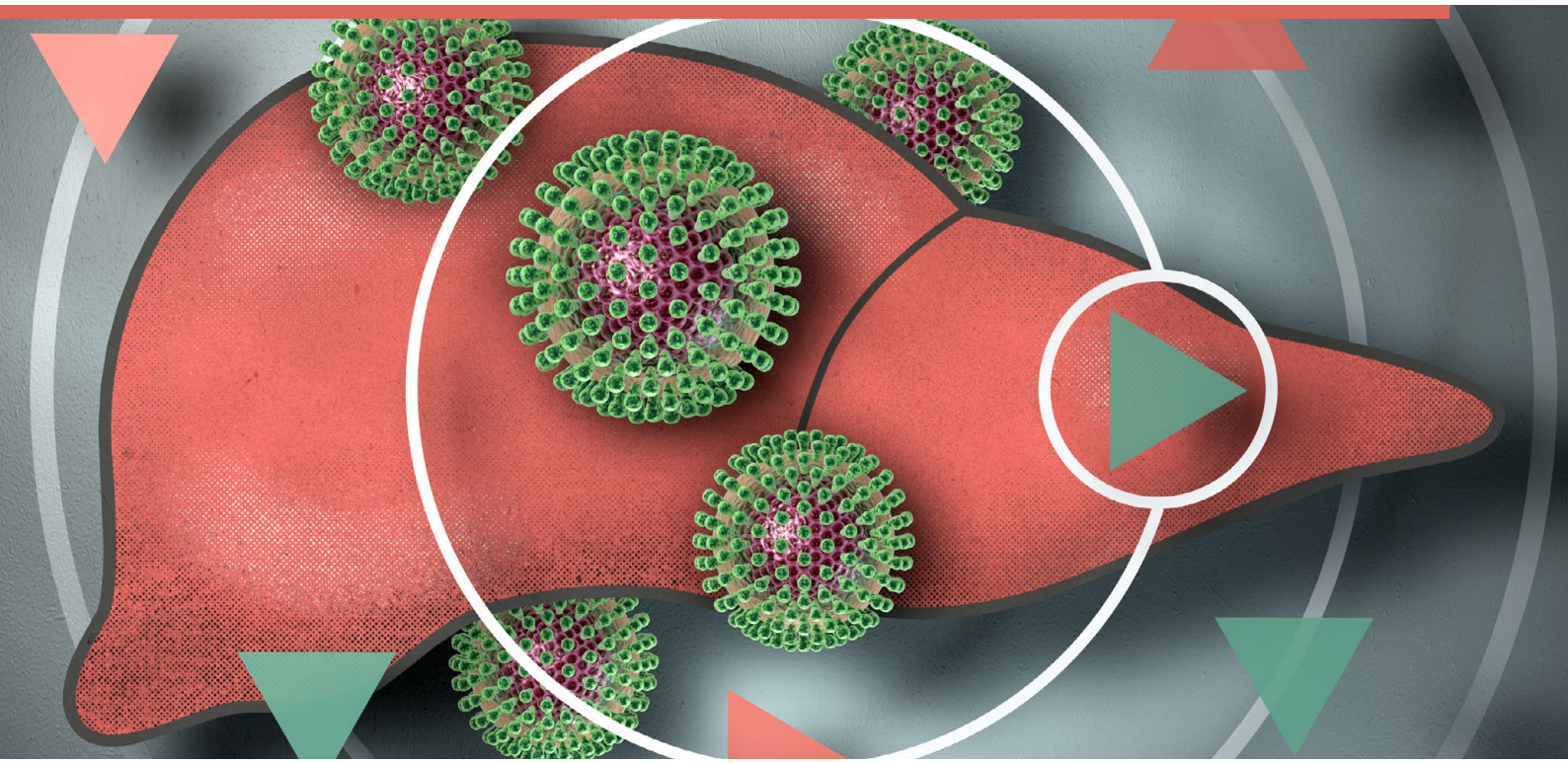

Hepatitis B: treatments now available for primary care

Tenofovir disoproxil and entecavir are once daily oral antiviral medicines, recommended as first-line treatments for patients with chronic hepatitis B; they are now fully funded without restrictions. Clinicians in primary care can help patients benefit from these medicines by testing those with risk factors for hepatitis B and ensuring they receive appropriate treatment in primary or secondary care.

KEY PRACTICE POINTS:

- There are more than 100,000 people with chronic hepatitis B in New Zealand; many of these people are unaware they are infected and are at increased risk of cirrhosis and hepatocellular carcinoma
- Most people with chronic hepatitis B would have been infected during birth or early childhood via incidental blood contact. Acute infection acquired in adulthood, e.g. via blood or sexual contact, rarely progresses to chronic infection.
- People born in New Zealand prior to the introduction of national vaccination in 1988 are most at risk of chronic hepatitis B infection, as well as immigrants from countries with limited access to vaccination
- There are large disparities in the burden of chronic hepatitis B in New Zealand; people of Māori, Pacific, South-East Asian or Chinese ethnicity have a higher prevalence
- Unlike treatments for hepatitis C, current treatments for chronic hepatitis B are not curative. Treatment is targeted to patients at risk of liver damage; in many cases treatment is life-long.
- Since 2018, the recommended first-line oral antiviral treatments for hepatitis B, tenofovir disoproxil and entecavir, have been able to be prescribed by general practitioners without requiring Special Authority approval
- Primary care clinicians can help patients to benefit from these medicines by:
  - Identifying and testing patients who may be at risk of hepatitis B infection
  - Ensuring that patients with chronic hepatitis B receive appropriate treatment in either primary or secondary care and are referred to the Hepatitis Foundation
  - Auditing practice records to identify patients already diagnosed with chronic hepatitis B who could benefit from monitoring, with or without treatment
- Primary care prescribers should be aware that immunosuppressive treatment, e.g. oral corticosteroids for ≥ 4 weeks, can lead to hepatitis flares caused by reactivation of the virus. Prophylactic treatment with tenofovir disoproxil or entecavir is usually required.
- In addition to childhood vaccination, vaccination for hepatitis B is recommended and funded for:
  - Household or sexual contacts of people with hepatitis B infection
  - People with a range of risk factors, such as HIV or hepatitis C infection, needle-stick injury or undergoing dialysis

This is a revision of a previously published article. What's new for this update:

- Updated statistics and links throughout the article
- Added in reference to a new funded hepatitis C treatment which has become available since the article was first published (Maviret [glecaprevir and pibrentasvir])
- Adefovir dipivoxil has been removed from the alternative treatment options list for patients with chronic hepatitis B infection as it is no longer manufactured and has been delisted from the New Zealand Pharmaceutical Schedule

Chronic hepatitis B infection affects more than 100,000 adults in New Zealand[1]

The hepatitis B virus (HBV) is acquired via perinatal transmission from mother to child, sexual contact or blood-borne transmission. Almost all people with HBV infection in New Zealand were infected at birth or in early childhood, via incidental blood transmission from other infected children, before hepatitis B vaccination was included in the National Immunisation Schedule.[1] Immigrants from countries with a high incidence of hepatitis B and unvaccinated travellers to those countries are the other main risk groups in New Zealand. People who are infected with HBV as adults, e.g. via sexual contact, are less likely to proceed to chronic infection (see: "Acute vs chronic hepatitis B").

Large ethnic disparities in chronic HBV infection and its consequences exist in New Zealand; chronic HBV infection affects approximately:[1–3]

- 8–9% of people of Chinese or South East Asian ethnicity
- 7% of people of Pacific ethnicity
- 6% of people of Māori ethnicity
- ≤ 1% of people of European or Indian ethnicity

Immigrants belonging to other ethnic groups, such as people from the Middle East, Africa or Latin American, may also have higher rates of chronic HBV infection due to a high prevalence in their country of birth. However, data for these groups are not available.

People living in socioeconomically deprived communities experience worse overall health outcomes as a result of HBV infection.[3] In particular, liver disease due to HBV infection disproportionately affects Māori and Pacific peoples. For example, a study in Middlemore hospital found that chronic HBV infection was the leading cause of cirrhosis in Māori or Pacific peoples, contributing to 53–76% of cases, compared to approximately 5% of cases in people of European ethnicity.[4]

The incidence of hepatocellular carcinoma is three to five times higher among Māori than Europeans in New Zealand, and approximately half of Māori with hepatocellular carcinoma have hepatitis B infection compared to approximately one-quarter of European people.[5,6]

People born in New Zealand prior to 1988 are at risk

Hepatitis B vaccination was first introduced in New Zealand in 1988 (see: "HBV vaccination"). The current National Immunisation Schedule includes HBV vaccination as part of the DTaP-IPV-HepB/Hib vaccine given at age 6 weeks, 3 months and 5 months.[1] Between 85–95% of children who receive a full vaccination course develop lifelong immunity, with no requirement for booster doses.[1] Additional steps to prevent transmission to a newborn if the mother has HBV infection include antiviral treatment for the mother and hepatitis B immunoglobulins and a vaccine dose administered to the infant within 24 hours of birth. Due to these preventive measures, most people born in New Zealand from 1988 onwards are not at risk of HBV infection.

Immigrants of any age and unvaccinated travellers are at higher risk

People who have migrated from countries with a high prevalence of HBV, and limited access to vaccination and perinatal preventive measures, e.g. the Pacific Islands, South East Asia and China, are at higher risk of chronic HBV infection. An assessment of immigrant children resettled in New Zealand between 2007–2011 found that approximately one-third had serology results suggesting they had not previously been vaccinated.[7] People from New Zealand who are unvaccinated and regularly visit countries with a high prevalence of HBV are at increased risk, particularly if they stay with people who are infected or have unprotected sex. Vaccination is recommended, but not funded, for travellers to high prevalence countries (see: "HBV vaccination").

Sexual transmission and blood contact

HBV is highly infectious and can be transmitted via fresh or dried blood or sexual fluids. It can remain on surfaces for up to one week.[1] Therefore transmission can occur through activities such as unprotected sexual contact, sharing drug injecting equipment, incidental transfer of blood to open wounds or broken skin (e.g. during play or sports), tattooing, piercing or cosmetic services such as hairdressing or manicures using improperly sterilised equipment and sharing items such as razor blades.[1]

Other people at risk include those with a higher occupational risk of needlestick injury or blood contact, e.g. healthcare workers, ambulance personnel, police, or people who undergo multiple percutaneous medical procedures, e.g. renal dialysis.

Most adults who contract HBV infection via sexual or blood contact will have acute infection only (see: "Acute vs chronic hepatitis B infection).

Vaccination is recommended for people at high risk of infection; many will be eligible for funded vaccination (see: "HBV vaccination").

Acute vs chronic hepatitis B

Infection with HBV begins with an acute phase. Detection of acute HBV infection is relatively rare; approximately 30 cases per year were notified* in New Zealand obetween 2016–2020.[8]

Approximately 70% of adults develop acute icteric hepatitis which is characterised by jaundice and other symptoms such as fever, nausea, vomiting and abdominal pain, with marked elevations in liver enzymes. Symptoms usually occur after a subclinical period of one and a half to six months following infection.[1,9] Children are usually asymptomatic following acute infection.

Management of patients diagnosed in the acute phase of infection is typically supportive, however, some patients may require referral to secondary care due to the development of severe hepatitis symptoms; fulminant hepatitis with hepatic necrosis occurs in less than 1% of patients following acute HBV infection.[9]

In most cases, adults who have acquired acute HBV infection will not progress to chronic infection.

* Acute HBV infection is a notifiable disease; chronic infection is not

Chronic HBV infections usually arise from perinatal or childhood exposures

Chronic HBV infection is defined as an infection lasting six months or longer. [1]Younger people are less likely to clear HBV infection from their body during the acute stage of infection, and have higher rates of progression to chronic infection:[1]

- Approximately 90% of infants aged less than one year who acquire HBV progress to chronic infection
- Approximately 30% of children aged one to four years who acquire HBV progress to chronic infection
- Less than 5% of adults who acquire HBV progress to chronic infection

People with chronic infection are at increased risk of liver disease

Most people with childhood-acquired chronic HBV infection will enter a long-term inactive phase associated with persistently normal serum ALT and low serum HBV DNA levels, which may last up to 30 years.[10] However, some people will enter an active phase of infection, which is associated with persistently elevated ALT levels, high levels of viral activity, liver inflammation and progressive liver fibrosis.

HBV vaccination

In addition to childhood vaccination as part of the National Immunisation Schedule:

- **Vaccination is recommended and funded for**:
  - Household or sexual contacts of people with an acute or chronic HBV infection
  - People with a range of risk factors, such as HIV or hepatitis C infection, needle-stick injury or undergoing dialysis*
- **Vaccination is recommended, but not funded, for:**[1]
  - People with increased risk from occupational or sexual exposure to body fluids and faeces, or receiving regular blood products (e.g. people with haemophilia)
  - People with developmental disability, current or prior injectable drug users, prison inmates, and immigrants from countries with a prevalence of infection of ≥2% or travellers to those countries†

Serology to check for immunity is not routinely required, but is recommended in some people at high risk, such as healthcare workers, people who inject drugs, sex workers and people who frequently change sex partners.*

* Refer to the Immunisation Handbook for full details on patients eligible for funded vaccination and recommendations on who should have post-vaccination serology: **www.health.govt.nz/publication/immunisation-handbook-2020**

† To check vaccination recommendations for different destinations, see: **https://wwwnc.cdc.gov/travel**. Hepatitis A vaccination is also recommended for travellers to countries with high rates of hepatitis A, therefore, travellers can be offered vaccination with the combined hepatitis A + B vaccine (Twinrix).[1]

People who inject drugs: risk of blood borne virus

People who inject drugs and share injecting equipment are at substantial risk of acquiring blood-borne viruses; predominantly hepatitis C, but also hepatitis B. Encourage people who inject drugs to avoid sharing injecting equipment and use needle exchange facilities. HBV vaccination is recommended, but not funded, for people who inject drugs.[1]

A list of needle exchange facilities and pharmacies involved in the New Zealand needle exchange programme is available from: **www.nznep.org.nz/outlets**

Know your ABCs: key similarities and differences in managing patients with hepatitis A, B and C

Hepatitis A, B and C are all viruses which infect hepatocytes and can lead to symptoms of acute hepatitis and acute elevations in liver enzymes such as alanine aminotransferase (ALT). Hepatitis B and C share similar routes of transmission, but injectable drug use, is the predominant mode of transmission for hepatitis C, while transmission from mother to child or between sexual partners or household contacts are the predominant modes of transmission for hepatitis B (Table 1).[12] Hepatitis A infection occurs via faecal-oral transmission; it causes acute hepatitis symptoms, however, does not lead to chronic infection and only rarely leads to persistent liver damage, although it contributes to liver complications if patients have concurrent hepatitis B or C.[1]

It is possible to have more than one hepatitis infection simultaneously. If patients test positive for both HBV and HCV infection, referral to secondary care is recommended for concurrent management.[13]

Further information on Hepatitis C is available from: "**Hepatitis C management in primary care has changed**"

Table 1: Key similarities and differences in the management of patients with hepatitis B and hepatitis C.[1, 14, 15]

	Hepatitis B	Hepatitis C
Similarities		
Transmission	Blood-borne, sexual or mother-to-child transmission	
Acute disease	Acute disease is notifiable; treatment is supportive	
Consequences of chronic infection	Chronic infection can cause liver fibrosis, cirrhosis and hepatocellular carcinoma, as well as complications affecting other organs	
Differences		
Means of infection	The majority of patients with chronic infection acquired the virus at birth or in early childhood; people who inject drugs are at risk but infection in adults rarely leads to chronic HBV	The majority of chronic infections in New Zealand are from injecting drug use
Transition from acute to chronic infection	The incidence of chronic infection depends heavily on age of acquisition; most children progress to chronic infection and most adults do not	20–25% of people infected with HCV clear the virus without medical intervention; children are more likely to spontaneously clear the virus
Is there a vaccine?	Yes; funded for all children and people with certain risk factors, e.g. HIV infection.* Vaccination is recommended but not funded for travellers to countries with a high prevalence of HBV infection, in addition to other high risk groups, e.g. people with increased risk from occupational or sexual exposure to body fluids and faeces.	There is no vaccine to prevent hepatitis C infection
Genotyping in infected patients	Is not routinely required. There are different genotypes of both HBV and HCV but they do not influence initial treatment options.	
Aim of treatment	Not curative: Long-term treatment aims to maintain HBV suppression thereby preventing liver damage and complications such as cirrhosis and hepatocellular carcinoma	Curative: A fixed duration of treatment aims to clear the viral infection
Who to treat	Patients at higher risk of liver damage from hepatitis B infection should be treated, guided by monitoring of HBV DNA and ALT levels	All patients who are eligible for approved treatments†
Duration of treatment	For some patients treatment is indefinite, for others treatment may last a number of months to years	Treatment with oral regimens typically ranges from eight to 24 weeks

* See: "HBV vaccination" for details on funding criteria for patients at high risk of infection

† Maviret (glecaprevir and pibrentasvir) is **funded** and effective against all six genotypes of hepatitis C virus. Patients with a prescription for Maviret can only be dispensed the medicine at pharmacies registered as a 'Maviret AbbVie Care Pharmacy'. For a list of these pharmacies, or for an "alternative distribution form", see: **www.maviret.co.nz**. Harvoni (ledipasvir with sofosbuvir) is an alternative funded treatment with Special Authority criteria for patients with advanced liver disease as a result of chronic hepatitis C.

Depending on viral and patient characteristics:

- 13–38% of adults with untreated chronic hepatitis B will develop cirrhosis over a five year period.[10]
- Of those with cirrhosis, approximately 4% per year develop liver failure (i.e. decompensated cirrhosis), with complications of jaundice, ascites, hepatic encephalopathy and gastroesophageal variceal haemorrhage.[11]
- Approximately 1–4% of people with HBV-related cirrhosis will develop hepatocellular carcinoma each year.[11] The risk of liver disease increases with age, with males aged over 40 years more likely to develop cirrhosis or hepatocellular carcinoma.[11]

It is estimated that approximately 40% of patients presenting with advanced HBV-related hepatocellular carcinoma in New Zealand are unaware that they have an HBV infection.[3]

Treatment is not curative

None of the current treatment options for chronic HBV are curative. Treatment reduces viral replication, improves liver function and reduces the risk of future complications. All current oral antiviral treatments suppress viral activity. However, a reservoir of HBV remains in the nucleus of hepatocytes, which can lead to viral reactivation after treatment has stopped. The aims of treatment for patients with chronic HBV infection therefore differ in important ways from patients with chronic hepatitis C infection (see: "Know your ABCs").

Testing for HBV infection

There are two main groups of people who should be tested for hepatitis B infection: those who may have been exposed during birth or early childhood and therefore now have chronic hepatitis B infection, and those with a potential exposure as an adult, which may have resulted in acute hepatitis B infection but in most cases will not proceed to chronic infection.

Consider testing people with risk factors for HBV infection, including:[1,13,16]

- Incomplete or unknown childhood vaccination status, particularly in people of Māori, Pacific, South East Asian or Chinese ethnicity*
- Age over 30 years*
- Incomplete or unknown childhood vaccination status*
- People born in countries with a high HBV prevalence, e.g. Pacific Islands, China, South East Asia, Middle East and Africa, or travellers to those countries

Table 2: Interpreting serology for HBV infection. Adapted from Ministry of Health and the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine.[1,17]

Serology markers*				Interpretation**
HBsAg	anti-HBs	anti-HBc		
		Total	IgM	
⊖	⊖	⊖	⊖	Patient is not infected and not immune; recommend vaccination if at risk
⊕	⊖	⊖	⊖	Either (1) early acute HBV infection or (2) transient positivity after vaccination (for up to 18 days post-vaccination on average, or for up to 52 days in patients undergoing haemodialysis)
⊕	⊖	⊕	⊕	Acute HBV infection
⊖	⊕ or ⊖	⊕	⊕	Acute HBV infection which is resolving
⊖	⊕ or ⊖	⊕	⊖	Immune due to previous infection†
⊖	⊕	⊖	⊖	Immune due to previous vaccination†
⊕	⊖	⊕	⊖	**Chronic HBV infection**

* Common antigen and antibody abbreviations – **HBsAg:** hepatitis B surface antigen, **anti-HBs**: antibody to HBsAg, **anti-HBc:** antibody to hepatitis B core antigen

† The Immunisation Handbook 2020 suggests that an anti-HBs titre of ≥10 IU/L is the minimally acceptable level for evidence of immunity.[1] However, theanti-HBs threshold can vary between laboratories; follow the interpretation guidance from the testing laboratory.[1]

** Interpretation should also take into account the clinical context and reasons for testing; consult with the testing laboratory or a clinician with experience managing hepatitis B if test results produce a pattern other than those shown in the Table.

- Mother or close family or household member with HBV infection
- Unprotected sex with an HBV-infected person
- Current or previous injecting drug user
- Chronic liver disease or incidental abnormal liver function tests
- Tattoo, piercing or other cosmetic procedure received using unsterile equipment, e.g. in prison, in locations with few safety standards
- Higher risk sexual activity, such as sex workers, men who have sex with men or unprotected sex while travelling in a country with high prevalence
- Following exposure to blood, e.g. sports, assault, needlestick injury

* In addition to other risk factors from the list

How to test for HBV infection

The three main initial tests to determine hepatitis B infection are:

- HBsAg – hepatitis B surface antigen; this shows current HBV infection and is always detected in chronic infection
- Anti-HBs or HBsAb – hepatitis B surface antibody, which is produced in response to the HBsAg; this shows whether there is immunity to HBV either from vaccination or infection
- Anti-HBc or HBcAb – hepatitis B core antibody, which is produced in response to the hepatitis B core antigen (HBcAg); this shows whether exposure to HBV has ever occurred. It is detected in people with current infection and previous acute infection that has now resolved, but not in those who are immune through vaccination.

Advice for patients after an HBV diagnosis

Advise patients with chronic HBV infection:[17, 20]

- To use condoms during intercourse*
- To avoid sharing razors or toothbrushes with their partner or household members
- To cover any open scratches or cuts
- That they cannot donate blood or semen
- To inform other healthcare professionals, including dentists, that they have HBV infection; if the patient is a healthcare professional, they may need to avoid conducting exposure prone procedures[21] †
- That they should not share medical devices which have blood contact, e.g. finger prick testing equipment
- That heavy alcohol use in people with chronic infection can contribute to liver damage; they should follow guidance on low-risk drinking, i.e. having at least two alcohol free days per week, and having no more than two standard drinks per day or ten per week for females, or three standard drinks per day or 15 per week for males[22] ‡

Reassuring patients of what they can continue to do without worrying about transmitting HBV can help reduce unnecessary stigma and anxiety. HBV is not transmitted, or associated with negligible risk of transmission, from:[17, 20]

- Sharing food and utensils
- Kissing on the mouth
- Coughing or sneezing
- Everyday contact, e.g. in a school or workplace
- Playing contact sports, as long as wounds are covered and they remove themselves from play to attend to any injuries involving blood
- Breast milk
- Urine, faeces or vomit, unless these contain blood

For further information on advice for patients after an HBV diagnosis, see: **www.hepatitisfoundation.org.nz/hepatitis/hepatitis-b**

* For people with one sexual partner, condoms can be discontinued if the partner's test results show they are immune, however appropriate precautions should be continued for protective sex as per usual sexual health guidelines

† Exposure prone procedures carry a risk of direct contact with a healthcare worker's skin and sharp objects or issues. For further information, see: **www.nhmrc.gov.au/sites/default/files/documents/infection-control-guidelines-feb2020.pdf**

‡ Patients with severe liver disease, such as cirrhosis, should be advised not to drink any alcohol

A combination of HBsAg, anti-HBs and anti-HBc can be used to assess whether a patient is infected, their immune status and whether an infection is in the acute or chronic stage (Table 2). Additional tests are usually added reflexively by the laboratory depending on results of initial tests. Include clinical information regarding the reasons for ordering HBV serology to assist the laboratory in interpreting results.

N.B. Testing for hepatitis B e antigen (HBeAg) and its corresponding antibody (anti-HBe) is useful to assess HBV activity, the stage of infection and corresponding risk of liver complications. However, this is not required to make an initial diagnosis. For more information, see: "An overview of HBV management for primary care".

If patients test positive for HBV infection

Inform all patients who test positive how HBV is transmitted and steps they can take to reduce the risk to sexual partners and others in their household (see: "Advice for patients after an HBV diagnosis").

Sexual partners and household contacts of infected individuals should undergo testing to check if they have become infected or if they are immune. If a patient is diagnosed in the acute stage of infection, rather than chronic, only household members or sexual partners who have had contact with the patient within the previous three weeks need to be tested.[18]

Acute HBV infection is a notifiable disease; follow advice from the Ministry of Health's Communicable Disease Control Manual: **www.health.govt.nz/our-work/diseases-and-conditions/communicable-disease-control-manual/hepatitis-b.**

Arrange follow-up for patients with chronic HBV infection
Patients with chronic HBV infection should be referred to the **Hepatitis Foundation**, secondary care*, or treated within primary care.

The **Hepatitis Foundation** of New Zealand has a national contract to provide clinical support and management in partnership with primary and secondary care, including:[19]

- Initial evaluation after a diagnosis has been made
- Organising ongoing **monitoring tests**, including blood tests and liver elastography (Fibroscan) assessments
- Patient support, education and access to a community hepatitis nurse

Patients can be referred by:

- Calling the **Hepatitis Foundation**: **0800 33 20 10**
- Completing and online form: **www.hepatitisfoundation.org.nz/node/16**

Maintaining up to date contact details is particularly important for patients with chronic HBV infection, since monitoring and treatment is lifelong. If patients are referred to the **Hepatitis Foundation**, ensure its staff are informed of any change of address or phone number. Consider setting up a register of patients enrolled in your practice with chronic HBV infection.

If patients are being managed in primary care, set up recalls for regular monitoring (see: "An overview of management in primary care").

* Patients with chronic HBV infection could be managed in secondary care by a gastroenterologist, hepatologist, infectious diseases specialist or general physician. Check with your Te Whatu Ora locality about referral protocols. For example, secondary care referral may be appropriate if patients have confirmed hepatitis B infection and:

- Severe symptoms or suspected cirrhosis; or
- High HBV DNA levels (e.g. > 2,000 IU/mL); or
- Are AFP-positive (a marker for hepatocellular carcinoma); or
- Concurrent hepatitis C infection; or
- An elevated ALT level for at least three months

Management of chronic HBV infection

Initial tests are required for patients with chronic HBV infection in order to assess the presence or severity of liver disease and the stage of infection (see: "An overview of treatment in primary care"). These tests can be arranged in primary or secondary care or by the **Hepatitis Foundation**.

All patients with chronic HBV infection require regular monitoring to assess the stage of infection and check for the development of liver fibrosis or cirrhosis (see: "An overview of management in primary care"). Patients at high risk of liver cancer, which includes those with severe fibrosis or cirrhosis or a family history of hepatocellular carcinoma, require regular liver ultrasound or CT scans to assess the development of hepatocellular carcinoma, ideally at six month intervals.[13]

Genotype testing is not required for chronic HBV infection: Different genotypes of the hepatitis B virus exist, however, genotype testing is not necessary for patients with chronic HBV infection as the results do not influence initial management.[23] Further investigation may be undertaken for some patients if treatment is unsuccessful, to test for the presence of genetic variants associated with resistance to hepatitis B treatments.

Many patients will now receive treatment with oral medicines in the community

The recommended first-line oral antiviral treatments for chronic HBV infection are tenofovir disoproxil or entecavir. These medicines were previously funded with Special Authority approval for the treatment of chronic HBV infection. However,

since 1 June, 2018, tenofovir disoproxil* and entecavir have been funded without restriction, allowing them to be prescribed more widely, including by general practitioners. As a result, more patients have been able to receive treatment for chronic HBV infection in the community. Pegylated interferon, which is administered by subcutaneous injection, is also used for some patients.

Lamivudine is another oral medicine which is indicated and funded for the treatment of chronic HBV infection.[24] However, lamivudine is no longer recommended as a first-line treatment as HBV often develops resistance to this medicine.[13] Adefovir dipivoxil was previously funded for the treatment of chronic HBV infection, however, it is no longer being manufactured and was delisted from the **New Zealand Pharmaceutical Schedule in March, 2021**.

* Tenofovir disoproxil is also used in combination with other antiviral medicines for the treatment of HIV infection. It remains funded with Special Authority approval when used for this indication.[25]

Treatment suppresses viral activity and is likely to reduce the risk of future complications

Unlike the management of chronic hepatitis C, where all patients eligible for treatment with approved medicines should receive treatment at diagnosis, treatment may not necessarily be required at diagnosis for patients with chronic HBV infection. Oral antiviral treatment is recommended for patients during stages of infection which are associated with liver damage, guided by the patient's risk factors, such as age, and the results of ALT and HBV DNA tests (see: "An overview of management in primary care").[13, 14]

First-line antiviral treatments result in suppression of HBV DNA levels in 61–93% of patients.[13] Approximately 70–90% of patients treated with tenofovir disoproxil or entecavir have a normalisation of elevated ALT levels after three months of treatment, and approximately 35–50% of patients treated with pegylated interferon after eighteen months of treatment.[13]

There is less evidence available regarding the long-term effects of treatment, however, analyses to date suggest that antiviral treatment reduces, but does not eliminate, the risk of complications such as hepatocellular carcinoma.[26] A meta-analysis including 8,060 patients who had received curative treatment for HBV-related hepatocellular carcinoma (e.g. via surgical resection or liver transplantation) demonstrated that post-treatment with tenofovir disoproxil or entecavir reduced the three-year risk of hepatocellular carcinoma recurrence by 37%.[27]

Table 3: Recommended dose frequencies of tenofovir disoproxil and entecavir for patients with renal impairment.

Creatinine clearance (mL/min)	Entecavir, 0.5 mg tablet * [30]	Tenofovir disoproxil, 245 mg tablet **[24,31]
≥ 50	Once daily	Once daily
30 – <50	Once every two days	Once every two days
10 – <30	Once every three days	Once every three to four days
< 10 or patients on haemodialysis	Once every five to seven days	Once every seven days or after a total of approximately 12 hours of dialysis

* Dose is 1 mg in patients with decompensated liver disease or resistance to lamivudine

** Doses are stated as 245 mg of tenofovir disoproxil; see above regarding tenofovir disoproxil salts

Table 4: When to initiate antiviral prophylaxis in patients taking immunosuppressive medicines.[32]

Prophylaxis is recommended in patients who are initiated on:	Prophylaxis is not necessary in patients who are initiated on:
■ Cancer chemotherapy ■ B-cell depleting agents such as rituximab ■ TNF inhibitors such as infliximab, adalimumab, etanercept ■ Oral corticosteroids at a dose equivalent to 10 mg of prednisone or greater for 4 weeks or longer	■ Methotrexate ■ Azathioprine ■ 6-mercaptopurine ■ Intra-articular corticosteroids

An overview of HBV management for primary care[11, 13, 23]

Stage of care	Aspect of care	Tests or criteria
Initial assessment (after a diagnosis has been made)	Assessments of liver health	■ Complete blood count ■ INR ■ Liver function tests, including AST, ALT, alkaline phosphatase and total bilirubin ■ Liver elastography scan (Fibroscan) – see note below*
	Assessments of HBV activity and stage of infection	■ HBeAg and anti-HBe serology ■ HBV DNA levels
	Assessments of other blood-borne viruses + hepatitis A (worsens liver complications if concurrent infection)	■ Hepatitis A, C and HIV serology
Regular lifelong monitoring	Assessments of HBV activity, stage of infection and liver health	■ Every six months: – Liver function tests – HBsAg – HBeAg – Alfa-fetoprotein (AFP) – Liver ultrasound or CT scan for patients at high risk of liver cancer† ■ Every year: – Complete blood count to assess thrombocytopaenia, as a marker of portal hypertension and cirrhosis
Treatment	When to initiate treatment	■ Oral antiviral treatment is recommended for patients during stages of infection which are associated with liver damage, guided by the patient's risk factors, such as age, and the results of ALT and HBV DNA tests. This includes patients who are/who have:[33] – HBeAg-positive or negative, with HBV DNA levels >2000 IU/mL, ALT > upper limit of normal (ULN) and/or moderate liver damage – Compensated or decompensated cirrhosis – HBV DNA levels >20,000 IU/mL and ALT > 2× ULN, regardless of liver damage – Chronic HBV (normal ALT and high HBV DNA) and aged over 30 years, regardless of liver damage – HBeAg-positive or negative and family history of hepatocellular carcinoma or cirrhosis
	Prior to initiating treatment, conduct tests which may influence the choice and dose of medicines	■ Renal function (creatinine clearance) – adjust dose of medicine accordingly, e.g. Table 3 ■ Pregnancy test for females
	Monitoring effectiveness and safety during treatment (in addition to regular monitoring detailed above)	■ Annual HBV DNA level ■ Monitoring of calcium, phosphate and creatinine levels in patients taking tenofovir disoproxil

* Referral criteria and wait times for liver elastography scans may vary across DHBs. If a liver elastography scan cannot be performed, calculating the ratio of aspartate aminotransferase (AST) levels to platelet concentration (APRI) may be used instead. For further information on calculating an APRI score, see: **https://bpac.org.nz/2016/hepc/default.aspx#assessment**

† Patients at high risk are those with severe fibrosis or cirrhosis or a family history of hepatocellular carcinoma

** Persistently elevated ALT levels refers to the results of at least three measurements taken three months apart

Most patients taking tenofovir disoproxil or entecavir experience adverse effects such as headache, nasopharyngitis, nausea and fatigue.[28] However, most adverse effects are mild and do not require patients to stop treatment. Tenofovir disoproxil can cause small reductions in eGFR and bone mineral density and monitoring of calcium, phosphate and creatinine levels is recommended.[13]

Reductions in dose frequency are required for patients with renal impairment

Tenofovir disoproxil and entecavir are dosed based on renal function, as measured by creatinine clearance (Table 3). Rare cases of lactic acidosis, sometimes fatal, have been reported for both tenofovir disoproxil and entecavir, and in some of these cases renal impairment may have been a contributing factor.[13, 28]

Prescribe "tenofovir disoproxil 245mg" not tenofovir disoproxil fumarate or tenofovir disoproxil succinate

Tenofovir disoproxil is available in several different salt forms in New Zealand and other forms may be introduced. These are all clinically equivalent and currently available tablets all contain 245 mg of tenofovir disoproxil.[29] Prescribers should not record the salt form on the prescription, e.g. "tenofovir disoproxil fumarate" but instead prescribe "tenofovir disoproxil 245 mg" as this will allow pharmacists to dispense the funded medicine.[25, 29]

Prophylactic antiviral treatment is recommended if patients initiate some immunosuppressive medicines

The use of immunosuppressive medicines such as chemotherapy, TNF inhibitors, or courses of oral corticosteroids equivalent to prednisone ≥ 10 mg/day for four weeks or more, are associated with an increased risk of hepatitis flares in patients with chronic HBV infection, occurring either during treatment or after the immunosuppressive medicine is stopped.[28, 32]

Due to this increased risk, prophylactic treatment with tenofovir disoproxil or entecavir is recommended when some immunosuppressive medicine regimens are initiated (Table 4). The risks of HBV reactivation and an appropriate length of prophylactic treatment can be discussed with the clinician managing the patient's HBV treatment; use of tenofovir disoproxil or entecavir is often required for six months or longer after the immunosuppressive medicine has been stopped.[13]

The Hepatitis Foundation of New Zealand is currently developing updated advice to assist clinicians who will be managing patients with HBV in primary care. For further information, see: **https://www.hepatitisfoundation.org.nz/healthcare-professionals/hepatitis-b-health-professionals**

Acknowledgement:TThis article is a revision of an original article published by bpac[nz] in 2018. The original article was reviewed by **Professor Ed Gane**, Professor of Medicine, University of Auckland, Chief Hepatologist and Deputy Director of the New Zealand Liver Transplant Unit and **Dr Alex Lampen-Smith**, Gastroenterologist and Clinical Director of the Hepatitis Foundation of New Zealand.

N.B. Expert reviewers do not write the articles and are not responsible for the final content. bpac[nz] retains editorial oversight of all content.

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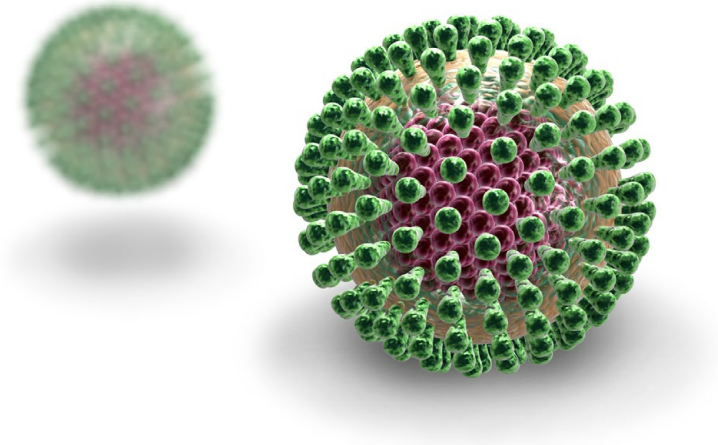

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