique challenges presented by the sociocultural and economic landscape of the GCC states. By standardizing care protocols and fostering regional and international collaborations, we can make significant strides in mitigating the burden of HDV. The journey toward effectively managing HDV in the region requires persistence and a shared commitment to improving public health. We hope

this statement not only serves as a guide but also as a catalyst for sustained action and cooperation in the battle against this health challenge.

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There are no conflicts of interest.

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