Treatment of chronic hepatitis B virus infection

KEY POINTS

- Patients with e antigen-positive or e antigen-negative chronic hepatitis B (immune clearance or immune escape phases) 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.
- Patient and doctor attention to the issue of adherence is critical for the success of therapy.
- Entecavir and tenofovir are first-line treatment options for oral antiviral therapy.
- Pegylated interferon is an alternative option in some patients.

Goals of therapy

The goal of therapy is to prevent, halt or even reverse the progression of liver injury towards cirrhosis, liver decomposition and liver cancer, which are the major causes of death in older 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 reverses decompensated 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 an individual patient, so that 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 for hepatitis B, language, literacy and culture are important considerations. Patient resources are available to aid communication; for example, the hepatitis B Bear, the Hepatitis B story and the Hep B Story App (https://www.menzies.edu.au/hepbstory/). See resources

Goals of treatment

- Normalise alanine aminotransferase (ALT) levels
- Achieve HBeAg loss in HBe Ag-positive patients
- Achieve sustained suppression of HBV viral replication
- Achieve HBsAg 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 risk 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 e antigen (HBeAg) status and the risk of HCC. Other factors to consider are family history of cirrhosis or HCC and extrahepatic manifestations (4). Barriers to treatment adherence need to be considered (Table 7.1), 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 variance in international consensus guidelines for treatment initiation and the art of decision making in the clinic (5). Previously, a liver biopsy demonstrating necroinflammation consistent with chronic hepatitis B (CHB) was a necessary prerequisite for reimbursed access to antiviral therapy in Australia. This requirement has now been removed although certain condition are still required to be met (relating to ALT and HBV DNA levels) before antiviral therapy can be prescribed in the Pharmaceutical Benefits Scheme (PBS).

A liver biopsy is no longer mandatory for reimbursement; however, in some settings, it may still have a role in decision making. Non-invasive techniques to indirectly measure the extent of liver fibrosis may be used to assist decision making in the absence of liver biopsy (6,7) (see: Clinical assessment of patients with hepatitis B virus infection).

There are two main classes of therapy for CHB:

- direct antiviral agents, which inhibit the function of the viral polymerase and thus prevent viral replication

- the IFNs, which are synthetic cytokines that act via multiple different intracellular biological pathways to eradicate viral infection.

Table 7.1 Potential barriers to hepatitis B virus treatment adherence ([8-10])	
The patient	Understanding of disease or reason for antiviral treatment. Cultural health beliefs, literacy or health literacy, language barriers. Competing priorities (e.g. health, employment and family issues). Other social issues (e.g. substance use, poverty and housing, stigmatisation). Distance, time and cost to attend appointments (including lost work time).
Doctor– patient interaction	Poor communication, including inadequate use of culturally appropriate resources or interpretation services (or both) when needed. Failure to appreciate barriers to adherence, and to employ strategies and appropriate one-to-one education.
Health system	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 practitioner (GP) knowledge of condition.
Nature of disease	Hepatitis B is asymptomatic. People feel well, so may discontinue treatment. Long-term therapy leads to treatment fatigue.

In practical terms, once 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 pegylated IFN (PEG-IFN) alfa-2a (180 μg/week), tenofovir (300 mg/day) and entecavir (0.5 mg/day) (Table 7.2). Several other oral agents – including lamivudine, adefovir and telbivudine – 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.

Table 7.2 Patients in whom treatment is indicated						
HBeAg status	**Fibrosis or cirrhosis**	**HBV DNA levels**	**ALT**	**Other considerations**	**PBS streamlined codes[a] for tenofovir 300 mg**	**PBS streamlined codes[a] for entecavir 0.5 mg**
Positive or negative	Cirrhosis (compensated or decompensated)*	Any detectable level	Any level		6980[#]	5036[#]

Positive or negative	None	> 20,000 IU/mL	> 2 x ULN ^	ALT repeated at least 1 month between observations and other causes excluded	6992#	4993#
Positive or negative	AND/OR moderate fibrosis ≥ F2β	> 2000 IU/mL	> ULN	To be covered by PBS, HBeAg-positive individuals must have HBV VL > 20,000 IU/mL however updated international guidelines now suggest > 2000 IU/mL irrespective of e status	6992#	4993#
Positive or negative	Cirrhosis ⌂	Any detectable level	Any	Failed HBV therapy for tenofovir Failed lamivudine therapy for entecavir	6983	5037@
Positive or negative	No cirrhosis	Repeatedly elevated HBV DNA levels 1 log > the nadir value or failure to achieve a 1 log reduction in HBV DNA within 3 months while on previous HBV therapy (except in patient with poor adherence to treatment)	> ULN while on HBV therapy of ≥ 6 months	Failed HBV therapy for tenofovir Failed lamivudine therapy for entecavir	6984	5044@

*cirrhosis diagnosed by liver biopsy, or patients with chronic HBV infection either with normal ALT and liver stiffness > 9 kPa, or with elevated ALT but < 5x ULN and liver stiffness of > 12 kPa ([12])

^ ULN for females is 19 IU/L and for males is 30 IU/L

β assessed by liver biopsy or transient elastography > 7 kPa

patient must be nucleoside analogue (NA) naive

@ dose of entecavir should be 1 mg daily

⌂ all patients with Child class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin < 30 g/L, bilirubin > 30 µmol/L) should have their treatment discussed with a transplant unit before therapy is started

ALT: alanine aminotransferase; CHB: chronic hepatitis B; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; IU: international unit; PBS: Pharmaceutical Benefits Scheme; ULN: upper limit of normal; VL: viral load

PBS Streamlined codes: GP HBV Section 100 prescribers accredited to prescribe by their state or territory can use streamlined codes. Streamlined codes may be updated from time to time, see www.pbs.gov.au/info/browse/publications For information on general practitioner prescribing see www.ashm.org.au

Older patients with significant viraemia but only mildly elevated ALT levels may have significant liver injury from a prior phase of CHB (11). A liver biopsy or other assessment of liver fibrosis (e.g. transient elastography) will assist in determining the need for therapy. Patients with advanced fibrosis or cirrhosis, irrespective of ALT (e.g. a Scheuer score of ≥ 3 or Metavir score of ≥ F2 on biopsy, a FibroScan® of > ~9 kPa with normal ALT or > 12 kPa with elevated ALT but < 5x ULN (12), or as assessed by other non-invasive tests) should be considered for antiviral therapy (see: Managing patients with advanced liver disease).

Who should be considered for therapy?

Hepatitis B e antigen (HBeAg)-positive patients

Patients who are positive for HBeAg should be considered for antiviral therapy if they also have elevated serum ALT (i.e. > 30 IU/L for males and >19 IU/L for females) that is persistent (i.e. 3–6 months without an alternative cause), and a serum HBV DNA level of greater than 2000 IU/mL and/or the presence of moderate fibrosis or F2 and above (4). The viral load cut off for treatment in this group was previously 20,000 IU/mL and this still stands in the PBS criteria (Table 7.2), however more recent evidence supports 2000 IU/mL. In contrast, those with a persistently normal ALT level (i.e. no evidence of hepatitis) require regular monitoring (see: Clinical assessment of patients with hepatitis B virus infection) but treatment is usually not of benefit. The regular monitoring ensures any move to a more active phase of infection (eAg-positive hepatitis or immune clearance phase) is identified in a timely fashion to allow treatment to be considered.

Hepatitis B e antigen (HBeAg)-negative patients

Patients with HBeAg-negative chronic hepatitis B (immune escape) are often older, with ALT levels and serum HBV DNA levels lower than in patients with HBeAg-positive CHB. Nevertheless, patients with eAg-negative chronic hepatitis B are at greater risk of liver injury and worse outcomes than younger patients with HBeAg-positive disease. It is therefore recommended that the threshold serum HBV DNA level for initiating antiviral therapy should be 2000 IU/mL, in combination with either an elevated ALT or evidence of accumulated significant liver damage (e.g. fibrosis, or moderate or severe inflammation, or both) (13). In general, other recommendations for therapy in HBeAg-negative patients are similar to those with HBeAg-positive disease.

Table 7.3 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 (4)				
HBeAg status	**Fibrosis or cirrhosis**	**HBV DNA levels**	**ALT**	**Other factors**
Positive	None	> 1,000,000 IU/mL	Normal	Age > 30 years
Positive or negative	Any	Any	Any	Family history of HCC or fibrosis; or presence of

				extrahepatic manifestations[#]regardless of family history

[#] Extrahepatic manifestations such as glomerulonephritis and vasculitis associated with hepatitis B

HCC: hepatocellular carcinoma

No treatment is required for patients with HBeAg-positive or negative disease who have HBV DNA levels < 2000 IU/mL, normal ALT, Metavir score F0 to F1, under 30 years of age and have no family history of cirrhosis or HCC. In these patients, ALT should be monitored every 6-12 months, and HBV DNA as well as fibrosis assessment should be undertaken every year.

Women of child-bearing age

Women with CHB interested in starting a family should consider the safety profile of various treatment options, and restricted access to treatment under PBS Section 100 criteria. Management decisions for patients initiated on treatment who later fall pregnant must be individualised. The abundant safety data for lamivudine and tenofovir in HIV-treated 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 immunoprophylaxis in pregnant women with a viral load of more than 7 $\log_{10}$ IU/mL. However, a recent study showed that tenofovir given to a cohort of pregnant women with a HBV viral load > 200,000 IU/mL at 28 weeks gestation showed a significantly lower mother-to-child transmission in the treatment group compared to the control group ([14]). There are limited data on the safety of entecavir in pregnancy, 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 treatments are nucleoside analogues (NAs) with a high barrier to resistance: tenofovir 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. influenza-like symptoms, fatigue, leukopenia, irritability, sleep disturbance and depression), but are neither universal nor easy to predict. In HBeAg-positive patients, HBe seroconversion occurred in 32% of patients up to 6 months after the end of treatment. Baseline predictors of response include genotype A infection, lower HBV DNA (20,000,000 IU/mL (7.3 $\log_{10}$ IU/mL)) and higher ALT levels (> 2 × 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 A 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-response, and treatment may be discontinued. A change in HBsAg titres 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 (< 2000 IU/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 HBsAg seroconversion. The main disadvantage is the side-effect profile. Flares of viral hepatitis resulting from enhanced immune clearance can be seen in up to 18% of patients and can be severe in those with advanced underlying liver disease. IFNs 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).

Treatment options

- Direct-acting antiviral agents can be chosen according to their potency, their side-effects and the chance of resistance. For treatment-naive patients, entecavir or tenofovir is the best currently available antiviral therapy. For lamivudine-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-duration 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 HBV 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 purine-derived 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 histology (19). It has few side-effects, the most common being headache (2–4%) and fatigue (1–3%). The rate of HBeAg clearance 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 drug resistance in that clinical scenario is extremely uncommon; it was reported in only 1.2% of cases after 5 years of study. Entecavir is not the best choice of therapy for patients with established lamivudine resistance. Even with a higher dose (1.0 mg daily), 50% of such patients develop entecavir resistance in 5 years. This is due to partial cross-resistance between lamivudine and entecavir.

Entecavir is contraindicated in pregnancy and thus is not a good choice in young women who might be planning to or may accidentally 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 disproxil fumarate

Tenofovir disoproxil fumarate (TDF) is an acyclic adenine nucleotide with potent activity against HBV. It has been used extensively in the treatment of human immunodeficiency virus (HIV) infection. The recommended dose of tenofovir is 300 mg daily. No patient included in the initial registration trial has developed tenofovir resistance after 8 years of follow up (20). Nephrotoxicity, including Fanconi syndrome, has been reported in patients receiving tenofovir although it is much less common than in the setting of HIV (19,21). The risk of renal toxicity is low; however, on 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 adefovir and tenofovir have similar pathways to resistance, the latter is highly effective in patients with prior adefovir resistance, with 60–90% of patients receiving tenofovir having undetectable HBV DNA after 1 year of therapy (22).

Tenofovir alafenamide

(Approved by Pharmaceutical Benefits Advisory Committee March 2017 but at the time of writing not yet available through the PBS)

Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir developed to enable more efficient delivery of the active metabolite to target cells hence the ability to use a lower dose, which offers the potential for an improved safety profile. It has already replaced tenofovir disproxil fumerate in a number of HIV co-formulated antiretroviral medications. Evidence for its use and safety benefits in chronic hepatitis B mono-infection are still emerging. The registration trials demonstrate non-inferiority of tenofovir alafenamide to tenofovir disoproxil fumarate in both eAg-positive and eAg-negative chronic hepatitis B at 48 weeks (23,24), maintained at 96 weeks. Those taking tenofovir alafenamide experienced smaller changes in bone mineral density and smaller declines in eGFR which were statistically significant at both weeks 48 and 96 (25). In a group of 540 people switched to open label tenofovir alafenamide at the end of the study statistically significant improvements in bone mineral density and creatinine clearance were seen within 24 weeks (26). It is anticipated that tenofovir alafenamide will become an alternative option to tenofovir disoproxil fumarate through the PBS. Longer-term data are needed to establish the clinical significance of switching to tenofovir alafenamide from tenofovir disoproxil fumarate in hepatitis B mono-infection.

Other agents and combinations

Lamivudine, adefovir and telbivudine 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 without significant side-effects. Unfortunately prolonged therapy with lamivudine resulted in high rates of viral resistance occurring in 14–32% of patients after 1 year of therapy, and 60–70% 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 nephrotoxicity at higher doses was a limiting factor. In Australia, as guided by PBS reimbursements, its role was 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.

Telbivudine is also a highly effective antiviral agent, but its utility is limited by the rather rapid emergence of resistance variants of HBV (30% in 3 years). A specific side-effect of telbivudine is myopathy, and patients on treatment should be monitored for muscle symptoms. Telbivudine has a pregnancy category B listing.

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

In summary, both nucleos(t)ide 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 pre-treatment and on-treatment factors.

In patients on antiviral agents, a rising ALT or HBV DNA level may indicate viral resistance or non-adherence. In patients on older 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 renal measures, particularly assessment for proteinuria, eGFR and (if tenofovir therapy is planned) fasting serum phosphate level. On-treatment monitoring is recommended 3 monthly for the first year. Full blood count, liver and renal function (and fasting serum phosphate for patients on tenofovir) and HBV serology (for patients who are HBeAg positive) and HBV DNA are recommended. Dose adjustments may be required, depending on renal dysfunction. After the first year, or when complete virological control has been achieved, 6-monthly monitoring is reasonable with entecavir and tenofovir, given their low rates of drug resistance in pivotal studies and in the clinical situation (30). One risk of such infrequent monitoring is reduced adherence to therapy. Shared attention to the issue of adherence by patient, specialist and general practitioner is critical for the success of therapy.

Monitoring on treatment	
• Regular monitoring is required to identify virological response, resistance and hepatitis flares, and to encourage adherence	
Pegylated interferon	**Direct antiviral therapies**
• Frequent monitoring until treatment dose stabilised, then every 4–6 weeks. Particular attention: FBC, white cell count differential and platelet count at each visit; adjust dosing as necessary	• 3 monthly for the first year, then 6 monthly. FBC, liver and renal function (and fasting serum phosphate for those on TDF) and HBV serology (for HBeAg positive) and HBV DNA is recommended

FBC: full blood count; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; TDF: tenofovir

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 Fanconi 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, IFNs have many side-effects. Anecdotally, IFN seems better tolerated in patients receiving treatment for HBV compared to those with hepatitis C virus infection. Despite this observation, patients taking IFN may experience many different side-effects that require careful management to achieve a safe and effective outcome. Treatment is usually supportive, and symptom 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 IFN treatment, and to undetectable for direct-acting antiviral therapy). For those in the HBeAg-positive phase of infection, HBeAg loss and development of anti-HBe (HBeAg seroconversion) heralds the possibility of sustained off-therapy biochemical and virological control. After a period of consolidation, a trial off therapy is undertaken to determine whether biochemical and virological control will be sustained in that individual. Failure may be due to reversion to HBeAg-positive or anti-HBe-negative state off therapy, or due to the emergence of HBeAg-negative chronic hepatitis (Immune escape phase) (32,33).

In patients in the immune escape phase of infection, biochemical and virological control is usually only achieved by long-term therapy, although IFN sometimes induces sustained off-therapy responses.

Stopping oral antiviral treatment

Anti-viral therapy can be discontinued if an individual loses HBsAg irrespective of the development of anti-HBs.

In non-cirrhotic HBeAg-positive patients, who have seroconverted to HBeAb positive and had a HBV DNA VL < 20 IU/mL over a sustained period, stopping therapy can be considered. Most guidelines recommend a 6–12 month consolidation period before stopping therapy. However, a proportion of patients will relapse after treatment is stopped making close monitoring and recommencement of treatment if needed essential. At 3 years post cessation of therapy approximately 50% of such patients will meet criteria for retreatment (34). In HBeAg-negative patients, the risk of virological relapse after stopping therapy is high, and patients usually continue lifelong therapy unless they undergo loss of HBsAg (35). The recent FINITE study investigated the possibility of stopping antiviral therapy in non-cirrhotic people with eAg-negative chronic hepatitis who had received tenofovir disoproxil fumarate for more than 4 years with a supressed 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 group described above where close off-treatment monitoring can be guaranteed.

New emerging therapies for hepatitis B

Unfortunately, although CHB can be controlled and the risk of liver cirrhosis and liver cancer reduced, currently there is no cure for hepatitis B. However, there is a 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 at various points in the lifecycle that are being studied in phase 1or 2 studies include: entry inhibitors which competitively bind to the NTCP receptor preventing HBV entry; RNA silencers which are small interfering RNAs directed at HBV RNA sequences; capsid inhibitors which act through aberrant core protein processing and hence disrupt capsid assembly; and HBsAg release inhibitors. Targeting cccDNA would seem necessary to truly cure hepatitis B. Although there are no therapeutic drugs currently available that target cccDNA directly there is preclinical work occurring in this area investigating the CRISP/Cas9 system as a platform to mutate or inactivate cccDNA (37).

Drug classes focused on modulating the host immune response that are under investigation include: toll like receptors, check point 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. It is crucial that while new drugs and new approaches are awaited, all patients with CHB are effectively managed, and treated as recommended by evidence-based guidelines, to minimise morbidity and mortality from liver failure and HCC.

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