Prevalence of hepatitis D virus co-infection in Austria – Finding the needle in the haystack

In the current issue of the Journal, Jachs et al. report on the prevalence and burden of disease of hepatitis B – hepatitis D (HBV-HDV) co-infection in Austria. Through a nationwide multi-center retrospective cohort study they identified 347 anti-HDV positive patients of whom 74 were still under active surveillance. Their study provides some valuable insights into the epidemiology of HBV-HDV co-infection in a low-endemic Western country, but also highlights several knowledge gaps and challenges that still remain. The first major issue to be resolved is case finding. Patients with HBV-HDV co-infection are often HBeAg negative and have low levels of HBV DNA, potentially resulting in false diagnoses of inactive HBV carriage. For this reason, current European Association for the Study of the Liver guidelines recommend systematic anti-HDV screening in HBsAg positive subjects. Previous studies have already shown that anti-HDV testing is often not performed, leading to underdiagnosis. In the current study conducted across a nationwide network of 10 hepatitis treatment centres, a total of 347 anti-HDV positive patients were identified during a 10-year period. In the light of infrequent anti-HDV testing, this is likely to be an underestimation of the prevalence of active hepatitis D is further complicated by infrequently performed HDV RNA assessment. In the Austrian cohort, only 58% of anti-HDV positive patients underwent subsequent HDV RNA testing, and in this subgroup only 62% patients had detectable HDV RNA. Based on these data, it appears that the HBV-HDV co-infected patients described in this cohort may only be the tip of the iceberg, with many patients still unidentified, and the true prevalence remaining unclear.

The low rate of anti-HDV testing is particularly worrisome because presence of HDV co-infection is associated with an increased risk of developing end-stage liver disease and hepatocellular carcinoma among HBsAg positive patients. In a previous Spanish study, 30% of HBV-HDV co-infected patients had cirrhosis at diagnosis and 31% of non-cirrhotic patients developed cirrhosis during a median of 8 years of follow-up. In the current Austrian cohort, 38% of patients had advanced chronic liver disease at study entry, underscoring the high risk of disease progression in these patients.

Among patients with HBV-HDV coinfection, achievement of undetectable HDV RNA, both treatment induced or spontaneous, is associated with a reduced risk of adverse clinical outcomes. While currently available nucleos(t)ide analogues may potently suppress HBV replication, they do not affect HDV RNA levels and appear to have no clear benefit in patients with HBV-HDV co-infection. At present, only treatment with (pegylated) interferon (IFN) has been shown to increase the chance of HDV RNA undetectability, although absolute response rates are low, and off-treatment relapse rates are daunting. The combination of low response rates and significant side effects has severely limited the application of IFN in clinical practice, which is nicely illustrated by the observation that only 50% of subjects in the current cohort (had) received IFN based therapy. Fortunately, several new compounds are in advanced stages of development. One of these is the entry-inhibitor bulevirtide which has been shown to result in HDV RNA suppression, both as monotherapy and in combination with pegylated IFN. Due to the high need for new treatment options and the promising results documented in the phase-2 studies it has gained provisional approval in Europe. However, the phase-3 studies are still ongoing. Thus, the optimal dosing, treatment duration and the need for combination with other antiviral drugs still needs to be determined. Moreover, the safety and efficacy of these novel regimens in patients with decompensated liver disease has not been established.

In the current cohort, liver related events were predominantly observed in patients with advanced chronic liver disease. While successful IFN therapy has been shown to reduce the risk of adverse outcomes, previous experience in patients with HBV and hepatitis C virus mono-infection has consistently shown that viral suppression and eradication does not abolish the risk of hepatocellular carcinoma (HCC) in patients with established cirrhosis. Early identification and treatment, thus averting the development of cirrhosis, is therefore essential to reduce the need for life-long follow-up and HCC surveillance despite successful antiviral therapy. The findings presented in the current study should therefore be considered a wake-up call for all those who care for patients with viral hepatitis: HDV case-finding through universal anti-HDV testing is of major importance in order to gain insight into the epidemiology of this deadly disease and to identify patients most likely to benefit from antiviral therapy once novel compounds become widely available.
CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT
Not applicable.

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REFERENCES