Check for updates

Received: 25 January 2022 | Revised: 27 May 2022 | Accepted: 8 June 2022

DOI: 10.1111/liv.15338

Liver INTERNATIONAL WILEY

MINI REVIEW

Hepatitis delta virus infection prevalence, diagnosis and treatment in the Middle East: A scoping review

Jeffrey V. Lazarus[1,2] | Ahmad Al-Rifai[3] | Faisal M. Sanai[4] | Abdullah Saeed Alghamdi[5] | Ala I. Sharara[6] | Motaz Fathy Saad[7] | Lena van Selm[1] | Saleh A. Alqahtani[8,9]

[1]Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain

[2]Faculty of Medicine, University of Barcelona, Barcelona, Spain

[3]Department of Gastroenterology and Hepatology, Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates

[4]Gastroenterology Unit, Department of Medicine, King Abdulaziz Medical City, Jeddah, Saudi Arabia

[5]Gastroenterology Unit, Department of Medicine, King Fahad General Hospital, Jeddah, Saudi Arabia

[6]Division of Gastroenterology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

[7]Department of Gastroenterology and Hepatology, Mubarak Al-Kabier Hospital, Jabriya, Kuwait

[8]Liver Transplant Center, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

[9]Division of Gastroenterology & Hepatology, Johns Hopkins University, Baltimore, Maryland, USA

Correspondence
Jeffrey V Lazarus, Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Calle del Rossellón 171, ES-08036 Barcelona, Spain.
Email: jeffrey.lazarus@isglobal.org

Funding information
Gilead Sciences, Grant/Award Number: N/A; Government of Catalonia; Ministry of Science, Innovation and Universities

Handling Editor: Dr. Alessio Aghemo

Abstract

Hepatitis D virus (HDV) infection is a global public health concern, especially because of its unique existence in the presence of hepatitis B virus infection. HDV infection is estimated to affect 12 million people globally. Having a clearer understanding of its prevalence in all regions of the world is essential for helping direct preventive and early interventional treatment. This mini-review assessed the literature over the last 10 years to determine the prevalence, diagnostic means and treatment guidelines available for HDV in the Middle East. The search found limited data available in 21 articles, of which 18 were studies focused on Iran. Prevalence rates ranged dramatically among the countries, and none of the 12 countries included in the search had specific HDV guidelines. This review highlights the urgent need for more precise data for the Middle East region to help establish early diagnosis and treatment options for HDV.

KEYWORDS
guidelines, hepatitis D virus, Middle East, prevalence, treatment

1 | INTRODUCTION

Hepatitis D virus (HDV) is a virus that exists only in the presence of hepatitis B virus (HBV); the latter is estimated to affect 300 million people globally.[1] A recent meta-analysis estimated the HDV prevalence in the global general population to be 0.16%, corresponding to approximately 12 million infections globally.[2] HDV has a high prevalence in central Asia, eastern Europe and central and west sub-Saharan Africa.[3]

Abbreviations: HDV, hepatitis D virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PEG-IFN, pegylated interferon; EU, European Union; HBcAb, Hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IgM, immunoglobulin M; PCR, polymerase chain reaction; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; WHO, World Health Organization.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
© 2022 The Authors. *Liver International* published by John Wiley & Sons Ltd.

Amongst HBV carriers, HDV prevalence estimates vary widely, with 5% being the most commonly accepted figure.[4] HBV/HDV co-infection is the most severe form of chronic viral hepatitis infection because of its rapid progression to liver disease and associated complications.[5]

HDV is an important contributor to liver disease. Of those with HDV infection, 10%–20% progress to cirrhosis within 2 years and 70%–80% within 5–10 years.[6] In addition, HDV causes about 18% of cirrhosis and 20% of hepatocellular carcinoma (HCC) cases amongst people with chronic HBV infection.[2] To date, there is no effective, extensively tested treatment for HDV. From 1980 until recently, pegylated interferon (PEG-IFN) was the only approved drug against HDV. However, response rates are relatively low, with only about a quarter to one-half of people responding at the end of therapy and over half the responders relapsing after treatment.[7] In 2020, bulevirtide was approved in the European Union (EU), but to date, only a few patients have used this treatment outside of clinical trials.[6,8]

The burden of HDV in the Middle East is heterogeneous in terms of geographical distribution and is not well documented,[9,10] with estimates varying greatly between countries. International guidelines recommend HDV testing for all hepatitis B surface antigen (HBsAg) positive patients, particularly for at-risk and vulnerable populations.[11–13] The prevalence of HBV in the wider Eastern Mediterranean Region is estimated to be 3.3%, corresponding to approximately 21 million people with chronic HBV infection.[14] In this region, HDV is an endemic infection.[15,16] A global review and meta-analysis of HDV seroprevalence studies from 2020 reported a prevalence of 0.12% in the general population and 3.5% in people with HBV in the Eastern Mediterranean Region.[2] However, this region includes countries that are not part of the Middle East and, in addition, the majority of the studies included in this analysis were over 10 years old. Therefore, the current HDV prevalence in the Middle Eastern region remains unknown. Here, we summarize the recent literature on HDV prevalence, testing and treatment in the Middle East.

2 | METHODS

We conducted a literature search in PubMed/Medline. Additional relevant articles were identified by manually searching for references and reviewing the grey literature via Google Scholar. Inclusion criteria were studies collecting primary data that were published in English in the last 10 years (January 1, 2012-March 31, 2022) in 12 countries of the Middle East: Bahrain, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, the United Arab Emirates and Yemen. The keywords used were: ('hepatitis D' OR 'hepatitis Delta' OR 'HDV') AND ('Middle East' OR 'Saudi*' OR 'United Arab Emirates' OR 'Kuwait' OR 'Oman' OR 'Iraq' OR 'Jordan' OR 'Qatar' OR 'Bahrain' OR 'Lebanon' OR 'Yemen' OR 'Syria' OR Riyadh OR Riad OR Abu Dhabi OR Kuwait City OR Muscat OR Baghdad OR Amman OR Doha OR Manama OR Beirut OR Sana OR Damascus). Reviews were excluded after scanning for relevant studies to be included.

Key points

- Globally, about 12 million people are estimated to have hepatitis D virus (HDV), which can lead to cirrhosis and liver cancer.
- We assessed the literature to determine the prevalence, diagnostic means and treatment guidelines available for HDV in the Middle East.
- The limited available data reported dramatically ranging prevalence rates amongst the countries and no country-specific HDV guidelines.
- This review highlights an urgent need for more precise data for the Middle East to contribute to early diagnosis and treatment options for HDV.

3 | RESULTS

A total of 21 articles were identified to be included for review (Table 1). Studies were from Iran ($n = 18$), Iraq ($n = 1$), Saudi Arabia ($n = 1$) and Yemen ($n = 1$). No data were found for Bahrain, Jordan, Kuwait, Lebanon, Oman, Qatar, Syria and the United Arab Emirates (See Figure 1).

3.1 | Prevalence

For Iran, studies in different regions of the country showed a high variation in prevalence, ranging from 0.0% to 0.53% in the general population and from 0.0% to 21.8% amongst HBV-positive individuals. Six studies tested for HDV antibodies in a sample from the general population and found a prevalence of 0.0% in Kurdistan ($n = 1613$) and South Khorasan ($n = 1245$),[17,18] 0.02% in Birjand, South Khorasan ($n = 5235$),[19] 0.03% in Qom ($n = 3690$),[20] 0.05 in Kermanshah ($n = 1979$),[21] 0.2% in Sistan and Baluchistan ($n = 3989$)[22] and 0.5% in Hormozgan ($n = 562$).[23]

Testing for HDV amongst 81 HBcAb-positive people in the Kurdistan region, 0.0% tested positive for HDV antibodies.[17] Similarly, in the bordering Kermanshah region, of 164 positive HBcAb samples, only one contained HDV antibodies (0.6%).[21] Another study in Kermanshah found an HDV seroprevalence of 1.7% in people with HBV ($n = 1749$), of which 48.3% tested positive for HDV RNA.[24] In the South Khorasan province, amongst 155 HBsAg-positive people, 0.0% tested positive for HDV.[18] In Birjand, South Khorasan, from 85 HBsAg-positive samples, 1.2% tested positive for HDV antibodies.[19] Amongst HBsAg positive people, the HDV antibodies prevalence was found to be 2.1% in both the Qom region ($n = 48$)[20] and an Iranian national study ($n = 854$).[25] In addition, the latter found a 0.6% HDV RNA prevalence among HBV-positive individuals. Similarly, a 2.2% HDV antibody prevalence was found in both Azar ($n = 46$)[26] and Tehran ($n = 660$); in the latter study, 60.9% of those antibody-positive tested positive for HDV RNA.[27] Two studies in Birjand, South Khorasan, found HDV antibodies in 3.1%

14783231, 2023, S1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15338 by Readcube (Labtiva Inc.), Wiley Online Library on [08/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Summary of included studies[a]

Country	Authors	Year	N[b]	Reported prevalence
Iran[31]	Alavian, S. M., Imanieh, M. H., & Imanieh, M. H.	2016	237	10.1% anti-HDV amongst HBV positive patients
Iran[17]	Alavian, S. M. et al.	2012	81	0.0% anti-HDV amongst HBV positive patients and general population
Iran[21]	Alavian, S. M. et al.	2012	164	0.6% anti-HDV amongst HBV positive patients and 0.05% among general population
Iran[25]	Attaran, M. S. et al.	2014	854	2.1% anti-HDV and 0.6% HDV-RNA PCR positive amongst HBV positive patients
Iran[33]	Bakhshipour, A., Mashhadi, M., Mohammadi, M., & Nezam, S. K.	2013	440	17.0% anti-HDV amongst HBV positive patients
Iran[23]	Behzadi, M. A. et al.	2019	65	5.0% anti-HDV amongst HBV positive patients
Iran[20]	Ghadir, M. R. et al.	2012	48	2.1% anti-HDV amongst HBV positive patients and 0.03% among general population
Iran[18]	Javanmard, D. et al.	2018	155	0.0% anti-HDV amongst HBV positive patients and general population
Iran[27]	Keshvari, M. et al.	2014	660	2.2% anti-HDV amongst HBV positive patients of whom 60.9% HDV-RNA PCR positive
Iran[29]	Khazaee, T. et al.	2015	300	3.3% anti-HDV amongst HBV positive patients
Iran[26]	Pouri, A. A. et al.	2020	46	2.2% anti-HDV amongst HBV positive patients
Iran[32]	Pournik, O. et al.	2013	390	10.5% anti-HDV amongst HBV positive patients
Iran[22]	Salehi, M. et al.	2012	135	5.9% anti-HDV amongst HBV positive patients and 0.2% among general population
Iran[24]	Sayad, B. et al.	2018	1749	1.7% anti-HDV amongst HBV positive patients of whom 48.3% HDV-RNA PCR positive
Iran[34]	Sharifan, P. & Amoueian, S.	2018	87	21.8% anti-HDV amongst HBV positive patients
Iran[19]	Sharifzadeh, G. et al.	2017	85	1.2% anti-HDV amongst HBV positive patients and 0.02% among general population
Iran[30]	Tahaei, S. M. E. et al.	2014	509	7.7% anti-HDV amongst HBV positive patients
Iran[28]	Ziaee, M., & Azarkar, G	2013	413	3.1% anti-HDV amongst HBV positive patients
Iraq[36]	Hussein, N. R. et al.	2015	45	6.6% anti-HDV amongst HBV positive patients
Saudi Arabia[35]	Jamjoom, G. A. et al.	2017	169	7.7% anti-HDV amongst HBV positive patients of whom 30.8% HDV-RNA PCR positive
Yemen[37]	Al-Nabehi, B. A. H. et al.	2015	14	0.0% anti-HDV amongst HBV positive patients and general population

Abbreviations: HBV: hepatitis B virus; HDV: hepatitis D virus; PCR: polymerase chain reactionn.

[a]All studies included in this review used a cross-sectional study design.

[b]Number of HBV positive patients included in the study.

($n = 413$)[28] and 3.3% ($n = 300$)[29] of HBV-positive samples. A study in the Hormozgan province found that among 562 individuals, 11.6% had anti-hepatitis B core antibodies, of which 5% had anti-HDV antibodies.[23] A study from Sistan and Baluchistan ($n = 135$) found HDV antibodies in 5.9% of HBV-positive samples.[22] Three studies in Tehran found an HDV antibody prevalence of 7.7% ($n = 509$),[30] 10.1% ($n = 237$)[31] and 10.5% ($n = 390$)[32] among HBV-positive individuals. Studies in other regions found considerably higher rates, with 17.0% and 21.8% of HBV-positive individuals testing positive for anti-HDV in Zahedan, Sistan and Baluchistan ($n = 144$),[33] and Razavi Khorasan province ($n = 87$),[34] respectively.

In Saudi Arabia, A single-centre study ($n = 169$) in Jeddah found an HDV seroprevalence of 7.7% in HBV-positive patients, of which 30.7% tested positive for HDV RNA.[35] A 2015 study from Iraq reported a 6.6% prevalence of anti-HDV antibodies in people with HBV ($n = 45$).[36] A 2015 study from Yemen tested 501 people for HBsAg, of which 14 tested positive, none of which tested positive for anti-HDV.[37] Table 2 presents an overview of the prevalence of HDV in both HBV-infected people and the general population in select countries of the Middle East.

Regarding transmission, 15 of the studies reported risk factors within the sample of HBV or HDV patients. The main factors that correlated with HBV were dental surgery,[17,18,21,33,36,37] tattoos,[21,33] family history,[18,33,36] sexual relations,[17] renal dialysis,[37] history of cupping or bloodletting procedures,[18,37] surgical operation,[36,37] blood transfusion,[36] history of prison[18] and addiction.[22] In addition, some studies reported frequent risk factors for HDV as a history of surgery,[24,30] dental procedures[30] and tattoos.[24]

14783231, 2023, S1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15338 by Readcube (Labtiva Inc.), Wiley Online Library on [08/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

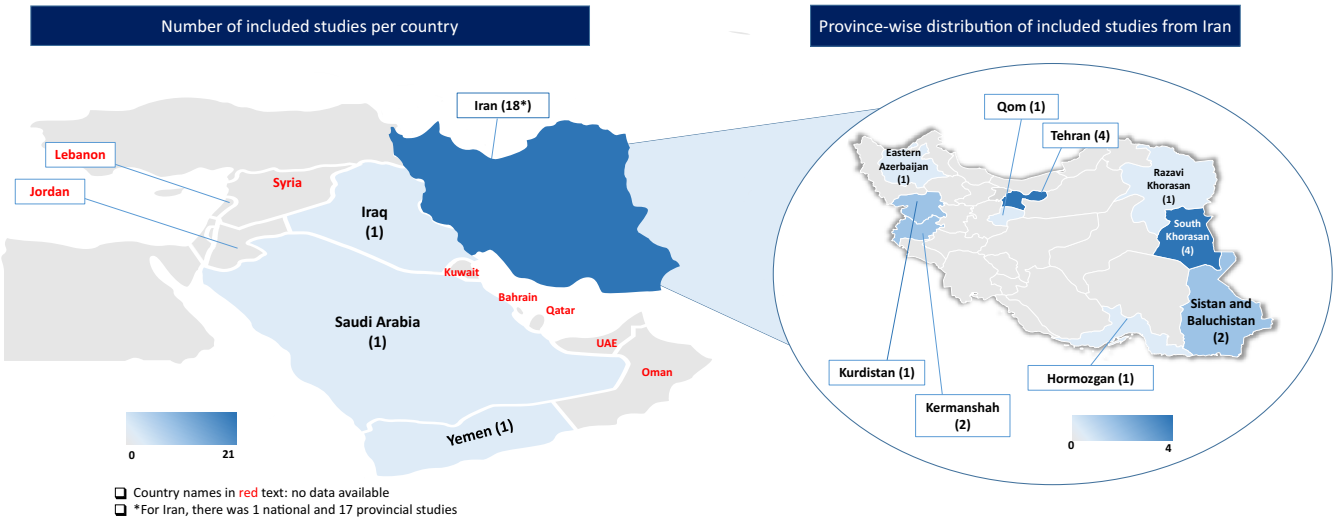

FIGURE 1 Overview of studies included in this review

TABLE 2 Overview of HDV prevalence in Middle Eastern countries[a]

Region/country	HDV prevalence general population	HDV prevalence in people who are HBV+
Bahrain	–	–
Iran	0.0%–0.2%[17–22]	0.0%–21.8%[17–34]
Iraq	–	6.6%[36]
Jordan	–	–
Kuwait	–	–
Lebanon	–	–
Oman	–	–
Qatar	–	–
Saudi Arabia	–	7.7%[35]
Syria	–	–
United Arab Emirates	–	–
Yemen	0%[37]	0.0%[37]

Abbreviations: HBV, hepatitis B virus; HDV, hepatitis D virus.
[a]HDV prevalence assessed via antibodies.

3.2 | Diagnosis and treatment guidelines

HDV-specific guidelines were not found for any of the 12 countries. Jordan, Lebanon and Saudi Arabia have local HBV guidelines; however, HDV is only explicitly mentioned in the HBV guidelines of Jordan and Saudi Arabia. Jordan's HBV and hepatitis C virus (HCV) treatment guidelines from 2016 include a section on HDV coinfection, stating that diagnosis is confirmed by detectable HDV RNA, immunohistochemical staining for HDV antigen, or immunoglobulin M (IgM) anti-HDV. It states that PEG-IFN is the only effective drug against HDV, and its efficacy should be assessed after 24 weeks by measuring HDV RNA levels. Additionally, nucleotides/nucleosides analogues are not indicated.[38] The HBV treatment guidelines for Saudi Arabia recommend testing for HDV during the pre-treatment assessment of HBV.[39] They state that HDV should be detected by the presence of HDV antibody positivity (IgM) and HDV RNA.[40] The guidelines mention that PEG-IFN treatment for 1 year appears to have positive long-term effects in patients, and the risk of viral relapse is emphasized.[40] Table 3 presents an overview of the HBV guidelines in the included Middle Eastern countries.

A review of the hepatitis B care pathway in the United Arab Emirates mentions no local guidelines, and most specialists follow the European Association for the Study of the Liver (EASL) guidelines.[41] Similarly, a review on the hepatitis B care pathway in Kuwait mentions that the last local existing guideline is from 2009 and that specialists currently follow EASL or the American Association for the Study of Liver Diseases (AASLD) guidelines.[42] The Lebanese Society of Gastroenterology published a guideline for diagnosing HBV with no information on HDV.[43] A 2016 review on hepatitis B and C in Syria mentions that testing and care for both conditions are free of charge. It also reports that there is no national strategy to control HBV and that no guidelines for prevention are in place; HDV is also not mentioned.[44] In Oman, Iran, Iraq, Qatar, Bahrain and Yemen, no national guidelines nor policies on HBV and/or HDV were identified.

14783231, 2023, S1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15338 by Readcube (Labtiva Inc.), Wiley Online Library on [08/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 Overview of the local HBV guidelines in Middle Eastern countries

Country	Local HBV guidelines	HDV mentioned in local HBV guidelines
Bahrain	–	–
Iran	–	–
Iraq	–	–
Jordan	✓	✓
Kuwait	Use EASL guidelines	–
Lebanon	✓	–
Oman	–	–
Qatar	–	–
Saudi Arabia	✓	✓
Syria	–	–
United Arab Emirates	Use EASL guidelines	–
Yemen	–	–

Note: ✓: Available; –: Not available.

Abbreviations: EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HDV, hepatitis D virus.

4 | DISCUSSION

Based on the limited availability of recent literature on HDV prevalence, testing and treatment guidelines in the Middle East, it appears that countries in the region have a low to moderate HDV prevalence. However, recent prevalence data were only available for Iran, Iraq, Saudi Arabia and Yemen, highlighting a large gap in screening, diagnosing, and reporting HDV in the rest of the region. Other countries in the wider region reported higher HDV rates, such as Pakistan, with a 2.4% prevalence in the general population and 17.0%–34.1% in HBV carriers; Turkey, with only a 0.03% prevalence rate in the general population but 2.8%–14.4% in people with HBV[9]; and Egypt, with one study reporting a 43.0% prevalence in HBV carriers.[45]

For more than half of the included countries, no HDV prevalence data were published in the last 5 years. For some countries, older HDV data are available. For Jordan, data from 1987 show an HDV prevalence of 1.5% among symptomless HBsAg carriers and 15.7% amongst people with acute hepatitis B.[46] For Kuwait, the latest available data are from 1988 and show that 9.0% of HBV-positive people had HDV antibodies.[47] In Yemen, in 1993, 2.0% of HBV-positive people ($n = 100$) were found to have HDV antibodies.[48] In Oman, in 1994, a small-scale study found that among 287 patients in treatment for renal disease 8.7% were HBV positive ($n = 25$) of which 12% were HDV positive ($n = 3$).[49] Finally, in Lebanon in 2007, out of a sample of 258 HBV carriers, 1.2% tested positive for HDV antibodies and 0.6% for HDV RNA.[50] For Bahrain, Qatar, Syria, and the United Arab Emirates, HDV prevalence data in the general population have not been identified at any point in time.

No recent data were available on testing and treatment of HDV in the Middle East. In 2021, the World Health Organization (WHO) reported that diagnosis and treatment of hepatitis B were low in the Eastern Mediterranean Region.[51] The latest review of HBV management in the Middle East dates from 2012,[2,7] highlighting the need for more up-to-date information which is relevant and applicable to the region. It reports that all seven included countries screened for HBsAg at blood transfusion services and that the United Arab Emirates and Saudi Arabia also routinely screened for anti-hepatitis B core antibodies. In addition, it reported that the most common routes for infection were perinatal transmission and transmission through blood transfusions and/or horizontal transmission.[52] However, new data should confirm that this is still the case. A 2020 modelling study on HBV elimination in Saudi Arabia showed that progress has been made in controlling HBV but that increased diagnosis and treatment are required to further reduce HCC and liver-related deaths. In addition, it shows that treating all HBV cases will be cost-effective if treatment prices can be reduced.[53]

All Middle Eastern countries have implemented HBV vaccination programmes in their national immunization schedules.[54] In the Eastern Mediterranean Region, HBV vaccine coverage exceeded 80% for the third dose, which is below the global average.[51] The birth dose coverage rates look more positive, although there are substantial differences among countries: Bahrain, Iran, Oman, and the United Arab Emirates have a 99% three-dose vaccination rate before the age of 1 year, while Jordan, Qatar and Saudi Arabia have 98%. The rates for the additional countries are: Kuwait 95%, Lebanon 90%, Yemen 86%, Iraq 73% and Syria 65%.[55]

Information on HDV treatment in the Middle East is needed to combat this disease, especially considering that the treatment differs from that of HBV and that nucleo(s)tide analogue drugs for the treatment of HBV fail to reduce HDV RNA levels in those with HBV/HDV co-infection.[56] AASLD, EASL and the Asian Pacific Association for the Study of the Liver guidelines recommend PEG-IFN for HDV treatment, which was the only approved HDV treatment until recently.[11–13,57] PEG-IFN is mostly used for 12–18 months, although studies on prolonged treatment after 1 year show mixed results.[9,13,56] Amongst

14783231, 2023, S1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15338 by Readcube (Labtiva Inc.), Wiley Online Library on [08/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patients with HDV on PEG-IFN, the virologic response is only achieved in approximately 25%–40% of patients, and late viral relapses occur frequently.[12,15,56] In 2020, the EU approved bulevirtide to treat adults with chronic HDV and compensated liver disease and a positive HDV RNA viremia.[8] The optimal treatment period has not yet been defined. The recommended dosage is 2 mg/day, either in monotherapy or combined with a nucleos(t)ide analogue.[6] Currently, only a few patients have been treated with bulevirtide, and the first real-life data show good efficacy and safety of the drug. However, more studies are needed to confirm these findings and explain the lack of HBsAg level decline and the HDV RNA relapse, which is often reported after discontinuation.[8] We did not find any studies that specifically use PEG-IFN or bulevirtide for HDV in the Middle East.

The results presented in this review are limited by the significant gaps in the literature and the quality of the studies included.

With a new treatment option on the horizon, further steps can be taken to combat HDV in the Middle East, in addition to HBV prevention. However, for patients to obtain the best benefit, HDV cases must be identified. HBV screening in collaboration with HDV screening for all HBsAg positive cases is paramount. With more routinely identified cases, linkage to care and the opportunity to be treated can be improved. In addition, the routine availability of HDV RNA assays is crucial to understanding the natural history of HBV/HDV co-infected populations and paving the path for adopting evolving therapies. This would also allow for reflex testing, in which all HBsAg-positive individuals are automatically tested for HDV.

5 | CONCLUSION

This review highlights the strong need for current data on HDV prevalence, testing, and treatment in the Middle East, especially for countries without data available at any point in time or countries that previously reported a high HDV prevalence. In addition, it shows that most countries do not regularly report HDV prevalence and treatment data. In line with efforts for HBV and HCV elimination set out by WHO in 2016,[58] efforts tailored to the region's epidemiology and health systems will contribute to eliminating HDV as a public health threat.

ACKNOWLEDGEMENTS

JVL and LVS acknowledge support to ISGlobal from the Spanish Ministry of Science, Innovation and Universities through the 'Centro de Excelencia Severo Ochoa 2019-2023' Programme (CEX2018-000806-S) and from the Government of Catalonia through the CERCA Programme. Open access funding enabled and organized by ProjektDEAL.

FUNDING INFORMATION

This study was funded in full by Gilead Sciences.

CONFLICT OF INTEREST

JVL acknowledges grants and speaker fees from AbbVie, Gilead Sciences and MSD and speaker fees from Genfit Intercept and Janssen, outside the submitted work. AA-R, FMS, ASA, AS, MFS, LVS and SAA have nothing to disclose.

ORCID

Jeffrey V. Lazarus https://orcid.org/0000-0001-9618-2299

Saleh A. Alqahtani https://orcid.org/0000-0003-2017-3526

REFERENCES

1. Lee AU, Lee C. Hepatitis D review: challenges for the resource-poor setting. *Viruses*. 2021;13(10):1912. doi:10.3390/V13101912
2. Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. *J Hepatol*. 2020;73(3):523-532. doi:10.1016/J.JHEP.2020.04.008
3. Miao Z, Zhang S, Ou X, et al. Estimating the global prevalence, disease progression, and clinical outcome of Hepatitis Delta virus infection. *J Infect Dis*. 2020;221(10):1677-1687. doi:10.1093/infdis/jiz633
4. WHO. Hepatitis D. https://www.who.int/news-room/fact-sheets/detail/hepatitis-d. Accessed December 17, 2021.
5. Yurdaydin C, Toy M. Hepatitis Delta virus infection: a large burden after all? *J Infect Dis*. 2020;221(10):1573-1575. doi:10.1093/INFDIS/JIZ634
6. Masetti C, Aghemo A. Bulevirtide for treatment of patients with HDV infection and compensated cirrhosis: a (huge?) step in the right direction. *Liver Int*. 2021;41:1441-1442. doi:10.1111/liv.14967
7. Sandmann L, Cornberg M. Experimental drugs for the treatment of hepatitis D. *J Exp Pharmacol*. 2021;13:461. doi:10.2147/JEP.S235550
8. Asselah T, Loureiro D, Le Gal F, et al. Early virological response in six patients with hepatitis D virus infection and compensated cirrhosis treated with Bulevirtide in real-life. *Liver Int*. 2021;41(7):1509-1517. doi:10.1111/liv.14950
9. Gokcan H, Idilman R. Hepatitis D infection in Asia: a perspective from an endemic region. *Clin Liver Dis*. 2021;18(1):26. doi:10.1002/CLD.1106
10. Vlachogiannakos J, Papatheodoridis GV. New epidemiology of hepatitis delta. *Liver Int*. 2020;40:48-53. doi:10.1111/liv.14357
11. Terrault NA, Lok ASF, Mcmahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560-1599. doi:10.1002/hep.29800
12. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. 2017;67(2):370-398.
13. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int*. 2016;2072(10):1-98. doi:10.1007/s12072-015-9675-4
14. WHO. Regional action plan for the implementation of the global health sector strategy on viral hepatitis 2017–2021. Published Online 2017.
15. Rizzetto M, Hamid S, Negro F. The changing context of hepatitis D. *J Hepatol*. 2021;74(5):1200-1211. doi:10.1016/J.JHEP.2021.01.014
16. Hayashi T, Takeshita Y, Hutin YJ-F, et al. The global hepatitis delta virus (HDV) epidemic: what gaps to address in order to mount a public health response? *Arch. Public Health*. 2021;79(1):180. doi:10.1186/s13690-021-00693-2
17. Alavian SM, Tabatabaei SV, Ghadimi T, et al. Seroprevalence of hepatitis B virus infection and its risk factors in the west of Iran: a population-based study. *Int J Prev Med*. 2012;3(11):770.
18. Javanmard D, Alavian SM, Abedi F, Hasan Namaei M, Asghari A, Ziaee M. High prevalence of hepatitis B virus infection in the village of Esfandiar in South Khorasan Province. *Iran*. 2018;18(8):65473. doi:10.5812/hepatmon.65473

14783231, 2023, S1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15338 by Readcube (Labtiva Inc.), Wiley Online Library on [08/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

19. Sharifzadeh G, Namaei MH, Ebrahimzadeh A, et al. Prevalence of hepatitis D virus infection and associated factors among HBsAg-positive patients in Birjand, Iran, 2012–2014. *Hepat Mon*. 2017;17(5):e42866. doi:10.5812/hepatmon.42866
20. Ghadir M-R, Belbasi M, Heidari A, et al. Prevalence of hepatitis D virus infection among hepatitis B virus infected patients in Qom Province, Center of Iran. *Hepat Mon*. 2012;12(3):205. doi:10.5812/HEPATMON.847
21. Alavian SM, Tabatabaei SV, Nourizad S, Mansouri F, Khademi N, Kafi-Abad A. Seroepidemiology of HBV infection in Kermanshah-west of Iran; a population based study. *Jundishapur J Microbiol*. 2012;5(4):564-573. doi:10.5812/jjm.4156
22. Salehi M, Alavian SM, Tabatabaei SV, et al. Seroepidemiology of HBV infection in south-east of Iran; a population based study. *Iran Red Crescent Med J*. 2012;14(5):283.
23. Behzadi MA, Leyva-Grado VH, Namayandeh M, et al. Seroprevalence of viral hepatitis a, B, C, D and E viruses in the Hormozgan province southern Iran. *BMC Infect Dis*. 2019;19(1):1027. doi:10.1186/s12879-019-4661-4
24. Sayad B, Naderi Y, Alavian SM, et al. Hepatitis D virus infection in Kermanshah, west of Iran: seroprevalence and viremic infections. *Gastroenterol Hepatol from Bed to Bench*. 2018;11(2):145-152.
25. Attaran MS, Sharifi Z, Hosseini SM, Samei S, Ataee Z. Prevalence of hepatitis B and hepatitis D coinfection in asymptomatic blood donors in Iran. *APMIS*. 2014;122(3):243-247. doi:10.1111/APM.12137
26. Pouri AA, Ghojazadeh M, Baiaz B, Hamzavi FS, Pourasghari B, Somi MH. Prevalence of hepatitis D virus among HBsAg-positive individuals, 2015-2016: azar cohort study. *Health Promot Perspect*. 2020;10(1):38-42. doi:10.15171/hpp.2020.07
27. Keshvari M, Alavian SM, Aghaee B, et al. Seroepidemiology and clinical features of hepatitis delta among HBsAg carriers: a study from hepatitis clinic of Iranian blood transfusion organization. *Transfus Med*. 2014;24(6):411-417. doi:10.1111/TME.12163
28. Ziaee M, Azarkar G. Prevalence of hepatitis D virus infection among patients with chronic hepatitis B attending Birjand hepatitis clinic (east of Iran) in 2012. *Hepat Mon*. 2013;13(8):11168. doi:10.5812/HEPATMON.11168
29. Khazaee T, Ebrahimzadeh A, Govaresh EM, 2015. Assessment of prevalence and determine infections of hepatitis C and hepatitis D in patients with chronic hepatitis B. govaresh.org. Published online 2015. http://www.govaresh.org/index.php/dd/article/view/1451. Accessed April 5, 2022.
30. Tahaei SME, Mohebbi SR, Azimzadeh P, et al. Prevalence of hepatitis D virus in hepatitis B virus infected patients referred to Taleghani hospital, Tehran, Iran. *Gastroenterol Hepatol Bed Bench*. 2014;7(3):144.
31. Alavian SM, Imanieh MH, Imanieh MH. Predictive factors in the incidence of cirrhosis in chronic hepatitis B virus infections. *Hepat Mon*. 2016;16(5):34790. doi:10.5812/HEPATMON.34790
32. Pournik O, Alavian SM, Ghalichi L, Hajibeigi B, Razavi AR, Eslami S. Lower intrafamilial transmission rate of hepatitis B in patients with hepatitis D coinfection: a data-mining approach. *Hepat Mon*. 2013;13(5):e7652. doi:10.5812/HEPATMON.7652
33. Bakhshipour A, Mashhadi M, Mohammadi M, Nezam SK. Seroprevalence and risk factors of hepatitis delta virus in chronic hepatitis B virus infection in Zahedan. *Acta Med Iran*. 2013;51(4):260-264. http://acta.tums.ac.ir/index.php/acta/article/view/4451. Accessed April 1, 2022
34. Sharifan P, Amoueian S. Histological and serological epidemiology of Hepatitis Delta virus coinfection among patients with chronic active hepatitis B virus in Razavi Khorasan Province, northeastern Iran. *Iran J Public Health*. 2018;47(12):1906.
35. Jamjoom GA, El-Daly MM, Azhar EI, et al. Prevalence and molecular characterization of hepatitis D virus in Saudi Arabia: a single-center study. *Saudi J Gastroenterol*. 2017;23(3):176-182. doi:10.4103/SJG.SJG_515_16
36. Hussein NR, Rasheed ZA, Taha AA, Shaikhow SK. The prevalence of hepatitis D virus infection amongst patients with chronic active hepatitis B virus infection in Duhok governorate. *Int J Pure Appl Sci Technol*. 2015;28(1):1-7. www.ijopaasat.in. Accessed October 20, 2021
37. Al-Nabehi B, Al-Shamahy H, Saeed W, et al. Sero-molecular epidemiology and risk factors of viral hepatitis in urban Yemen. *Int J Virol*. 2015;11(3):133-138. doi:10.3923/ijv.2015.133.138
38. Qaseer B. Jordan Viral Hepatitis B & C 2016. The Hashemite Kingdom of Jordan Ministry of Health. Published 2016. https://www.researchgate.net/publication/308790306_Jordan_viral_hepatitis_B_C_2016. Accessed October 26, 2021.
39. Abaalkhail FA, Al-Hamoudi WK, Khathlan A, et al. SASLT practice guidelines for the management of hepatitis B virus – an update. *Saudi J Gastroenterol*. 2021;27(3):115-126. doi:10.4103/SJG.SJG_539_20
40. Abaalkhail F, Elsiesy H, AlOmair A, et al. SASLT practice guidelines for the management of Hepatitis B Virus. *Saudi J Gastroenterol*. 2014;20(1):5-25. doi:10.4103/1319-3767.126311
41. Al Zaabi M, Al Quraishi H, Al Rifai A, et al. Hepatitis B care pathway in the United Arab Emirates: current situation, gaps, and actions. 10.33590/emjhepatol/19-00061
42. Hasan F, Bahbahani A, Askar H, et al. Hepatitis B prevention and care pathway in Kuwait: assessing the current situation, identifying gaps and recommending actions. Published Online 2019. www.ncbi.nlm.nih.gov/pubmed/. Accessed October 25, 2021.
43. Lebanese Guidelines for the Treatment of HBV Infection. Lebanese Society of Gastroenterology. https://lsge.org/local_guidelines. Accessed October 26, 2021.
44. Bashour H, Muhjazi G. Hepatitis B and C in the Syrian Arab Republic: a review. *East Mediterr Health J*. 2016;22(4):267-273. www.moh. Accessed October 26, 2021
45. Makhlouf NA, Morsy KH, Mahmoud AA. Hepatitis D virus infection among hepatitis B virus surface antigen positive individuals in upper Egypt: prevalence and clinical features. *J Infect Public Health*. 2019;12(3):350-356. doi:10.1016/J.JIPH.2018.12.001
46. Toukan AU, Abu-El-Rub OA, Abu-Laban SA, et al. The epidemiology and clinical outcome of hepatitis D virus (delta) infection in Jordan. *Hepatology*. 1987;7(6):1340-1345. doi:10.1002/HEP.1840070627
47. Al-Kandari S, Nordenfelt E, Al-Nakib B, Hansson BG, Ljunggren K, Al-Nakib W. Hepatitis delta virus infection in acute hepatitis in Kuwait. *Scand J Infect Dis*. 1988;20(1):15-19. doi:10.3109/00365548809117212
48. Guneid AME, Gunaid AA, O'Neill AM, Zureikat NI, Coleman JC, Murray-Lyon IM. Prevalence of hepatitis B, C, and D virus markers in yemeni patients with chronic liver disease. *J Med Virol*. 1993;40(4):330-333. doi:10.1002/JMV.1890400413
49. Al-Dhahry SHS, Aghanashinikar N, Al-Marhuby HA, Buhl MR, Daar AS, Al-Hasani MK. Hepatitis B, Delta and human immunodeficiency virus infections among Omani patients with renal diseases: a seroprevalence study. *Ann Saudi Med*. 1994;14(4):312-315.
50. Ramia S, El-zaatari M, Sharara AI, Ramlawi F, Farhat B. Current prevalence of hepatitis delta virus (HDV) infection and the range of HDV genotypes in Lebanon. *Epidemiol Infect*. 2007;135(6):959-962. doi:10.1017/S0950268806007643
51. WHO. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Published July 15, 2021. https://www.who.int/publications/i/item/9789240027077. Accessed November 18, 2021.
52. Esmat G. A review of chronic hepatitis B epidemiology and management issues in selected countries in the Middle East. *J Viral Hepat*. 2012;19(1):9-22. doi:10.1111/J.1365-2893.2011.01511.X
53. Sanai FM, Alghamdi M, Dugan E, et al. A tool to measure the economic impact of hepatitis B elimination: a case study in Saudi Arabia. *J Infect Public Health*. 2020;13(11):1715-1723. doi:10.1016/J.JIPH.2020.09.004

14783231, 2023, S1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15338 by Readcube (Labtiva Inc.), Wiley Online Library on [08/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

54. Pattyn J, Hendrickx G, Vorsters A, Van Damme P. Hepatitis B vaccines. *J Infect Dis*. 2021;224(Supplement_4):S343-S351. doi:10.1093/INFDIS/JIAA668
55. Razavi-Shearer D, Gamkrelidze I, Nguyen MH, et al. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol*. 2018;3(6):383-403. doi:10.1016/S2468-1253(18)30056-6
56. Niro GA, Ferro A, Cicerchia F, Brascugli I, Durazzo M. Hepatitis delta virus: from infection to new therapeutic strategies. *World J Gastroenterol*. 2021;27(24):3530. doi:10.3748/WJG.V27.I24.3530
57. Yurdaydin C, Abbas Z, Buti M, et al. Treating chronic hepatitis delta: the need for surrogate markers of treatment efficacy. *J Hepatol*. 2019;70(5):1008-1015. doi:10.1016/j.jhep.2018.12.022
58. WHO. Global health sector strategy on viral hepatitis 2016–2021. Towards Ending Viral Hepatitis Published online 2016. https://apps.who.int/iris/bitstream/handle/10665/246177/WHO?sequence=1. Accessed November 4, 2021.

How to cite this article: Lazarus JV, Al-Rifai A, Sanai FM, et al. Hepatitis delta virus infection prevalence, diagnosis and treatment in the Middle East: A scoping review. *Liver Int*. 2023;43(Suppl. 1):116-123. doi: 10.1111/liv.15338

14783231, 2023, S1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15338 by Readcube (Labtiva Inc.), Wiley Online Library on [08/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License