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Increase in HDV replication during steroid therapy – potential implications for testing and treatment strategies

To the Editor:

We read with great interest the new clinical practice guidelines (CPGs) on HDV infection as published in a recent issue of the *Journal*.[1] The new guideline advocates widespread testing of HBsAg-positive individuals for co-infection with HDV, as previous studies have shown that risk-based testing leads to under-diagnosis and missed opportunities for linkage to care.[2] The CPGs also support consideration of antiviral therapy in all individuals with chronic hepatitis D (CHD), given the high risk of progression to advanced chronic liver disease and liver cancer. A topic that was not covered in the CPGs is the importance of testing for and treatment of HDV co-infection in HBsAg-positive individuals undergoing immunosuppression. The relevance of this issue is demonstrated by a recent case we encountered in our hospital.

The case concerns a 33-year-old male with no relevant medical history, who presented in another hospital with right upper quadrant pain. Additional analysis performed for elevated liver enzymes revealed CHD with signs of moderate fibrosis (liver stiffness measurement 9.7 kPa with FibroScan). He was treated with pegylated interferon monotherapy for 48 weeks. During treatment transaminases fluctuated, nonetheless they stayed elevated around >1-2x the upper limit of normal. After one year of treatment, HDV RNA (tested on an in-house developed PCR assay with a lower limit of detection of 5.78 IU/ml) was negative, HBV DNA levels were low and HBsAg levels stable.[3] However, his transaminases remained elevated. Further analysis showed elevated IgG (28.5 g/L) and anti-nuclear antibody positivity. A liver biopsy was performed which showed probable cirrhosis and portal/septal inflammation compatible with auto-immune hepatitis as well as a viral aetiology. Because of the advanced fibrosis, tenofovir disoproxil fumarate was initiated, and a decision was made to start a trial of prednisone as a treatment for potential concomitant auto-immune hepatitis. Unfortunately, liver enzymes significantly deteriorated during prednisone therapy, with a peak ALT of 226 U/L. Prednisone was tapered and stopped within 2 months, and over the subsequent weeks the liver enzymes declined to baseline levels. The patient was subsequently referred to our centre for evaluation. Retroactive testing of stored blood samples revealed that the patient had experienced HDV RNA relapse after the initial negative sample, and that HDV RNA was already detectable at the start of prednisone therapy (HDV RNA 4.75×10^5 IU/ml). HDV RNA levels showed a marked increase after initiation of prednisone therapy, and this increase was mirrored by an ALT flare. After cessation of prednisone, HDV RNA levels decreased, which was again mirrored by a decrease in ALT levels to baseline levels. During this episode, HBV DNA remained completely suppressed and HBsAg levels remained stable, supporting the hypothesis that the ALT flare was HDV-related (Fig. 1).

Reactivation of HBV during immunosuppression is a well-recognized complication associated with a high risk of adverse clinical outcomes. HBV screening before the start of immunosuppressive medication is therefore recommended, as is initiation of prophylactic antiviral therapy during high-risk immunosuppressive regimens.[4] The effect of immune suppression on HDV replication and the risk of hepatic flares in individuals with CHD has not been well studied. The current case clearly demonstrates that individuals with CHD treated with steroids, and potentially other immunosuppressive agents, are at risk of increased HDV replication and subsequent hepatitis. The underlying mechanism for this observation is currently unknown, but it may be due to a loss of immune control as a result of immunosuppressive therapy, or potentially to stimulation of a glucocorticoid-responsive element in the viral replication cycle as has previously been demonstrated for HBV.[5,6]

Nonetheless, this unique case highlights the importance of universally testing for HDV coinfection and follow-up by PCR in HBsAg-positive individuals, especially in individuals with an indication for immunosuppression, even in those already on nucleo(s)tide analogue therapy. Moreover, in individuals with a previously positive anti-HDV test, repeated HDV-RNA PCR testing is advisable irrespective of prior treatment or HDV RNA negativity, since late relapse might occur. The CPGs recommend that all individuals with CHD should be considered for antiviral treatment, although access to treatment is currently limited in many areas. Perhaps individuals with CHD who become immune compromised could be prioritised for HDV-targeted therapy, such as bulevirtide, irrespective of fibrosis and/or inflammatory activity, in order to reduce the risk of ALT flares that are likely to result in discontinuation of the immunosuppressive regime. Lastly, these recommendations are

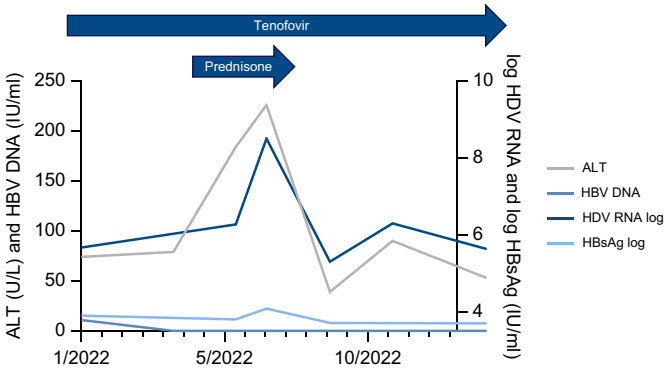

Fig. 1. The effect of prednisone use on HDV RNA, ALT, HBV DNA and HBsAg in an HBV-HDV co-infected patient on tenofovir therapy.

based on one case and future studies should be conducted to confirm our findings.

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Supplementary data

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