Management of hepatitis D in general practice

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Background
Hepatitis D virus (HDV) requires the presence of hepatitis B virus for replication and infection, and is associated with accelerated progression to cirrhosis and an increased risk of hepatocellular carcinoma. Approximately 4% of Australians living with hepatitis B are infected with HDV, although it is likely that HDV remains underdiagnosed.

Objectives
This paper highlights the importance of screening for HDV in patients living with chronic hepatitis B (CHB) and provides an overview of diagnosis and treatment approaches for general practitioners (GPs), with the hope of reducing preventable liver-related morbidity and mortality in people living with CHB and HDV coinfection.

Discussion
The diversity of risk factors and geographical origins of patients in the multicultural Australian populace highlights the need for routine testing for HDV in patients diagnosed with CHB. GPs have a pivotal role in the diagnosis of HDV and should, if possible, promptly refer patients to non-GP specialist physicians to consider HDV therapy.

HEPATITIS D VIRUS is a small single-stranded RNA virus that is classically thought to require the surface antigen of hepatitis B virus (HBV) to facilitate virion assembly, transmission between hepatocytes and dissemination between hosts.[1] Although some in vitro and animal in vivo data suggest that HDV can use other surface glycoproteins to propagate independent of HBV, in general, human HDV infection is only possible if an individual has comorbid chronic hepatitis B (CHB).[2] It has been previously estimated that HDV affects 12 million people worldwide;[3] however, some estimates suggest that the global burden is much greater, with up to 60 million individuals infected with HDV.[4–10] Of the eight genotypes of HDV,[11,12] genotype 1 is predominant worldwide and in Australia.[13] Transmission of HDV in endemic regions often occurs within families through contact with infected bodily fluids or blood, whereas in non-endemic regions at-risk populations include men who have sex with men (MSM) and people who inject drugs (PWID). The aims of this article are to highlight the importance of screening for HDV in patients with CHB infection in primary care and to provide an overview of diagnosis and treatment.

Acute infection with HBV and HDV simultaneously (acute coinfection) is clinically indistinguishable from classical acute HBV and is often transient and self-limited.[14] In contrast, HDV superinfection of an individual with CHB can present as a severe acute hepatitis or as an exacerbation of CHB, with progression to chronic HDV infection occurring in 80–100% of cases.[15] HDV superinfection can also present as a rapidly progressive fulminant hepatitis necessitating urgent admission and potential liver transplantation.[16]

Chronic HDV infection may be asymptomatic, whereas some infected individuals may develop a spectrum of symptoms ranging from malaise, anorexia and fatigue through to acute liver failure.[17] Chronic HDV infection is one of the most severe forms of viral hepatitis, associated with accelerated progression to cirrhosis, with 50–70% of patients developing cirrhosis within 5–10 years, a threefold increase compared with patients with HBV monoinfection.[18] Patients with chronic HDV are also at greater risk of hepatic decompensation, hepatocellular carcinoma (HCC) and fulminant hepatitis than those with CHB monoinfection.[19–21] The five-year mortality rate of patients with HDV is twice that of those with HBV monoinfection.[22] In addition, HDV-infected patients accounted for approximately 25% of hepatitis B surface antigen (HBsAg)-positive liver transplant recipients in the European Liver Transplant Registry.[18] Although there are nuanced guidelines for HCC surveillance in patients with CHB monoinfection,

all patients with HDV/HBV coinfection should be offered HCC surveillance.[23]

To summarise:

- HDV requires active HBV infection to replicate
- Australian patients living with CHB who subsequently contract HDV are at a very high risk of developing chronic HDV/CHB coinfection
- patients living with HDV/CHB coinfection have an increased risk of hepatic decompensation, HCC and death compared with patients living with CHB monoinfection.

Epidemiology of HDV in Australia

There is substantial variability in the seroprevalence of HDV among HBsAg-positive carriers worldwide.[24] HDV infection is endemic within regions including western Africa, central and northern Asia, the Middle East, Eastern Europe and the Amazonian and Mediterranean basins.[8,24] In Western countries, HDV infection is largely confined to high-risk population groups, such as PWID and, importantly, those who have migrated from countries with a high burden of HDV disease.[8,24]

Based on annually reported data from the National Notifiable Disease Surveillance System, the primary source of hepatitis D epidemiological data in Australia, an average of 48 cases of newly diagnosed HDV were notified each year between 2010 and 2016.[25] Studies conducted across Australia have demonstrated a seroprevalence of HDV infection of 4.1% among 4407 HBsAg-positive people tested in Queensland between 1997 and 2016; similarly, HDV positivity was seen in 4.8% of 2314 Victorians tested between 2000 and 2009.[26,27] In Australia, most patients living with chronic HDV coinfection are born overseas, most commonly in Sudan, Vietnam or Pakistan.[13] This reflects changes in migration patterns and highlights the need to screen all Australians born in these regions for chronic HBV infection, because many are born in regions traditionally considered to have a low prevalence of HDV.[13] Compared with the period 2000–09,[27] the population of patients diagnosed with HDV between 2010 and 2016 is associated with increasing average age, a reduction in male predominance and PWID.[13]

Screening and diagnosis of HDV

Australian consensus guidelines recommend screening for HDV in all patients who test positive for HBsAg.[23] The recommended screening assessment for HDV is serum anti-HDV IgG, followed by HDV-RNA polymerase chain reaction (PCR) if confirmed.[23] Antibody testing is imperfect: false positives may occur via cross-reactivity with other viral antibodies, although HDV-RNA PCR testing is both sensitive and specific.[28] Screening for both HDV and CHB (which may also be underdiagnosed in Australia)[29] should also be considered in PWID and HIV-positive patients, MSM and immigrants from endemic areas.[30] There should be high suspicion for HDV in patients with HBV with persistently elevated liver tests despite suppressed viral load, because HDV coinfection directly suppresses HBV replication.[26,31] Hepatitis D virus is a notifiable disease in Australia, and thus must be notified within 5 days of diagnosis. Australian guidelines recommend that individuals with HDV infection are referred to non-GP specialist care (including hepatologists and/or infectious diseases physicians) due to the increased risk of poor outcomes, as well as to consider the initiation of treatment.

To summarise:

- guidelines support GP specialists screening for CHB in individuals at risk
- screening for HDV infection in patients living with CHB should occur at least once
- patients with HDV/CHB coinfection should, if possible, be referred to non-GP specialists for consideration of treatment initiation.

Goals of HDV treatment and treatment options

The principal goal of chronic HDV treatment is to prevent the development of complications, including cirrhosis, hepatic decompensation and HCC, and to reduce overall mortality. However, surrogate markers and endpoints of HDV treatment are not well defined.[32] The ideal endpoint of HDV treatment efficacy would be the clearance of HBsAg or functional HBV cure with or without anti-HBsAg seroconversion. However, a more practical endpoint of anti-HDV therapy is to achieve a serum or plasma HDV-RNA titre below the lower limit of detection by PCR, both during and following treatment.[22,32] However, given the high risk of late post-treatment virological relapse following interferon (IFN)-based therapies, a sustained response should be confirmed well beyond the discontinuation of treatment.[17]

Pegylated (PEG) IFN-α is the only available licensed treatment against chronic HDV infection with proven (albeit limited) anti-viral efficacy.[30,33] Recent studies investigating the efficacy of PEG-IFN-α have described HDV-RNA negativity in 15–40% of patients 24 weeks after the completion of 48 weeks of therapy.[30,34,35] However, PEG-IFN-α has limited use in clinical practice because it is contraindicated in patients with decompensated liver disease, significant psychiatric comorbidities and autoimmune conditions.[17] In addition, PEG-IFN-α therapy is associated with a number of adverse effects, including myalgias and arthralgias, flu-like symptoms, haematological toxicities and/or the exacerbation of psychiatric illnesses.[36]

Comprehensive Australian guidelines have been recently released for the treatment of CHB.[23] Unfortunately, the mainstay of CHB therapy (oral nucleos(t)ide analogues [NAs]) have shown no efficacy against HDV when used alone or in combination with PEG-IFN-α.[37] However, when combined with PEG-IFN-α, NAs have been shown to reduce HBsAg titres, and may be helpful in suppressing residual HBV replication in patients with HDV infection and advanced liver disease.[34]

There are several novel agents currently being evaluated as alternatives to PEG-IFN-α, including bulevirtide, which inhibits the sodium taurocholate cotransporting polypeptide, thereby

blocking the entry of HDV and HBV into hepatocytes.[38] Bulevirtide has shown promising results in Phase III clinical trials, in which a reduction in HDV-RNA has been observed after 24 weeks of therapy when bulevirtide was administered as a monotherapy or in combination with PEG-IFN-α.[38] For the many patients with HDV in whom PEG-IFN-α therapy is contraindicated, bulevirtide monotherapy may represent a promising suppressive strategy. Bulevirtide received conditional approval for the treatment of HDV by the European Medicines Agency in 2020.[23]

To summarise:

- PEG-IFN-α, although often poorly tolerated, has historically been the sole treatment for patients living with HDV
- GPs should be aware that patients treated with PEG-IFN-α with underlying psychiatric comorbidities may experience a worsening of symptoms and should be monitored for a deterioration in their mental state
- new therapeutic options for HDV are on the horizon and are likely to be better tolerated.

Conclusion

HDV is an important virus that can cause severe and rapidly progressive liver disease in patients with CHB. The Australian primary care population is at risk for HDV due to a combination of ethnic diversity and lifestyle factors. All patients living with CHB should be tested for HDV infection at least once. Patients living with HBV–HDV coinfection should ideally be offered a referral for specialist input and should be enrolled in an HCC surveillance program. With new treatments on the horizon, even patients who are disinterested in or unsuitable for PEG-IFN-α may soon be eligible for better-tolerated therapies with greater efficacy, and even the potential for cure.

Key points

- HDV infection is associated with accelerated progression to cirrhosis and HCC.
- Approximately 4% of Australians with HBV are diagnosed with HDV; however, this is likely an underestimation due to underdiagnosis.
- The diversity of risk factors and geographical origin of patients living with HDV in Australia highlights the need for routine testing of patients diagnosed with CHB.
- Patients living with HDV should be promptly referred to non-GP specialist physicians for risk stratification and consideration of initiating HDV therapy or enrolment in clinical trials.
- Current treatments are limited to PEG-IFN-α, but other novel agents are on the horizon.

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