Treatment of chronic hepatitis B virus infection

**KEY POINTS**

- Patients with a positive or an antigen-negative chronic hepatitis B virus (previously referred to as a chronic carrier or chronic inactive carrier) should be considered for antiviral therapy. Treatment is indicated for those with any of the following high hepatitis B virus (HBV) DNA, elevated alanine aminotransferase levels or evidence of inflammation/fibrosis on liver biopsy or marked fibrosis on fibroscan.
- All patients with cirrhosis are candidates for treatment.
- Patients and doctors need to be aware of adherence as critical for the success of therapy.
- Treatments for XIs are first-line treatment options for oral antiviral therapy.
- Peginterferon is an alternative option in some patients.

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### Goals of therapy

The goal of therapy is to prevent, halt or even reverse the progression of liver injury towards cirrhosis, liver decompensation and liver cancer, which are the major causes of death in patients with hepatitis B virus (HBV) infection (1). This is achieved by controlling viral replication, either with direct-acting antiviral therapy or indirectly using interferon (IFN) to stimulate immune control. Control of viral replication reduces compensated liver disease and reduces the risk of hepatocellular cancer (HCC) (2,3). The challenge for the clinician is to determine the phase of infection and anticipated natural history for any individual patient, as therapy can be tailored to those likely to benefit. The terminology used to describe the phases of hepatitis B infection has varied between countries and over time (further detailed in Natural history of hepatitis B virus infection) (4). In communicating information to patients about their treatment choices, hepatitis B, language, literacy and culture are important considerations; relevant resources are available to aid communication: for example, the hepatitis B story and the Hep B Story App (https://www.mendes.earth/health). See Patient resources.

**Goals of treatment**

- Primary goals of therapy are to improve both quality of life and survival of people with HBV infection via:
  - Normalise alanine aminotransferase (ALT) levels.
  - Achieve HBeAg loss in HBeAg positive patients.
  - Achieve sustained suppression of HBV viral replication.
  - Achieve HBeAg loss with or without anti-HBs seroconversion.
  - Reduce risk of progression to cirrhosis and hepatocellular carcinoma.

- The other relevant goals of therapy are the prevention of hepatitis B reactivation, vertical transmission, prevention and treatment of extrahepatic manifestations, regression of fibrosis or cirrhosis in patients with established liver disease, reduction of risk of HCC recurrence after potential curative therapies for patients with HCC, and the prevention of liver failure in acute hepatitis B (4).

### Indications for antiviral therapy

The decision to commence antiviral therapy is based on a number of factors, including the patient’s age, serum HBV DNA levels, extent of hepatic fibrosis, ALT levels, hepatitis B virus (HBV) genotype and status of the HBV. Other factors to consider include family history and history of alcohol or HCV and concomitant medications. Barriers to treatment adherence need to be considered (Table 5.1) because liver damage can be worsened by non-adherence. Many guidelines are available on this subject with some inconsistencies in recommendations (5). A recent review summarises the various international consensus guidelines for treatment initiation and the set of decision-making in the clinical setting (6). A recent HBV TMF meeting demonstrates that treatment initiation for hepatitis B (HBF) in patients with chronic hepatitis B (CHB) is necessary for patients with advanced liver disease (7). This review has been removed because of certain conditions are still required to be met (e.g., CD4+ and HBV DNA level) before antiviral therapy can be specified in the official guidelines (1999).

A liver biopsy is no longer mandatory for reimbursement; however, in some settings, it may still have a role in the decision-making non-invasive techniques to indirectly measure the extent of liver fibrosis should be used to assist decision-making in preference to liver biopsy (8). There are two main classes of therapy for HBV.

- Direct antiviral agents, which inhibit the function of the viral polymerase and thus prevent viral replication.
- The use of synthetic inhibitors which act via multiple different antiviral pathways to inhibit viral replication.

### Table 5.1: Potential barriers to hepatitis B virus treatment adherence (19.5)

<table>
<thead>
<tr>
<th>The patient</th>
<th>Understanding of disease or reason for antiviral treatment, cultural health beliefs, literacy of health literacy, language barriers. Competing priorities (e.g., health, employment and family issues). Other social issues (i.e. substance use, poverty and housing, stigmatisation). Distance, time and cost to attend appointments (including lost work time).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor-patient interaction</td>
<td>Poor communication, including inadequate use of culturally appropriate resources or interpretation services or being too busy. Failure to appreciate barriers to adherence, and to employ strategies and appropriate one-to-one education.</td>
</tr>
<tr>
<td>Health system</td>
<td>Geographical and system barriers to treatment access, including specialist availability, local availability of antiviral therapy for ongoing supply, hospital outpatient waiting lists and outpatient appointment waiting time, general practitioners' knowledge of treatment.</td>
</tr>
</tbody>
</table>
In practical terms, since the decision to commence antiviral therapy has been made, the physician should choose one of the three agents that are currently approved by the Australian Government's Therapeutic Goods Administration (TGA) and reimbursed under the PBS for the initial treatment of CHB in Australia. These agents are peginterferon (PEG-IFN-α2b and α2a), telbivudine (200 mg/d) and entecavir (0.5 mg/d). Several other oral agents – including tenofovir, adefovir and fulepivir – have been registered for the treatment of CHB but are not preferred due to inferior potency or inferior barrier to resistance.

When choosing the most appropriate anti-HBV therapy, it is important to consider the advantages and disadvantages of each treatment option. The choice of therapy must take into account the drug's efficacy, safety, chance of achieving desired endpoints, anticipated duration of therapy and the likelihood of developing resistance.

PBS Streamlined codes: all PBS Section 100 community prescribers accredited to prescribe by their state or territory can use streamlined codes. Streamlined codes may be updated from time to time, see www.pharmaco.gov.au/streamlinedpublications.

For information on general practitioner and nurse practitioner prescribing see www.austhealth.gov.au.

| Table 5.1 Patients in whom treatment may be considered. These indications are not currently covered under the PBS but are included in the most up to date international guidelines (9).

| Hepatitis B e antigen (HBeAg)-positive patients |
| Hepatitis B e antigen (HBeAg)-negative patients |

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| HCC: hepatocellular carcinoma |

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| * Extraventricular manifestations such as glomerulonephritis and vasculitis associated with hepatitis B |

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Patients with cirrhosis

People living with hepatitis B and cirrhosis are at increased risk of hepatic decompensation and developing HCC. Treatment with antiviral therapy reduces these risks and all individuals with cirrhosis should be offered treatment.

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Women of childbearing age

Women with CHB interested in starting a family should consider the safety profile of various treatment options, and restricted access to treatment under FDS Section 105 criteria. Management decisions for pregnant women who later fall pregnant must be individualised. The abundance of safety data for lamivudine and tenofovir in well-controlled patients may facilitate a discussion on the risks and benefits of treatment; this discussion should also include the possibility of a flare of disease activity during pregnancy, and the likelihood of vertical transmission despite immunosuppression in pregnant women with high viral loads. A recent study showed that tenofovir given to a cohort of pregnant women with a HIV viral load > 100,000 c/ml at 28 weeks gestation showed a significantly lower mother-to-child transmission in the treatment group compared to the control group (14). Initiation of treatment is not recommended in this situation. There are limited data on the safety of tenofovir in pregnant women, and its use is not recommended. Initiating a patient with PEG-IFN before starting family planning could be an alternative option because this treatment is limited to a defined duration. More detailed advice on management of hepatitis B in pregnancy is given in Managing hepatitis B virus infection in pregnancy and children.

Therapeutic options

There are two main treatment options for treatment. The first-line treatment is nucleoside analogues (NA) with a high barrier to resistance and entecavir. An alternative option in highly selected patients is PEG-IFN.

Interferons

The use of conventional IFN has been supplanted by the use of PEG-IFN, which has the advantage of weekly dosing and probably of improved efficacy. The recommended standard dosing of PEG-IFN alfa-2a is 180 μg given weekly for 48 weeks. The side-effects are similar to conventional IFN (e.g. depression, fatigue, flu-like symptoms, irritability, sleep disturbance and depression, but are not universal and not easy to predict). HBeAg-positive patients. HBeAg seroinversion occurred in 32% of patients up to 6 months after the end of treatment. Baseline predictors of response include genotyping, a lower HBV DNA (10,000,000 c/ml) and higher ALT levels (> 2 x ULN). A small but significant proportion of patients treated with IFN also achieve hepatitis B surface antigen (HBsAg) seroconversion. This is seen particularly in genotype B and is uncommon in Asian patients. Genotype D-HBV patients have the lowest response rates to PEG-IFN therapy. Given the expense and side-effect profile of IFNs, it would be helpful to identify non-responders early, although rules for stopping IFN have not been clearly established. Failure to suppress the virus by 6 months is usually indicative of non-responsiveness, and treatment may be discontinued. A change in hepatitis status has been suggested as a useful predictor of response, but the test is not widely available in Australia, and its applicability across different genotypes requires further evaluation (15, 16).

PEG-IFN also has a role in the treatment of HBeAg-negative patients. Sustained control of viral replication (> 1000 c/ml) is seen in 20% of patients after completion of therapy (17). Control of viral loads to these levels should reduce progression to clinically significant liver disease.

The main advantage of Peg-IFN is the fixed duration of therapy (which is particularly attractive to younger patients), and the chance for HBeAg seroconversion. The main disadvantage is the side-effect profile. Rates of adverse events resulting from entecavir immune clearance can be seen in up to 15% of patients and can be severe in those with advanced underlying liver disease. These are contraindicated in patients with decompensated cirrhosis.

Interferon-based regimens are not the best choice for patients with cirrhosis and are contraindicated in patients with decompensated cirrhosis. PEG-IFN is generally contraindicated in pregnancy and breastfeeding (see: Managing hepatitis B virus infection in pregnancy and children).

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Treatment options

- Direct-acting antiviral agents can be chosen according to their potency, side-effects and the chance of resistance. For treatment-naive patients, entecavir or tenofovir is the best currently available oral antiviral therapy. For tenofovir-resistant patients, tenofovir added to lamivudine therapy is most effective.
- Pegylated interferon has a different mechanism but comparable efficacy to antiviral agents, with the disadvantage of increased side-effects and the advantage of a shorter, fixed-dose therapy without drug resistance. Interferon is not the best choice in patients with cirrhosis.
- Therapy should be Individualised.

Antiviral therapy

Long-lasting, treatment-maintained suppression of H BV DNA without resistance is achievable in most patients with entecavir or tenofovir. A sustained off treatment response is uncommon, and long-term therapy should be anticipated (18), particularly in patients in the HBeAg-negative phase of infection.

Entecavir

Entecavir, a nucleoside analogue, is a highly effective inhibitor of viral replication. Long-term (at least 3 years) entecavir therapy appears to result in the reversal of fibrosis and cirrhosis, and continued improvement in liver function (7). It has few side-effects, the most common being headache (3%) and fatigue (1%). The rate of marker clearing with entecavir is similar to that seen with other antiviral agents. Entecavir is recommended at a dose of 0.5 mg for treatment-naive patients. HBV DNA suppression is used to assess antiviral activity; resistance can be assessed using viral sequencing. Entecavir is contraindicated in pregnancy (19) and patients with advanced liver disease. Entecavir is not the best choice for patients with established lamivudine resistance. Entecavir is not a suitable alternative for patients with hepatitis B and advanced cirrhosis. In patients with advanced liver disease, entecavir is not a suitable alternative (20).

Entecavir is contraindicated in pregnancy and thus is not a good choice in young women who might be planning to try or may inadvertently become pregnant.

Entecavir absorption is affected by food, and it should be taken on an empty stomach, 2 hours before or after a meal. This food requirement should be discussed with the patient before therapy is started.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate (TDF) is a non-nucleoside RT inhibitor with potent activity against HIV. It has been used extensively in the treatment of human immunodeficiency virus (HIV) infection. The recommended dose of tenofovir is 300 mg daily. It has been included in the initial registration trials and has developed tenofovir resistance after 8 years of follow-up (21). Tenofovir has been associated with renal toxicity (19, 22). The risk of renal toxicity is low, however, in treatment, monitoring of renal function (estimated glomerular filtration rate, eGFR) and serum phosphate concentration is important to avoid progressive renal injury. Tenofovir is the agent of choice for patients with lamivudine resistance, because lamivudine and tenofovir have different mutational pathways to resistance. Although adenoviruses and tenofovir have similar pathways to resistance, the latter is highly effective in patients with prior adenovirus resistance, with 60-60% of patients receiving tenofovir having detectable HBV DNA after 1 year of therapy (23).

Tenofovir alafenamide

(Applied by Pharmaceutical Benefits Advisory Committee March 2017 but not yet available through the PBS)

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- Tenofovir disoproxil fumarate is a non-nucleoside RT inhibitor with potent activity against HIV. It has been used extensively in the treatment of human immunodeficiency virus (HIV) infection. The recommended dose of tenofovir is 300 mg daily. It has been included in the initial registration trials and has developed tenofovir resistance after 8 years of follow-up (21). Tenofovir has been associated with renal toxicity (19, 22). The risk of renal toxicity is low, however, in treatment, monitoring of renal function (estimated glomerular filtration rate, eGFR) and serum phosphate concentration is important to avoid progressive renal injury. Tenofovir is the agent of choice for patients with lamivudine resistance, because lamivudine and tenofovir have different mutational pathways to resistance. Although adenoviruses and tenofovir have similar pathways to resistance, the latter is highly effective in patients with prior adenovirus resistance, with 60-60% of patients receiving tenofovir having detectable HBV DNA after 1 year of therapy (23).

Tenofovir alafenamide

(Applied by Pharmaceutical Benefits Advisory Committee March 2017 but not yet available through the PBS)
Lamivudine, adefovir and telbuvudine are no longer recommended as first-line therapies in Australia; however, they may still be widely prescribed in lower-middle income countries.

Lamivudine was the first antiviral agent made available for the treatment of CHB in Australia. It is an oral nucleoside analogue, well tolerated and with significant side-effects. Unfortunately, lamivudine resistance occurs in 14-32% of patients after 1 year of therapy, and 60-73% of patients after 5 years of therapy (27).

Adefovir is an acyclic nucleotide analogue and an effective antiviral agent. The recommended dose of 10 mg restricted adefovir's antiviral potency, but nevirapine at higher doses was a limiting factor. In Australia, as guided by PHS reimbursements, its role is limited to the treatment of patients with lamivudine resistance. Initially adefovir was used as monotherapy in patients with lamivudine resistance, but the development of resistance to adefovir was common in this situation and it quickly became apparent that combination therapy provided much better control of viral replication (28). Adefovir has largely been replaced by tenofovir due to the latter's superior antiviral activity.

Telbuvudine is also a highly effective antiviral agent, but its utility is limited by the rapid emergence of resistance variants of HBV (32% in 3 years). A specific side-effect of telbuvudine is myopathy, and patients on treatment should be monitored for muscle symptoms. Telbuvudine has a pregnancy category D listing.

For patients naive to therapy, it might be predicted that dual (direct acting antiviral) therapy might be superior to single agent therapy. As the case for HIV, although to date no benefit has been demonstrated (29). Combining DIs with direct acting antiviral therapy has also not been shown to be superior although studies in this area are ongoing.

In summary, both nucleoside analogues and Peg-IFN can be prescribed as first-line treatment options for CHB. However, Peg-IFN should only be considered for patients with a high chance of response based on on-treatment and on-treatment factors.

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In patients on antiviral agents, a rising ALT or HBV DNA level may indicate viral resistance or non-adherence. In patients on other antiviral agents, a switch to one of the new agents must be undertaken.

Goals of monitoring in patients who are on treatment

- Monitor treatment response and adherence
- Detect adverse effects of treatment
- Identify emergence of resistance
- Identify and treat progression of liver disease

Monitoring patients on antiviral therapy

While on therapy, patients should be monitored regularly to document virological response to treatment, detect adverse events early in their evolution, identify the emergence of viral resistance and encourage adherence. In patients on direct acting antiviral therapies, baseline assessment should include viral measures, particularly assessment for polyomavirus-related and HBV-induced liver disease.

- On-treatment monitoring is recommended.
- Treatment is continued if the patient is tolerating the therapy and shows viral suppression.
- The viral load should be monitored at baseline and then every 6 weeks. Viral load more than 1000 IU/mL should be reported.
- Treat the patient with peg-IFN and tenofovir.
- If the viral load is less than 1000 IU/mL, the patient can be switched to monotherapy.

Monitoring on treatment

- Regular monitoring is required to identify virological response, resistance and hepatitis flares, and to encourage adherence

Table: Pegylated interferon

<table>
<thead>
<tr>
<th>Pegylated interferon</th>
<th>Direct antiviral therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent monitoring until treatment dose stabilized, then every 4-6 weeks. Periodic attention RBC, white cell count differential and patient count at each visit, adjust dosing if necessary</td>
<td>3 monthly for the first year, then 6 monthly. FBC, liver and renal function and fasting serum phosphorus for those on TDF and TAF and TAF for those on peg-IFN and TAF and TAF use is recommended</td>
</tr>
</tbody>
</table>

Treatment-related side-effects

The safety profile of oral agents is similar to that of placebo. As mentioned previously, entecavir is well tolerated, with negligible side effects. There have been reports of nephrotoxicity and favours syndrome developing in patients on tenofovir disoproxil fumarate therapy, although the risk of renal injury is low and can be managed with routine monitoring (as described) plus dose adjustments when required. Tenofovir alafenamide may become the better option for those with renal impairment and other high-risk patients when it becomes available through the PBS.

In contrast, Peg-IFN have many side effects. Fortunately, Peg-IFN is better tolerated in patients receiving treatment for HBV compared to those with hepatitis C virus infection. Despite this observation, patients taking Peg-IFN may experience many different side effects that require careful management to achieve a safe and effective outcome. Treatment is usually supportive, and symptoms-based (31).

End point of therapy

The ultimate goal is viral eradication, reflected by sustained off therapy HBsAg loss and development of protective anti-HBs, but this objective is rarely achieved. Instead, for most of those affected, the aim is biochemical control (i.e. normalisation of ALT) and virological control (i.e. suppression to <2000 IU/mL for on-treatment, and to be undetectable for down-acting antiviral therapy). For those in the HBV post-chronic phase of infection, HBV DNA loss and development of anti-HBc is a surrogate marker of the possibility of sustained off therapy biochemical and virological control. After a period of consolidation, a trial of off therapy is undertaken to determine whether biochemical and virological control will be sustained in that individual. Failure may be due to reversion to HBsAg positive or anti-HBc negative state off therapy, or due to the emergence of HBV-negative chronic hepatitis (previously referred to as "immune escape phase") (32,33).
Stopping oral antiviral treatment

Antiviral therapy can be discontinued if a non-structural individual loses HBsAg irrespective of the development of anti-HBs.

In non-cirrhotic HBeAg-positive patients, who have seroconverted to anti-HBs positive and had a HBeAg Decline \( <0.7 \) units over a sustained period, stopping therapy can be considered. Most guidelines recommend a 6+12 month treatment duration before stopping therapy. However, a proportion of patients will relapse after treatment is stopped making close monitoring and recommencement of treatment if needed essential. In 3 years post cessation of therapy approximately 50% of such patients will meet criteria for reinfection (36). In HBeAg-negative patients, the risk of immunological relapse after stopping therapy is high, and patients usually continue lifelong therapy unless they undergo liver biopsy (58). The recent META study investigated the possibility of stopping antiviral therapy in non-cirrhotic people with HBV-negative chronic hepatitis who had received tenofovir disoproxil fumarate for more than 4 years with a suppressed viral load for more than 3.5 years. Of those randomised to stop therapy, 62% remained off therapy at week 144. There were no unexpected safety issues identified with stopping therapy (36). This trial only included 42 people, however it provides support for consideration of this approach in the specific subgroup described above where close-off treatment monitoring can be guaranteed.

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New emerging therapies for hepatitis B

Unfortunately, although HBeAg can be controlled and the risk of liver cirrhosis and liver cancer reduced, currently there is no cure for hepatitis B. However, there is considerable amount of research effort being invested into moving towards a cure for hepatitis B. It is likely that, as for other chronic viral infections, combination therapy targeting multiple different sites will be needed.

New drug classes that act directly on HBV in various points in the lifecycle that are being studied in phase 1 or 2 studies include entry inhibitors which competitively bind to the HBV reverse transcriptase protein; entry inhibitors which are small interfering RNAs directed at HBV RNA sequences; capsid inhibitors which act through abortive core processing and hence disrupt capsid assembly, and HBV release inhibitors. Targeting coxsackie virus B1 may seem necessary to truly cure hepatitis B. Although there are no antiviral drugs currently available that target coxsackie directly there is preclinical work occurring in this area investigating the CRISPR/Cas system as a platform to mouse or inactivate coxsackie B1 (37).

Drug classes focused on modulating the host immune response that are under investigation include toll-like receptors, checkpoint inhibitors and therapeutic vaccines. It is likely that a combination of therapies will be needed to enable chronic HBV to be cured and that it will need to be individualised to each patient, stage of liver disease and genotype of the virus. In addition, while trials of new drugs and new approaches are awaited, all patients with CMT are effectively managed, and treated as per guidelines recommended by evidence-based guidelines, to minimise mortality and morbidity from liver failure and HCC.

References