

# MANAGING HEPATITIS B VIRUS INFECTION IN COMPLEX SITUATIONS

# 10

**Benjamin Cowie**

Victorian Infectious Diseases Service, Royal Melbourne Hospital and Victorian Infectious Diseases Reference Laboratory, North Melbourne, VIC.

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Chapter 4: Natural history of chronic hepatitis B virus infection  
Chapter 5: Primary prevention of hepatitis B virus infection  
Chapter 7: Treatment of chronic hepatitis B virus infection  
Chapter 8: Managing patients with advanced liver disease  
Chapter 9: Hepatitis B virus-related hepatocellular carcinoma

## KEY POINTS

### Facts

- Ninety per cent of the mother-to-child transmission of hepatitis B virus (HBV) is preventable.
- Several antiviral drugs used in the treatment of human immunodeficiency virus (HIV) infection are also effective against HBV.
- The reactivation of HBV infection in the setting of immunosuppression can also occur in people who have a history of resolved acute HBV infection.

### Myths

- Mothers with HBV infection should not breastfeed.
- Children with HBV do not develop cirrhosis, hepatocellular carcinoma (HCC) or other manifestations of advanced liver disease.
- People with HIV should not be concerned about viral hepatitis, as complications take many years to develop.

There are a number of special situations in which the complexity of managing the care of a patient with hepatitis B virus (HBV) infection is increased. Primary care practitioners are optimally placed to recognise and respond to these situations, and coordinate a management plan that maximises the health and wellbeing of the patient with HBV infection.

## Pregnant women and HBV

Worldwide, the majority of people with chronic HBV infection acquired the infection at birth or in early childhood. Given that age at infection determines the risk of progression

to chronicity (see Chapter 4: Natural history of chronic hepatitis B virus infection), with 90% of neonatal infections resulting in chronic infection, averting the vertical transmission of HBV is critical. For many women with HBV infection who are pregnant or planning pregnancy, the possibility of HBV transmission to their child is a cause of significant distress. Adequate counselling and addressing the mother's concerns are crucial, emphasising the availability of highly effective treatment to prevent transmission. It is also an opportunity to assess the HBV status of other family and household members and to vaccinate all those who are susceptible.

Routine antenatal HBsAg screening is essential to allow the identification and treatment of as many neonates at risk of infection as possible.<sup>1</sup> If pre-test counselling identifies maternal risk factors for HBV infection, but serology indicates HBsAg negativity and no immunity, plans should be made to initiate vaccination of the mother following delivery.

The risk of vertical transmission is determined by the intensity of maternal HBV replication, with highly replicative infection characterised by a high HBV DNA viral load and HBeAg positivity (see Chapter 3: Hepatitis B virus testing and interpreting test results). Up to 90% of infants born to HBeAg-positive mothers acquire the infection if untreated, compared to less than 10% of those born to HBeAg-negative mothers.<sup>2,3</sup> When the appropriate prophylactic treatment is given, there is no evidence that mode of delivery (vaginal or caesarean) affects the risk of infection, and although HBsAg and HBV DNA are detectable in breast milk, breastfeeding is not associated with an increased risk of transmission and should not be discouraged.

A pregnant woman diagnosed with HBV should be referred to a physician experienced in the management of viral hepatitis. Pregnant women with established chronic hepatitis, especially those with cirrhosis, should be monitored for any deterioration in their liver disease throughout their pregnancy. A flare in the mother's hepatitis is sometimes seen after delivery, presumably secondary to the recovery from the pregnancy-induced immune tolerance state. Although HBV antiviral therapy is not approved in pregnancy, lamivudine has been taken by many pregnant women for the treatment of HIV infection without evidence of adverse foetal effects.

For a susceptible woman exposed to HBV during pregnancy, prophylaxis should be initiated immediately (Table 10.1). If acute HBV infection occurs during pregnancy, the risk of infection to the foetus is low in the first two trimesters but rises to 75% in the third trimester.<sup>2</sup> The mother should be referred for supportive care and monitored for features

**Table 10.1: Prophylaxis for women exposed to hepatitis B virus during pregnancy**

<b>1. HBIG* 400 IU, IM, single dose</b>
<b>2. Hepatitis B vaccine 1.0 mL, IM, 3 doses at 0, 1 and 6 months</b>
<b>3. Other considerations:</b> <ul style="list-style-type: none"> <li>▪ Both HBIG and hepatitis B vaccine should be administered without delay</li> <li>▪ HBIG and HBV vaccine can be administered simultaneously at different sites</li> <li>▪ Serological monitoring for infection must extend to at least six months post-exposure</li> <li>▪ Vaccinate the infant as per usual schedule unless infection occurs in the mother</li> <li>▪ If the mother acquires infection, manage the infant as per maternal chronic HBV infection</li> </ul>
<small>* Hepatitis B immunoglobulin (HBIG) is only available through the Australian Red Cross Blood Service</small>

of fulminant hepatitis (see Chapter 4: Natural history of chronic hepatitis B virus infection, and Chapter 7: Treatment of chronic hepatitis B virus infection). The infant should receive hepatitis B vaccine and HBIG at birth as described in the next section.

**Should pregnant women with HBV infection receive lamivudine?**

For some time, it has been observed that the efficacy of vaccination plus hepatitis B immunoglobulin (HBIG) in preventing perinatal infection is below the expected 90% in women with highly replicative infection (e.g. HBV DNA viral load >10<sup>8</sup> copies/mL). Earlier studies suggested a reduction in neonatal infections could be achieved if women received lamivudine therapy. A recent randomised controlled trial supported this hypothesis, although significant loss to follow up in the placebo arm complicated analysis.<sup>4</sup> Furthermore, there is a real concern that using lamivudine in women with highly replicative disease will induce HBV resistance mutations that will complicate the future treatment for the mother, and could also be transmitted to the infant if infection occurs despite therapy. Lamivudine is not licensed, nor funded through the Section 100 (Highly Specialised Drugs Program) of the Pharmaceutical Benefits Scheme (PBS) for this use, but it is offered to women with high viral burdens in some institutions.

## Paediatric management

For a neonate born to a mother with HBV infection, hepatitis B vaccination reduces the risk of infection by 70%; the addition of HBIG, derived from the plasma of blood donors with high anti-HBs levels, augments this risk reduction to 90%.<sup>5</sup> This combined active and passive vaccination approach for the prevention of perinatal infection is outlined in Table 10.2. Children diagnosed with HBV infection should be referred to a paediatrician experienced in viral hepatitis.

All susceptible household members should be vaccinated against HBV, and the affected child should also be vaccinated against hepatitis A. As with adults with chronic HBV infection, children should be periodically monitored for disease activity, progression and the development of hepatocellular carcinoma. Although there are even less data informing the frequency of monitoring in children than in the adult context, annual screening for HCC with serum alpha fetoprotein testing has been recommended, together with periodic

Table 10.2: Prophylaxis for perinatal hepatitis B virus exposure

1. **HBIG\*** 100 IU, IM, single dose

2. **Hepatitis B vaccine** 0.5 mL, IM, 4 doses at 0, 2, 4 and 6 or 12 months

3. Other considerations:

- Preferably both HBIG and hepatitis B vaccine should be administered immediately after birth in opposite thighs (i.e. not into the same site)
- HBIG should not be delayed beyond 12 hours after birth
- Hepatitis B vaccine should be given within 24 hours of birth; if delay is unavoidable, vaccine must be given within seven days
- Doses of hepatitis B vaccine subsequent to the birth dose are combined vaccines as per the standard schedule (final dose at 6 or 12 months depending on vaccine used)
- Serological assessment for infection (HBsAg and anti-HBs) should be performed three months after the final dose of hepatitis B vaccine (not before nine months of age)

\* Hepatitis B immunoglobulin (HBIG) is only available through the Australian Red Cross Blood Service

Acute HBV infections in infants and children are more commonly asymptomatic than these infections in adults, but when clinical manifestations do occur, they are generally similar to those in adults. Fulminant disease is uncommon, but in infants it appears to be associated with maternal HBeAg-negative chronic hepatitis. Most chronic infections are asymptomatic and do not affect development.<sup>6</sup>

The management principles for children with chronic HBV are generally the same as those for adults (see Chapter 5: Primary prevention of hepatitis B virus infection, Chapter 7: Treatment of chronic hepatitis B virus infection, Chapter 8: Managing patients with advanced liver disease, Chapter 9: Hepatitis B virus-related hepatocellular carcinoma). Counselling the patient and family regarding the natural history of the disease, modes of transmission and treatment options should be undertaken.

liver ultrasounds, and clinical and biochemical monitoring of disease activity every six to 12 months.<sup>6</sup>

The selection of patients for antiviral therapy is similar to the adult context. Treatment is generally reserved for patients with ALT values repeatedly more than twice the upper level of normal, as treatment efficacy is much higher in this setting (see Chapter 7: Treatment of chronic hepatitis B virus infection). The available treatments are conventional interferon-alfa and lamivudine.<sup>6,7</sup> The advantages of interferon-alfa are the finite duration of therapy and the lack of induction of antiviral resistance. Both efficacy and toxicity profiles in children are similar to those in adults, and patients with normal ALT (being the majority of children who acquired the infection at birth) are unlikely to achieve favourable outcomes. The use of pegylated interferon to treat HBV in children has not yet been investigated (but was examined

in children with hepatitis C virus [HCV infection). Lamivudine is an alternative that is well tolerated and effective at suppressing viral replication, but this antiviral therapy is associated with the relatively rapid emergence of viral resistance. Paediatric use of adefovir remains under investigation.<sup>7</sup>

## Co-infections

An estimated 0.5–1% of Australians with chronic HBV infection also have HIV infection; 4–6% of HBsAg-positive people are believed to be co-infected with HCV. These rates are higher than in the general population, related to the shared modes of transmission and hence epidemiological associations of these viruses. Hepatitis D virus (HDV) only exists as a co-infection with HBV.

### HBV/HIV co-infection

The majority of HIV-positive men who have sex with men (MSM) have serological evidence of past or chronic HBV infection. In the Australian HIV Observational Database cohort of more than 2000 HIV-positive participants, over 6% of those tested were seropositive for HBsAg.<sup>8</sup> The progression to chronic infection following acute HBV is much more common in people with HIV infection, with the likelihood of failing to clear HBV related to the degree of immunodeficiency.<sup>9</sup>

Co-infection with HIV has a significant impact on the natural history of chronic HBV infection. High HBV DNA levels and detectable HBeAg are more common in patients with HIV co-infection, and the rate of viral reactivation is also higher, particularly in more immunocompromised patients.<sup>10</sup> Even anti-HBs-positive patients with a history of resolved HBV infection can experience reactivation, with reappearance of HBsAg and HBV DNA in the setting of advanced immunodeficiency. Occult chronic HBV infection (HBsAg negative but HBV DNA positive) is also more common in patients with HIV infection.

In the setting of HBV/HIV co-infection, the progression to advanced liver disease, such as cirrhosis and HCC, is more rapid and liver-

related mortality is higher, despite typically lower ALT values and reduced inflammatory activity on biopsy. This disparity of less necro-inflammatory activity, but faster disease progression is incompletely understood. In contrast to the significant impact of co-infection on the natural history of HBV, there is little evidence to suggest that HBV affects the progression of HIV infection.

With the profound reduction in acquired immune deficiency syndrome (AIDS)-related mortality and in the incidence of opportunistic infections since the introduction of highly active antiretroviral therapy (HAART), liver-related morbidity and mortality has assumed an increasing burden on the health of people with HIV infection. The co-infection with hepatitis viruses explains a significant proportion of this burden. Another cause of hepatic damage in people with HIV infection is the toxicity of a number of antiretroviral agents; this toxicity is more pronounced in patients with pre-existing liver disease, such as chronic viral hepatitis.<sup>11</sup>

The selection of patients requiring treatment for HBV in the setting of HIV co-infection is similar to the HIV-negative context, and the aims are essentially the same. One very important consideration is that some of the agents used to treat HIV (such as lamivudine, tenofovir and emtricitabine) are also active against HBV. Thus, the incorporation of one or more of these drugs into a HAART regimen allows treatment of both infections without increasing the therapy burden. Furthermore, co-infection is the only context in which combination therapy for HBV is possible under the PBS, an approach which is likely to delay the development of HBV antiviral resistance (as it does in HIV).<sup>7,11</sup> In patients not requiring HIV therapy, monotherapy for HBV with agents also active against HIV (such as lamivudine) should be avoided, as this can induce resistance mutations that will make designing subsequent HAART regimens more difficult. It was previously thought that the anti-HBV drug, entecavir, had no anti-HIV activity, however, recent reports indicate that entecavir can induce resistance mutations in HIV<sup>12</sup> and its use as HBV monotherapy in the context of HIV co-infection is being re-evaluated. Pegylated

interferon-alfa, as a non-nucleoside-based therapy, can be considered for patients in this context, provided they have adequate hepatic reserve, although its efficacy is reduced in the context of HIV infection, particularly with more advanced immunodeficiency.<sup>11</sup>

Another reason to incorporate HBV active agents in a HAART regimen is to avert immune reconstitution hepatitis. The immune reconstitution inflammatory syndrome describes a pathology deriving from resurgent immune attacks on chronic infections in patients with HIV, following the commencement of HAART. HBV flares in the setting of immune reconstitution are more common in patients with a high baseline HBV viral load<sup>11</sup>, and can result in significant liver disease and mortality, particularly in patients with advanced liver disease and poor hepatic reserve. However, flares can also lead to HBeAg clearance and the suppression of viral replication in some patients.<sup>9</sup> Caution when changing HAART regimens in co-infected patients is also necessary, as ceasing HBV-active agents can cause reactivation. Continuation of these antivirals should be considered even if they add little to the patient's HIV therapy.

### **HBV/HCV co-infection**

In contrast to the co-infection with HIV, it is common for patients with HCV co-infection to have a reduced replication of HBV, with lower viral loads than in patients with HBV monoinfection. This is because HCV directly interferes with the HBV replication. It is a common finding in HBV/HCV co-infection that one of the viruses predominates in terms of viral replication, with the suppression of the other virus.<sup>9</sup> As with HIV, occult (HBsAg-negative) HBV infection is also seen more commonly in patients with HCV co-infection.

Acute co-infection (usually arising through injecting drug use) has been associated with an increased incidence of fulminant hepatitis. Chronic HBV/HCV co-infection is usually associated with a more severe liver disease, an increased risk of progression to cirrhosis and a higher incidence of HCC. A recent Australian study showed that co-infection with HBV and

HCV was associated with much higher mortality rates (liver-related and all cause) than infection with either HBV or HCV alone; patients with co-infection had mortality rates approximately three times higher than patients with HBV infection only.<sup>13</sup>

In patients with chronic HBV/HCV co-infection meeting the criteria for therapy for either infection, consideration should be given to combination therapy with pegylated interferon-alfa plus ribavirin, even if the HBV infection predominates. Reactivation of previously suppressed HBV replication following treatment of HCV with standard interferon plus ribavirin has been reported, leading to suggestions that combination with additional anti-HBV agents should be considered. This approach is not universally followed.

### **HBV/HDV co-infection**

In non-endemic countries such as Australia, HDV infection is most commonly associated with injecting drug use (IDU). HDV is a defective virus that requires co-infection with HBV to synthesise new virions. Similar to the situation of HBV/HCV co-infection, HDV infection results in the suppression of HBV replication with sometimes low or even undetectable HBsAg levels.

Acute co-infection with HBV/HDV is typically indistinguishable from HBV monoinfection, but has been associated with a higher incidence of fulminant hepatitis. The rate of progression to chronicity is no different from that for HBV infection alone. HDV superinfection of a patient with existing chronic HBV can present as an acute hepatitis flare, and progression to chronic HDV infection is almost universal. Chronic HBV/HDV co-infection has been associated with a more severe liver disease and the increased incidence of HCC and mortality. Treatment of HBV/HDV co-infection is with interferon-alfa, conventional or pegylated, for a period of one year<sup>7</sup>, although treatment eradicates the virus in only a minority of patients and relapse following therapy is common. Lamivudine is ineffective against HDV and the addition of ribavirin to interferon also confers no benefit.

## Reactivation during immunosuppression

The natural history of HBV infection is fundamentally related to the dynamic balance between the viral replication and the host's immune response (see Chapter 4: Natural history of chronic hepatitis B virus infection). Therefore, it is not surprising that immunosuppressive therapy can have a marked impact on chronic HBV infection. Reactivation of HBV replication is common during cancer chemotherapy and following immunosuppression for transplantation or for the treatment of autoimmune diseases. It is particularly associated with glucocorticoid therapy as, in addition to suppressing host immunity, glucocorticoids act directly on the virus to enhance transcription.

HBV reactivation due to the institution of immunosuppressive medication is initially associated with a rise in the serum HBV DNA viral load. A hepatitis flare with a rise in ALT levels can follow, particularly when the immunosuppressive therapy is reduced or withdrawn; restoration of the immune function causes a sudden increase in the destruction of infected hepatocytes. This is similar to the immune reconstitution inflammatory syndrome seen with HAART for HIV infection.

Although most hepatitis flares in the context of immunosuppression are asymptomatic, a full spectrum of presentations is possible, through to liver failure and death. Suggested risk factors for reactivation have included use of glucocorticoids, high baseline HBV DNA viral load, HBeAg positivity, young age and male gender.<sup>14</sup> The rate of withdrawal of immunosuppression is an important determinant of the severity of flares. The increased incidence of flares observed in the setting of cancer chemotherapy, compared with other immunosuppressive regimens, may relate to the cyclical nature of such therapy, with repeated episodes of immune suppression and restoration.

Prophylaxis with lamivudine has been shown to markedly reduce the incidence of reactivation, hepatic flares and associated mortality. Prophylaxis should be given to all HBsAg-positive patients prior to chemotherapy or other immunosuppressive therapy;<sup>7</sup> such pre-emptive treatment has been shown to be superior to starting treatment once reactivation has been detected.<sup>14</sup> To allow prophylaxis to occur, all patients being prepared for such treatment should be screened for the presence of HBsAg, anti-HBs and anti-HBc. Although most experience in such prophylaxis has been with lamivudine, the possibility of inducing drug resistance mutations is a significant concern. Entecavir is associated with a lower rate of resistance induction and is likely to assume an increasing role in this setting. Interferon is contraindicated in patients with significant autoimmune disease or in the post transplantation setting, due to its immunomodulatory activity.

HBV is detectable in the hepatocytes of any person who has ever had the infection, even those who are anti-HBs positive. In the setting of profound immunosuppression, HBsAg-negative patients can also reactivate and develop severe flares. This situation is more common in isolated anti-HBc-positive patients than in those with detectable anti-HBs, but the occurrence in the latter group is also described. Some protocols extend the recommendation for antiviral prophylaxis to isolated anti-HBc-positive patients, but few recommend prophylaxis in anti-HBs-positive patients. Recognising the possibility of reactivation and acting promptly is therefore important in all patients undergoing immunosuppression.

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