

# Primary care management of chronic viral hepatitis

# 11

---

<b>Robert Feller</b>	Hepatologist, Royal Prince Alfred Hospital and St Vincent's Hospital, Sydney, New South Wales.
<b>Simone Strasser</b>	Hepatologist, Royal Prince Alfred Hospital, Camperdown, New South Wales.
<b>Jeff Ward</b>	Executive Officer, Hepatitis C Council of Queensland, Brisbane, Queensland.
<b>Gillian Deakin</b>	General Practitioner, Bondi, New South Wales.

---

## Introduction

A primary care role in the management of chronic viral hepatitis involves the provision of information, support and referral as well as initial and ongoing clinical assessment and monitoring. The primary care clinician may undertake tasks such as specific diagnosis and initial assessment of the severity of disease, counselling the patient about the current understanding of the disease process and potential complications, as well as general issues of diet, mental health, lifestyle, transmission and vaccination.<sup>1,2</sup> With recent advances in the treatment of hepatitis B and C, the primary care clinician has an important role in presenting the patient with specific treatment options and potential side effects.<sup>3</sup> This chapter focuses on the primary care management of chronic hepatitis C, with some consideration of treatment options for chronic hepatitis B.

## Clinical evaluation and diagnosis

The initial approach of the clinician must include consideration of the non-viral and viral aetiologies for hepatitis (Table 11.1). Elevated liver enzymes are often a trigger for consideration of viral hepatitis.

The most common causes of abnormal liver function tests (LFTs) seen in clinical practice include fatty liver, alcoholic liver disease and drug toxicity (usually transient) as well as chronic viral hepatitis.

A diagnosis of chronic hepatitis requires persistently abnormal liver function tests for a period of six months. Thus, the strict definition is one of duration rather than severity (Chapters 5 and 7).

The majority of patients with chronic viral hepatitis will be asymptomatic or have non-specific symptoms such as fatigue and lethargy, and only some will have signs of compensated or decompensated cirrhosis.

## Key points

- Patients with active chronic viral hepatitis should be monitored every six months. Liver biopsy is the definitive investigation to assess the degree of hepatic inflammation, fibrosis and cirrhosis.
- Effective antiviral therapy is available for chronic hepatitis B and C in many patients.
- For patients with chronic hepatitis C, the rate of progression to cirrhosis is usually very slow and antiviral treatment may not be indicated in all cases.
- Most patients with adult-acquired chronic hepatitis B infection will not suffer long-term sequelae, but approximately 25% of people with chronic hepatitis B from infancy develop cirrhosis or hepatocellular cancer (HCC). Antiviral treatment is indicated in many patients with active chronic replicative hepatitis B.
- Depending on viral genotype and other cofactors, 30–70% of patients have a sustained response to currently approved HCV treatments.
- A course of antiviral treatment for HBV can induce sustained HBeAg seroconversion in 30–40% of patients, as well as clinical improvements and survival benefits. Potential benefits of antiviral therapy for chronic hepatitis B include 'e' antigen seroconversion, improved liver function, improved liver histology and reduced progression to cirrhosis and its complications.
- Primary care management of chronic viral hepatitis includes education and counselling, psychosocial support and dietary and lifestyle advice. It also involves monitoring the disease process and identifying if and when referral to a specialist is required.
- Prevention education and vaccination against other hepatitis viruses are important in the management of chronic viral hepatitis.

Chapter 7 contains a detailed discussion of the clinical presentation of chronic viral hepatitis.

A sound understanding of modes of transmission, risk behaviours and epidemiology should permit a detailed risk assessment in patients with suspected hepatitis of unknown aetiology (Chapters 1–3). In cases where clinical and risk assessment suggest the possibility of chronic viral hepatitis, viral serology should include hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody (anti-HCV) and human immunodeficiency virus (HIV) antibody (anti-HIV), as appropriate, following pre-test discussion and informed consent (Chapter 9). Patients with advanced HIV infection may lose anti-HCV reactivity. Therefore, serum HCV RNA should be assessed if acute or chronic HCV infection is suspected in HIV patients with negative antibody results. Further considerations are dependent upon whether the patient has chronic HCV or chronic HBV infection.

## Hepatitis C

### Initial assessment

A detailed history should include an estimation of the duration of exposure, age at infection and whether there are important contributing factors to hepatic fibrosis. These factors may include a history of significant alcohol consumption, obesity and diabetes, which are risk factors for non-alcoholic fatty liver disease. Concomitantly, the patient should be evaluated for ongoing risks, such as injecting drug use and ongoing, excessive alcohol consumption.

Initial assessment of a patient with hepatitis C should address whether or not the patient has active disease, inactive disease or has cleared infection, as well as their likelihood of having significant fibrosis. Patients are more likely to have significant fibrosis if they have had a long duration of infection (>20 years), have a history of significant alcohol use (which may be remote), or have been overweight or obese. Chapter 7 discusses virological markers, liver function tests, liver imaging, liver biopsy and other investigations which form the basis of this assessment.

Patients should have liver enzymes monitored every one to two months for several months to establish whether enzymes are persistently abnormal, persistently normal, or fluctuating. It should be kept in mind that while patients with persistent elevation of alanine aminotransferase (ALT) levels are at higher risk of significant liver damage and disease progression, even patients with normal liver enzymes may be at risk of progressive disease.

TABLE 11.1 Important causes of chronic hepatitis	
Aetiology	Diagnostic test
<b>Fatty liver</b> (incl. non-alcoholic steatohepatitis)	Risk factors, imaging ± biopsy
<b>Alcohol</b>	History ± biopsy
<b>Viral</b> Hepatitis B Hepatitis C (Hepatitis D)	Viral serology (Tables 10.3, 5.3 and 5.4)
<b>Metabolic</b> Haemochromatosis	Iron studies, HFE gene test
Wilson's disease	Serum copper, caeruloplasmin, 24-hour urinary copper
Alpha-1-antitrypsin deficiency	Serum alpha-1-antitrypsin
<b>Autoimmune hepatitis</b>	Anti-nuclear antibody(ANA), anti-smooth muscle antibody (SMA), immunoglobulins and biopsy
<b>Drugs</b>	History ± biopsy
<b>Cryptogenic</b>	

Patients with positive anti-HCV and persistently normal ALT levels should be evaluated for the presence of viraemia with an HCV RNA (qualitative) test, as some may have cleared infection spontaneously. The HCV RNA test is rebatable under Medicare for this indication.

Patients found to be HCV RNA negative should be reassured that while they have probably been exposed to HCV in the past, they have apparently cleared infection. It is recommended that patients with normal liver function and no detectable HCV RNA have their liver enzymes checked one year after initial evaluation; if HCV RNA remains negative and liver enzymes are normal, no further follow-up is necessary.

Patients with normal or abnormal ALT levels and detectable HCV RNA may be considered for antiviral therapy; however, if they choose not to be treated at the time they should be followed every six to 12 months. Regular follow-up of patients with hepatitis C allows for monitoring of flares of activity, assessment of disease progression and discussion of current therapies.

See Table 11.2 for a summary of serological and virological markers.

**TABLE 11.2 Interpretation of HBV, HCV and HDV serology**

Virus	Marker	Significance
<b>*Hepatitis B (HBV)</b>	HBsAg	Persistent infection
	anti-HBs	Past infection (natural immunity) or vaccination (acquired immunity)
	HBeAg	Highly infectious (absence may indicate mutant form)
	anti-HBc IgM	Acute infection*
	anti-HBc IgG	Current or past infection
	HBV DNA	Circulating virus
<b>Hepatitis C (HCV)</b>	anti-HCV	Current or past infection
	HCV RNA	Circulating virus** indicating current infection
<b>Hepatitis D (Delta) (HDV)</b>	anti-HDV	Current or past infection (only in HBsAg-positive patient)

Ag = antigen; s = surface; c = core; anti = antibody.  
 \*May be only indicator of infection in 'window period' between disappearance of sAg and appearance of sAb.  
 \*\*May be useful in high-risk HCV antibody-negative patient.

### Ongoing monitoring of patients with chronic hepatitis C

The aims of follow-up in patients with chronic hepatitis C are to:

- Reinforce the need for lifestyle changes
- Decide which patients are appropriate for antiviral therapy
- Determine appropriate timing of referral to a specialist
- Monitor patients with cirrhosis for complications, such as hepatic decompensation and hepatocellular carcinoma (HCC)

For patients with chronic hepatitis C, ongoing monitoring is recommended every six to 12 months, unless there are specific reasons for more frequent monitoring (e.g. encouraging behaviour change). Tests to be conducted may include:

- Liver enzymes
- Full blood count
- Prothrombin time or international normalised ratio (INR)
- Hepatic ultrasound to screen for HCC in patients with cirrhosis
- Serum alpha-fetoprotein (AFP) to screen for HCC in patients with cirrhosis

### Assessment for antiviral therapy

Previously in Australia, antiviral therapy was funded only for patients at highest risk of histologic progression. However, with increasing data to support the efficacy of antiviral therapy, it is now available to any previously untreated patient 18

years or older with compensated liver disease. Any patient with chronic hepatitis C should be advised of the potential benefits of antiviral therapy, and much of the assessment should be related to appropriate timing of therapy. Patients at highest risk of histologic progression (those with significant cofactors, long duration of infection, haematologic or biochemical markers of fibrosis such as low platelet count or aspartate aminotransferase [AST] higher than ALT, moderate or severe fibrosis on liver biopsy) should be encouraged to consider therapy as soon as practicable. For other patients, timing of treatment can be based on other lifestyle issues such as work, social circumstance, control of substance abuse, and desire for pregnancy.

When evaluating current disease severity and risk of progression to fibrosis and cirrhosis, clinical examination should be conducted (Chapter 7) and the investigations listed above should be performed. The finding of an elevated ALT level indicates the presence of necroinflammatory activity but is not predictive of cirrhosis or significant fibrosis. Thrombocytopenia, prolonged INR or hypoalbuminaemia all suggest the presence of cirrhosis with some degree of hepatic decompensation and portal hypertension. However, patients with well-compensated cirrhosis due to hepatitis C may have a completely normal platelet count, INR and serum albumin level for many years. Hepatic ultrasound may show features of cirrhosis or fatty infiltration but is commonly normal.

Liver biopsy remains a very useful procedure for confirming or excluding significant fibrosis. However, a number of non-invasive fibrosis tests are currently under evaluation and may eventually replace liver biopsy in the majority of patients. Despite the removal of a mandatory liver biopsy to access antiviral therapy, it remains useful for guiding a patient's decision, particularly if they are ambivalent about therapy.

Liver biopsy is a relatively safe procedure. It is usually performed as a day-stay procedure, under ultrasound guidance using local anaesthetic only. Patients commonly experience some minor abdominal discomfort and right shoulder tip pain but severe pain is unusual. There is a small risk of significant bleeding (1:300) and death (1:10,000).

There are several systems in use for recording the degree of fibrosis in a liver biopsy. Most of these systems use a scoring system ranging from 0 (no fibrosis) to 4 (definite cirrhosis). The finding of minimal disease activity and no fibrosis (stage 0) suggests a very low likelihood of disease progression. Consequently, the patient may be reassured, and toxic and expensive therapy may be avoided.

Patients with stage 1 fibrosis may be offered antiviral therapy if there is associated moderate to severe inflammation, while patients with stage 2–4 fibrosis should be offered antiviral therapy, provided no contraindications are present.

Consideration of duration of infection is also important in the assessment of disease severity, rate of progression and need for treatment. For example, patients who have stage 1 fibrosis after three years of infection may have greater need for treatment than a person with stage 1 fibrosis after ten years.

Viral genotype impacts on length of treatment and likely response and, as discussed in the treatment section, genotype testing may assist the patient in making the decision to start treatment. Alternatively, genotype testing may be delayed until the patient sees a specialist.

In determining whether a patient is appropriate for antiviral treatment, the primary care clinician may also consider the patient's social support and whether he or she is likely to adhere to treatment.

Local hepatitis C councils or drug user groups may provide information and peer support for people considering treatment (Chapter 15).

### Shared care and referral

The primary care clinician has an important role in assessing which patients with chronic hepatitis C should be referred for specialist review. Such patients include those who wish to undergo antiviral treatment, those with persistently elevated ALT levels, those with clinical or laboratory features

**TABLE 11.3 Pre-referral investigation checklist**

• Liver enzymes (usually three tests are conducted over six months)
• HCV serology (anti-HCV)
• HBV serology (HBsAg, anti-HBs, HBeAg, HBV DNA)
• HIV serology (if indicated)
• FBC, electrolytes, creatinine, coagulation studies (INR/APTT)
• Alpha-fetoprotein
• Liver ultrasound

suggestive of cirrhosis, and those who request specialist evaluation. Liver clinics usually offer additional services that may be of benefit to patients. Such services include clinical nurse consultants, psychologists, psychiatrists, social workers and dieticians.

Table 11.3 outlines investigations to conduct prior to referral. Referral to a liver clinic or hepatologist, which can be made at any time, is necessary for specialist pre-treatment assessment. Ongoing support and management of the patient on treatment may be conducted by primary care clinicians and specialists in a shared-care setting.

### Monitoring for complications of liver disease

Patients with HCV-associated cirrhosis should be monitored for deteriorating liver function and for the development of HCC. Often a specialist is involved in the care of a patient with cirrhosis but frequently the patient will attend his or her general practitioner when new symptoms develop. Concerning features include:

- Falling serum albumin levels
- Prolongation of prothrombin time
- Development of jaundice
- Development of other clinical signs (e.g. peripheral oedema, ascites, muscle wasting)

Patients with these features should be considered for referral to a liver transplant unit.

HCC is becoming a major clinical problem in patients with HCV-associated cirrhosis. The current recommendations regarding screening for HCC include ultrasound and AFP levels every six months, to detect small lesions that may be amenable to curative treatment.

## Hepatitis B

### Initial assessment

The natural history of HBV infection varies according to age at acquisition of infection, mode of transmission and ethnic background. In people with the infection since infancy, hepatitis B proceeds through fairly predictable stages: a prolonged immunotolerant phase; a phase of attempted immune-mediated clearance, and then a quiescent phase. Not all patients pass through the immune clearance phase, and some can continue to have hepatic flares for many years, particularly if an HBeAg-negative (pre-core) mutant emerges (Chapter 1).

The aim of the initial evaluation of a patient with chronic hepatitis B is to assess the stage and severity of disease. Full viral serology and other investigations to be conducted during initial assessment are discussed in detail in Chapter 7. Serology results (Table 11.2) should be assessed in the context of liver function and the age of the patient. For example, a patient aged less than 20 years who is positive for surface and 'e' antigen (HBsAg+ and HBeAg+) and has normal liver enzymes does not require antiviral therapy. However, this patient should be told that he or she has a high likelihood of developing flares of hepatitis over subsequent years. Follow-up should be recommended so that hepatitis flares can be identified and antiviral treatment given at an appropriate time.

Patients over 20 years with abnormal liver function tests should have HBeAg status checked. If HBeAg+, they have active infection with wild-type HBV. If HBeAg is negative, they have a high likelihood of infection with an HBeAg-negative mutant. In this situation, HBV DNA should be performed to determine if viraemia is present. If HBV DNA is <104 copies/mL, and the patient has abnormal LFTs, alternative diagnoses should be considered.

HBsAg+, HBeAg-negative and anti-HBe+ patients with normal liver enzymes are in a relatively inactive phase of disease, although they may already be cirrhotic.

### Ongoing monitoring of patients with chronic hepatitis B

All HBsAg+ patients should be followed, regardless of their apparent virologic status at initial evaluation. The six-monthly review of patients with chronic hepatitis B includes:

- A check for signs of chronic liver disease or decompensation
- Serum liver enzymes, FBC, coagulation studies and AFP
- Liver ultrasound if cirrhotic or family history of HCC

HBsAg+, HBeAg-negative women with no evidence of active liver disease are generally at low risk of progression and require only yearly check-ups to

make sure that their status has not changed. For reasons that remain unclear, men with the same serologic status, particularly those with infection since infancy, remain at risk of HCC development regardless of the presence or absence of cirrhosis. They should be seen twice a year for review.

Patients with known cirrhosis should undergo serum AFP testing and ultrasound every six months to screen for HCC. Because non-cirrhotic patients are also at risk of HCC, screening is recommended by some physicians but this policy is not universally adopted.

Patients with active liver disease (that is, with abnormal liver enzymes) should be closely monitored and considered for antiviral therapy. In HBeAg+ patients, the long-term response to antiviral therapy is significantly better if treatment is initiated during a hepatic flare (ALT > twice normal) rather than when enzymes are normal or only mildly elevated (ALT < twice normal).

Patients with HBeAg-negative disease (pre-core mutant) and elevated ALT levels should be considered for liver biopsy with a view to antiviral therapy as they have a high likelihood of significant fibrosis. Patients with known cirrhosis without decompensation should also be considered for antiviral therapy as there is evidence of reduced progression to decompensated liver disease and HCC.

## General management issues for patients with viral hepatitis

### Discussion about routes of viral transmission

Patients with viral hepatitis will commonly be concerned about the risks of transmitting the infection to others. Issues regarding sexual transmission, mother-to-child transmission, blood-borne transmission and casual contact transmission should all be discussed.

Hepatitis C is transmitted primarily through blood-to-blood contact. The sharing of grooming tools that can cause skin abrasion (such as razors, toothbrushes and tweezers) should be avoided.

Injecting drug users must be encouraged to use sterile water, needles and syringes, as well as new injecting equipment such as spoons, filters and tourniquets each time they inject (Chapter 3 and Appendix 4).

Patients may be concerned about sexual transmission of HCV. There appears to be a very low risk of sexual transmission of HCV, although sexual behaviours that potentially involve exposure to HCV-infected blood may pose a more significant risk. There is conflicting evidence concerning an increased risk

of HCV transmission during anal intercourse and condoms may be recommended in this context. A recent increase in cases of acute hepatitis C among HIV-positive men who have sex with men (MSM) has been reported from a number of countries.<sup>4</sup> These cases seem to be associated with sexual (per mucosal) transmission rather than injecting drug use but whether this relates to biological factors (e.g. higher HCV viral loads in HIV co-infection) or behavioural factors is as yet unclear.

There clearly is a risk of transmitting HCV from mother to child, although the risk is low (approximately 5%).<sup>5</sup> This risk is significantly higher if the mother has HIV-HCV co-infection.

Currently, there is no indication for elective caesarean section in mothers with HCV infection.

However, it should be noted that there is some evidence that prolonged rupture of membranes and use of invasive foetal monitoring may increase the risk of mother-to-child transmission of HCV,<sup>6</sup> and decisions about intervention may need to be made on a case-by-case basis. Breastfeeding is not generally considered to present an additional risk of HCV transmission. However, breastfeeding should be suspended if the nipples are cracked or if the baby has cuts in or outside the mouth.

In Australia, many people with HBV infection are migrants who contracted infection as infants.

With universal HBV vaccination of neonates and administration of hepatitis B immunoglobulin to infants of mothers with HBV infection, there are very few new cases of vertically acquired HBV in Australia. Most cases are acquired sexually or through direct blood-to-blood contact. People with HBV infection should ensure the safety of sexual partners by recommending vaccination and using safe sex methods.

Any patient who is HBsAg+ may transmit HBV sexually. Other recommendations to prevent blood-to-blood HBV transmission are as for prevention of HCV transmission.

Risk of transmission and infection is discussed in detail in Chapter 2. Communication of safe sex and safe injecting messages is covered in Chapter 3 and Appendix 1-3.

### Lifestyle issues

The possibility of lifestyle modification needs to be discussed with the patient, particularly in relation to alcohol consumption and recreational drug use.

Alcohol intake should be minimal. There is no doubt that excessive alcohol consumption (>50 g/day) leads to disease progression and a poorer response to treatment in chronic HCV. A drink containing 10 grams of alcohol, such as a can of medium-light beer (3.5% alcohol) or a nip (30mL) of spirits,

**TABLE 11.4 How to reduce alcohol consumption**

• Plan at least two alcohol-free days per week
• Switch to low alcohol or alcohol-free drinks
• Avoid situations where there will be pressure to drink, e.g. rounds at the pub
• Alternate non-alcoholic and alcoholic drinks
• Drink a daily maximum of two drinks

is regarded as a 'standard drink'. A can of regular beer (4.9% alcohol) equals 1.5 standard drinks (15 grams alcohol). A bottle of wine (9.5–13% alcohol) equals about seven to eight standard drinks (70–80 grams alcohol).<sup>7</sup> Australian guidelines published by the Digestive Health Foundation recommend that people with viral hepatitis should drink alcohol infrequently or at low levels, and should consider not drinking at all. Specific strategies are set out in Table 11.4. People with cirrhosis should be encouraged to stop drinking alcohol completely.

People who continue to inject drugs are of particular concern. Those using in a chaotic manner, particularly in an unsafe environment, are less at risk from chronic hepatitis C infection than from major overdose, acquisition of other viral infections, and other health concerns. In such patients, these areas should be addressed first rather than treatment for chronic hepatitis B or C. Referral to treatment programs and support groups may be appropriate. In people who inject only occasionally, or who are on stable drug dependency programs, treatment for hepatitis C and B can be carried out successfully. All people should be counselled regarding the risk of HCV re-infection after successful viral clearance if risk behaviour continues.

### Nutrition

There is considerable, unsubstantiated dietary information and advice directed at people with chronic viral hepatitis. In November 2000, the Dietitians' Association of Australia supported dietary advice for people with hepatitis C. This advice strongly warns against restrictive diets which recommend exclusion of all dairy foods, red meat, caffeine-containing drinks, and food containing added sugar, artificial colours and preservatives.<sup>8</sup> Instead, a well-balanced diet is recommended. For most people with hepatitis C, dietary recommendations are the same as for the general population (encouraging: grilled rather than fried food; lean meats and fish; reduced-fat products; wholemeal bread; vegetables and fruit; pasta; minimisation of fat for spreading and cooking). People with advanced liver disease, or other conditions such as coeliac disease or diabetes may be referred to a specialist dietitian for further advice.

Overweight or obese patients should be advised of a gradual weight-reduction program, particularly as there is increasing evidence of interaction between HCV, obesity and type 2 diabetes in accelerating progression to fibrosis. Those who may have fatty liver need to avoid a precipitous drop in weight as this can induce deterioration in liver function.

Many people with active hepatitis C report nausea and intolerance to certain foods and drinks. Referral to a dietitian may be appropriate to ensure the patient is consuming necessary vitamins and minerals.

Patients with advanced liver disease who develop protein-calorie malnutrition should be seen by a specialist dietitian. Such patients often require protein supplementation, and should be encouraged to eat high-energy foods frequently throughout the day. Very few, if any, patients with advanced liver disease should be subjected to protein restriction. This is a change from the previous doctrine that all patients with hepatic encephalopathy should be protein restricted.

### Fatigue and other symptoms

People with chronic hepatitis C may report fatigue, malaise, headache, rash and aching muscles and joints. Consideration should be given to specific food and drinks that may be triggering symptoms, as well as work, family or other commitments, which may exacerbate stress and fatigue. Patients may benefit from planning rest periods during the day or incorporating light-to-moderate exercise into their routines to reduce fatigue.

For reasons that are unexplained, patients with chronic hepatitis B infection seem to experience less fatigue than patients with chronic hepatitis C, unless they are having a hepatitic flare.

### Vaccination

Co-infection with more than one hepatitis virus may be associated with more severe liver disease.

Superinfection with hepatitis A infection (HAV) in a patient with chronic hepatitis B or C, or acute hepatitis B in a patient with chronic hepatitis C may precipitate the development of acute liver failure. In the long term, patients with HBV and HCV co-infection tend to be more likely to progress to cirrhosis and to develop HCC. Thus, HAV and HBV vaccination should be offered to all patients with chronic hepatitis C, and HAV vaccination should be offered to chronic hepatitis B patients (Chapter 5).

### Psychosocial support

Patients may experience social isolation, anxiety or discrimination related to infection with viral hepatitis, which may be compounded by physical symptoms. The primary care clinician can begin by listening to the patient and demonstrating sensitivity

to linguistic and cultural differences, which may impact on an individual's response to viral hepatitis. Provision of verbal and written information relating to transmission or disease natural history may allay fears (Chapter 15). Referral to counselling or support services may be indicated for patients with complex emotional, family and relationship or disclosure issues. All patients should be made aware of services such as counselling and support groups, telephone helplines and community organisations.

Information about services is available from any teaching hospital unit or the local hepatitis C council (Chapter 15).

### Complementary therapies

There is little evidence that herbal medicines have a profound antiviral effect despite many patients reporting some symptomatic improvement and the ability of some agents to induce a fall in ALT.<sup>9,10</sup>

Most preparations are safe but some have reported hepatotoxicity and should be avoided (e.g. mistletoe, valerian, heliotropium, kombucha tea). Close monitoring of liver biochemistry is recommended at the commencement of any herbal medicine.

### Steroids, chemotherapy and viral hepatitis

Severe flares of hepatitic activity may be seen following a course of corticosteroids or other immunosuppressive or cytotoxic therapy, particularly in patients with chronic hepatitis B. Such flares may be fatal. For instance, HBsAg+ patients receiving chemotherapy have a 5% mortality from acute liver failure. All patients undergoing chemotherapy or other immunosuppressive treatments should be screened for HBsAg and if positive should be commenced on prophylactic antiviral therapy. People with HCV infection may also have mild flares of activity in such circumstances. However, acute liver failure does not occur.

### Antiviral therapy for viral hepatitis

#### Aims of treatment

There are a number of aims of antiviral therapy in chronic viral hepatitis. These include:

- Eradication of infection
- Prevention of disease progression
- Improvement in histologic markers
- Improvement of symptoms
- Improved survival

All these aims can be achieved in a significant proportion of patients with hepatitis C or hepatitis B with currently available therapies.

#### Antiviral therapy – hepatitis C

The major aim of treatment is to achieve viral eradication. In hepatitis C, viral eradication is defined by the achievement of a sustained virological response (SVR); that is, negative HCV RNA by a

**TABLE 11.5 Treatments for hepatitis B and C. Section 100 Highly Specialised Drugs Program of the PBS\*****LAMIVUDINE (ZEFFIX)** 100 mg daily taken orally (except in patients with HIV co-infection – the dose is 300 mg daily)

<b>Condition</b> Chronic hepatitis B	<b>Criteria</b> <ul style="list-style-type: none"> <li>• Histological evidence of chronic hepatitis B on liver biopsy**</li> <li>• Abnormal serum ALT levels</li> <li>• HBeAg positive and/or HBV DNA positive</li> <li>• Absence of pregnancy and lactation</li> <li>• Female patients using effective contraception</li> <li>• Persons with advanced liver disease should have their treatment discussed with a transplant unit prior to initiating therapy</li> </ul>	<b>Caution</b> The development of lamivudine resistance in patients with cirrhosis or who are immunosuppressed may be associated with a severe flare of hepatitis and progression to liver failure.
---	--	--

**INTERFERON ALFA-2A (ROFERON-A)**  
**INTERFERON ALFA-2B (INTRON A)** 5–10 million units subcutaneously 3 times weekly for 16–24 weeks

<b>Condition</b> Chronic hepatitis B	<b>Criteria</b> <ul style="list-style-type: none"> <li>• Chronic hepatitis B on liver biopsy**</li> <li>• HBeAg+ and/or HBV DNA+</li> <li>• HBV infection &gt;6 months abnormal ALT</li> <li>• Absence of class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin &lt;30 g/l, bilirubin &gt;30 mmol/l)</li> <li>• Absence of pregnancy and lactation</li> <li>• Female patients using effective contraception</li> </ul>	<b>Caution</b> Pegylated interferon alfa has been associated with depression and suicide. Patients with a history of mental illness should be warned of the risks. Psychiatric status must be monitored during therapy.
---	--	--

**PEGYLATED INTERFERON ALFA-2A PLUS RIBAVIRIN (PegasysRBV Combination Therapy)**  
**PEGYLATED INTERFERON ALFA-2B PLUS RIBAVIRIN (Pegatron Combination Therapy)**

Dosage variable. Refer to relevant product information. For patients with genotype 2 or 3 without cirrhosis or bridging fibrosis the treatment course is limited to 24 weeks. For patients with genotype 1, 2, 3, 4, 5 or 6 with cirrhosis or bridging fibrosis, treatment course is limited to 48 weeks. Patients with genotype 1, 4, 5 or 6 who are eligible for 48-week treatment may only continue treatment beyond 12 weeks if HCV RNA is negative or viral load has dropped by at least 2 logs (a second HCV RNA assay is not necessary at week 24). Patients with genotype 1, 4, 5, or 6 who are HCV RNA positive at week 12 but have attained at least a 2-log drop in HCV viral load may only continue treatment after 24 weeks if plasma HCV RNA is negative at week 24. Patients with genotype 2 or 3 with cirrhosis or bridging fibrosis may only continue treatment after 24 weeks if HCV RNA is negative at 24 weeks.

<b>Condition</b> Chronic hepatitis C in patients 18yrs or older, with compensated liver disease, and with no prior interferon or peg-interferon.	<b>Criteria</b> <ul style="list-style-type: none"> <li>• Abnormal ALTs plus anti-HCV+ and HCV RNA+</li> <li>• Absence of pregnancy and lactation in women (including partners of male patients)</li> <li>• Patient (male or female) and his/her partner must use effective forms of contraception (one for each partner)</li> </ul>	<b>Caution</b> As for interferon above ribavirin is a teratogen (category X – drugs with a high risk of causing permanent damage to the foetus) and must not be given to pregnant women. Pregnancy in women taking ribavirin and in the female partners of men taking ribavirin must be avoided during treatment and for 6 months following treatment. N.B. Even though liver biopsy is no longer mandatory, many hepatologists will still recommend it for staging of liver disease.
---	---	---

**ADEFOVIR DIPIVOXIL** 10mg daily taken orally. Patients may receive treatment in combination with lamivudine for the first 3 months only of PBS-subsidised adefovir dipivoxil therapy (patients who are immunocompromised may receive the same treatment for 12 months). Thereafter, PBS-subsidised adefovir dipivoxil must be used as a monotherapy.

<b>Condition</b> Patients with chronic hepatitis B who have failed lamivudine therapy.	<b>Criteria</b> <ul style="list-style-type: none"> <li>• Absence of pregnancy and lactation in women</li> <li>• Female patient and her partner must use effective forms of contraception (one for each partner)</li> <li>• Repeatedly abnormal ALTs (&gt;1.2 x upper normal limit) while on concurrent antihepadnaviral therapy of 6 months or more in conjunction with anti-HBe+ and/or HBV DNA+</li> </ul>	
---	--	--

**TABLE 11.5 Treatments for hepatitis B and C. Section 100 Highly Specialised Drugs Program of the PBS\***

<b>PEGYLATED INTERFERON ALFA-2A MONOTHERAPY (PEGASYS) 180 micrograms subcutaneously once weekly</b>	
<p><b>Condition</b> Monotherapy in patients with chronic hepatitis B and compensated liver disease who satisfy all of the following criteria:</p>	<p><b>Criteria</b></p> <ol style="list-style-type: none"> <li>(1) Histological evidence of chronic hepatitis on liver biopsy (except in patients with coagulation disorders considered severe enough to prevent liver biopsy)</li> <li>(2) Abnormal serum ALT levels in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or HBV DNA positive)</li> <li>(3) Have received no prior peginterferon alfa therapy for the treatment of hepatitis B</li> <li>(4) Female patients of child-bearing age are not pregnant, not breast-feeding, and are using an effective form of contraception</li> <li>(5) Are not persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30g per L, bilirubin greater than 30 micromoles per L)</li> </ol> <p>Treatment is limited to 1 course of treatment for a duration of up to 48 weeks.</p>
<b>ENTECAVIR MONOHYDRATE 0.5mg daily</b>	
<p><b>Condition</b> Patients aged 16 years or older with chronic hepatitis B who satisfy all of the following criteria:</p>	<p><b>Criteria</b></p> <ol style="list-style-type: none"> <li>(1) Histological evidence of chronic hepatitis on liver biopsy (except in patients with coagulation disorders considered severe enough to prevent liver biopsy)</li> <li>(2) Abnormal serum ALT levels in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or HBV DNA positive)</li> <li>(3) Female patients of child-bearing age are not pregnant, not breast-feeding, and are using an effective form of contraception</li> </ol> <p>Persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30g per L, bilirubin greater than 30 micromoles per L) should have their treatment discussed with a transplant unit prior to initiating therapy.</p> <p>Note: PBS-subsidised entecavir monohydrate must be used as monotherapy.</p>
<b>ENTECAVIR MONOHYDRATE 1.0 mg daily</b>	
<p><b>Condition</b> Patients aged 16 years or older with chronic hepatitis B who have failed lamivudine therapy and who satisfy all of the following criteria:</p>	<p><b>Criteria</b></p> <ol style="list-style-type: none"> <li>(1) Repeatedly elevated (greater than 1.2 times the upper limit of normal) serum ALT levels while on concurrent antihepadnaviral therapy of greater than or equal to 6 months duration in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or serum HBV DNA positive)</li> <li>(2) Female patients of child-bearing age are not pregnant, not breast-feeding, and are using an effective form of contraception</li> </ol> <p>Persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30g per L, bilirubin greater than 30 micromoles per L) should have their treatment discussed with a transplant unit prior to initiating therapy.</p> <p>Note: PBS-subsidised entecavir monohydrate must be used as monotherapy.</p> <p>Patients should have undergone a liver biopsy at some point since initial diagnosis to obtain histological evidence of chronic hepatitis. Patients with Child's class B or C cirrhosis should have their treatment discussed with a transplant unit prior to initiating therapy.</p> <p>No Caution section for these last treatments.</p>
<p>*Details correct at July 2007.</p> <p>**Patients with severe coagulation disorders not required to undergo biopsy. Monotherapy with interferon alfa-2a and -2b is no longer the standard for HCV therapy. The longer-acting pegylated interferons have replaced them except where the patient is intolerant to ribavirin.</p>	

sensitive qualitative test six months after the completion of six or twelve months of therapy.

The most effective therapy for hepatitis C is a combination of once-weekly subcutaneously administered pegylated interferon plus twice-daily oral ribavirin. Such treatment is available in Australia under Section 100 of the Pharmaceutical Benefits Scheme (PBS). Refer to Table 11.5.

The combination of pegylated interferon and ribavirin produces an overall SVR of greater than 50%,<sup>11,12</sup> a significant improvement over the SVR rates achieved with interferon monotherapy (<10%) or standard interferon (given three times a week) plus ribavirin (40%).

The likelihood of response is much higher in patients infected with genotype 2 or 3 (80% SVR rate after six months of combination pegylated interferon and ribavirin) than genotype 1 or 4 (50% SVR rate after 12 months of therapy). While HCV genotype is the most powerful predictor of response, other predictors of SVR include low viral load, minimal hepatic fibrosis, female gender and age (younger than 40 years). Recently the rapidity of on-treatment response has emerged as a major factor in predicting sustained virologic response.

By monitoring on-treatment response, patients can be counselled as to their likelihood of viral eradication. Patients who have a greater than 2 log (100-fold) reduction in viral load by week 12 (termed an early virologic response) have an approximately 70% chance of sustained virologic response.<sup>13</sup> Conversely, patients with genotype 1 who fail to achieve a greater than 2 log drop in viral load at week 12 should have their treatment ceased as there is a negligible chance of viral eradication. Additionally, patients with genotype 1 who achieve undetectable HCV RNA at week 4 of therapy (termed a rapid virologic response) have a 90% chance of viral eradication and may even be able to shorten their treatment duration.<sup>14</sup> There is currently significant effort being directed at determining whether measurement of early on-treatment virological responses may allow some patients to have treatment duration shortened, and whether other patients may benefit from longer duration of therapy.

The benefits of achieving an SVR include a reduced risk of progression for patients at all stages of disease and probably a lower incidence of HCC development.

In addition, there have been reports of significant regression of fibrosis, even in cirrhotic patients. Patients who have failed to respond to either interferon monotherapy or combination interferon plus ribavirin are not eligible for further treatment under current Section 100 guidelines but may pay for their own treatment or may be able to access

combination pegylated interferon plus ribavirin through compassionate-use protocols.

Therapy may be for six or 12 months duration, depending on HCV genotype.<sup>15</sup> When discussing the benefits and risks of treatment, the GP can request genotype testing.

Medicare funding covers genotype testing. This information may help to guide a patient who is ambivalent about having treatment. In particular, patients with genotype 2 or 3 can be counselled that they have a high chance of eradicating the virus with six months of treatment.

Patients with genotype 1 infection can also be informed of their likelihood of eradicating infection. While this rate is lower, it should not dissuade patients from attempting treatment but remains an important discussion point. These discussions may take place before specialist referral.

There are significant numbers of patients with hepatitis C who respond poorly to therapies or have contraindications to therapy. Decisions about therapy in these individuals are made on a case-by-case basis by the specialist. These include patients with HCV and HBV co-infection, HCV and HIV co-infection, chronic renal failure, cryoglobulinaemia and with HCV recurrence after liver transplantation.

### HIV and HCV co-infection

HIV and HCV co-infection is associated with higher HCV viral load and an accelerated rate of HCV disease progression.<sup>16</sup> There is no fundamental difference in the management of HCV in the presence of HIV although certain antiretroviral agents (e.g. didanosine, zidovudine) are contraindicated or should be avoided if possible. Patients with HIV and HCV co-infection who either have stable CD4 cell counts on antiretroviral therapy, or who do not require antiretroviral therapy may be considered for combination pegylated interferon plus ribavirin. Management of such patients may be difficult, particularly in patients already taking multiple medications, as side-effects, drug interactions and poor tolerability are common and therapy should be carried out by a specialist experienced in this area.<sup>17</sup>

### Who should be treated for hepatitis C?

Antiviral therapy is currently reimbursed for patients who are 18 years or older with:

- Anti-HCV positivity
- Detectable serum HCV RNA
- Compensated liver disease
- No prior treatment with interferon alfa or pegylated interferon alfa

In the past, to access reimbursed antiviral therapy, patients have required abnormal liver enzymes and a liver biopsy showing at least a moderate degree of fibrosis. Neither of these features are now required.

Table 11.5 details who can receive treatment for hepatitis C through Section 100 of the PBS. The major contraindications to therapy include:

- Decompensated liver disease
- Major psychiatric conditions, particularly severe depression
- Autoimmune disease
- Significant cardiac disease
- Pregnancy (ribavirin is a teratogen – patients and their partners must avoid pregnancy during therapy and for six months after cessation of treatment due to the possibility of birth defects)

Although interferon is contraindicated in people with depression it may be used safely in patients with controlled depression and anxiety disorders or controlled seizure disorders. If the patient is being treated by a psychiatrist or neurologist, discussion with the specialist is recommended before the initiation of interferon therapy.

### Side effects

Side effects are common but do not usually require discontinuation of treatment. However, patients do require significant support and encouragement throughout treatment. Adverse effects of therapy include flu-like symptoms, irritability, weight loss, insomnia, vomiting, depression and anxiety, mild hair loss, rash, cough, myelosuppression and induction of autoimmunity, particularly thyroid disease.

Ribavirin treatment always induces a degree of intravascular haemolysis, which results in a fall in haemoglobin in most patients. This anaemia may result in tiredness, shortness of breath and precipitation of myocardial ischaemia in at-risk patients. Depression may occur as a result of serotonin depletion caused by interferon, and SSRIs may be considered for management or prophylaxis.

Given the wide range and potential seriousness of side effects, patients must be closely monitored during therapy. Currently, most treatment is provided through public hospitals and patients have ready access to nurse specialists to advise and support them through therapy. In general, patients on therapy are seen once a week for the first month, and then each month until the end of treatment, with blood counts and biochemistry evaluated at each visit. Dose modification guidelines are followed when side-effects or laboratory changes require intervention.

### The decision to treat

Given the likelihood of significant side effects, decisions about whether to treat and when to treat are often difficult. When discussing therapy with a patient, issues and commitments such as work, study, relationships, substance abuse and pregnancy should be considered.

### The shift to primary care

While most treatment is based in public hospitals at present, there is an important trend towards treatment in the community. This will involve primary care clinicians taking on a greater role in the support and monitoring of patients on therapy. Many hospitals have put together shared-care packages with specific information and guidelines about management during therapy. In addition, a small number of GPs in NSW and ACT have been approved to prescribe combination therapy as part of a Section 100 (PBS) community prescribing pilot project. To ensure the highest chance of achieving viral eradication, it is important to support patients through a complete course of therapy.

### Antiviral therapy – hepatitis B

Until recently the only treatments available for patients with chronic hepatitis B were interferon alfa and lamivudine (see Table 11.5). In the last few years, a number of new agents have been approved for the treatment of patients with chronic hepatitis B.<sup>18</sup> These include the nucleoside analogue entecavir, and the immunomodulator pegylated interferon alfa 2a. Both are subsidised through Section 100 of the PBS.<sup>19,20</sup> In addition a nucleotide analogue, adefovir dipivoxil, is also approved although only subsidised in patients with lamivudine-resistance. Another nucleoside analogue, telbivudine, is also approved but not yet subsidised.

The choice between these agents is based on a number of factors. A four- to six-month course of standard interferon is associated with HBeAg loss in 30–40% of patients and, in early trials, approximately 10% lost HBsAg.<sup>21,22</sup> Long-term benefits include improved survival and a reduction in the incidence of HCC. Interferon is of particular benefit in those patients with high ALT and low HBV DNA levels. Interferon may be hazardous to those with advanced liver disease and is associated with significant side-effects. Recently, pegylated interferon alfa 2a given weekly for 48 weeks has been shown to be effective in both HBeAg positive and HBeAg negative disease.<sup>23,24</sup>

Lamivudine (100 mg daily) is well tolerated and highly effective in suppressing HBV replication and improving liver histology. It is very effective against HBeAg negative mutant HBV and is useful in both compensated and decompensated cirrhosis. The rate of HBeAg seroconversion in HBeAg positive patients after 12 months of lamivudine therapy, however, is less than that with Pegylated interferon and cessation of lamivudine treatment is frequently associated with virological and biochemical relapse. Unfortunately, lamivudine therapy is also associated with the emergence of resistant strains (YMDD variants), and the incidence of mutations increases with duration of treatment. Although not usually associated with clinical deterioration, these variants may induce a severe hepatitis and liver

failure in cirrhotic or immunosuppressed patients. Lamivudine is also of benefit in patients with HIV/ HBV coinfection, as it is effective against both viruses. However, such patients have a high likelihood of developing lamivudine-resistant HBV, which may be associated with rapidly progressive disease.

Adefovir is a nucleotide agent with anti-HBV activity. Addition of adefovir dipivoxil in HBV mono-infected patients with lamivudine resistance is effective.<sup>25</sup> Adefovir is available via Section 100 for patients who have failed lamivudine and have elevated serum ALT (>1.2 times the upper limit of normal) and are HBeAg and/or HBVDNA positive. Continuation of lamivudine when adefovir is added appears to prevent the development of adefovir resistance<sup>26</sup> but currently dual agent therapy is subsidised for only three months on the PBS in immunocompetent individuals. Adefovir monotherapy may be associated with emergence of drug-resistant mutants and a clinical flare of hepatitis.

Entecavir is approved and reimbursed via Section 100 for, and is effective in, both therapy naïve patients and patients with evidence of lamivudine resistance. In clinical trials it has been proven to be superior to lamivudine in naïve patients with both HBeAg positive and HBeAg negative disease.<sup>27,28</sup> It has a very low rate of resistance in naïve patients. Whilst entecavir is still active in lamivudine resistant disease, the entecavir resistance rate in this setting is much higher. Telbivudine is another nucleoside agent which has been recently approved, but is not yet available through PBS-subsidy. Telbivudine is well tolerated, and very potent against hepatitis B, but is associated with some emergence of drug resistance, particularly in those patients that fail to rapidly suppress HBV DNA to undetectable levels. It is ineffective in individuals with lamivudine resistance.

Tenofovir is a nucleotide analogue with dual HIV and HBV activity. It is currently licensed for HIV therapy but not for use in HBV mono-infected patients. In HIV/HBV coinfecting patients it is highly effective against HBV in both treatment naïve and lamivudine experienced patients.<sup>29</sup> It is well tolerated and has a very low rate of HBV resistance. It is likely to become licensed for use in HBV mono-infection in the near future.

### Who should be treated?

In compensated patients with chronic HBV, antiviral therapy is indicated where there is:

- active viral replication (HBeAg+ and/or HBV DNA positive)
- persistently elevated ALT levels
- histological evidence of chronic injury

The initial aim of treatment is to suppress viral replication as indicated by HBeAg seroconversion (loss of HBeAg and appearance of anti-HBe) and loss of HBV DNA. Optimal duration of therapy is

unknown but the current recommendation is to continue therapy for at least 6–12 months after seroconversion occurs. Once therapy has stopped, at least 15% of patients will undergo seroreversion (i.e. they become HBeAg+ again).

Patients with HBeAg-negative infection should also be considered for therapy although the optimal duration of therapy is not known and patients may need to continue treatment indefinitely.

Patients who are HBeAg-negative with abnormal LFTs should have an HBV DNA performed to identify pre-core mutant disease. If HBV DNA is positive, then liver biopsy and treatment with an antiviral agent should be discussed, particularly for patients with moderate or marked hepatic fibrosis.

### Liver transplantation in viral hepatitis

Chronic hepatitis C and hepatitis B are the leading indications for liver transplantation in Australia.

Patients should be referred to a transplant unit when they develop signs of hepatic decompensation, such as ascites, encephalopathy, bacterial infections (particularly spontaneous bacterial peritonitis), muscle wasting or worsening fatigue. It is best to try to identify subtle signs of impending liver failure (Chapters 5 and 7), so that early referral can be made. Liver transplantation is also indicated in some patients with HCC. Detailed management of end-stage liver disease is beyond the scope of this publication.

### Summary

Chronic hepatitis poses challenges of diagnosis, general management, selection for treatment and care during treatment. It is important that a patient's concerns be addressed by the provision of information about the disease and access to counselling and psychosocial support. The primary care clinician has a vital role in the assessment and monitoring of patients with chronic viral hepatitis. Shared care is the preferred model of care for patients with chronic viral hepatitis and effective communication between GPs, specialists and referral centres is required for optimal patient management.

## References

- 1 Farrell GC, editor. Hepatitis C. A management guide for general practitioners. *Aust Family Physician* 1999;28:SI3–88.
- 2 Farrell GC, Liaw Y-F, McCaughan GW, editors. Consensus statements on the prevention and management of hepatitis B and hepatitis C in the Asia-Pacific region. *J Gastroenterol Hepatol* 2000;15:815–41.
- 3 Schiff ER, Hoofnagle JH, editors. Update on viral hepatitis. *Hepatology* 2000;32:SI 1–199.
- 4 Danta M, Brown D, Bhagani S, Pybus O, Sabin C, Nelson M, et al. for the HIV and Acute HCV (HAAC) group. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS* 2007;21(8):983–91.
- 5 Conte D, Fraquelli M, Prati D, Colucci A, Minola E. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of vertical transmission in a cohort of 15,250 pregnant women. *Hepatology* 2000; 31:751–5.
- 6 Gibb DM, Goodall RL, Dunn, DT. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet* 2000;356 (9233):904–07.
- 7 National Health and Medical Research Council (NHMRC). Australian Drinking Guidelines: Health risks and benefits. Canberra: NHMRC, October 2001.
- 8 Albion Street Centre. Nutrition and hepatitis C: information for health care workers. 2000. Available at: [www.sesahs.nsw.gov.au/albionstreetcentre](http://www.sesahs.nsw.gov.au/albionstreetcentre)
- 9 Batey RG, Batey RG, Bensoussan A, Fan YY, Bollipo S, Hossain MA. Preliminary report of a randomized, double blind placebo-controlled trial of a Chinese herbal medicine preparation CH-100 in the treatment of chronic hepatitis C. *J Gastroenterol Hepatol* 1998;13:244–7.
- 10 Parés A, Planas R, Torres M, Caballería J, Viver JM, Acero D, et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. *J Hepatol* 1998;28(4):615–21.
- 11 Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958–65.
- 12 Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçalves FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347:975–82.
- 13 Davis GL, Wong JB, McHutchinson JG, Manns MP, Albrecht J. Early virologic response to treatment with pegylated interferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2003; 38:645–52.
- 14 Jensen DM, Morgan TR, Marcellin P, Pockrus PJ, Reddy KR, Hadziyannis S, et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon -2a(40kd) ribavirin therapy. *Hepatology* 2006; 43:954–60
- 15 McCaughan GW, Strasser SI. Emerging therapies for hepatitis C virus (HCV) infection: importance of HCV genotype. *Aust NZ J Med* 2000;30:644–6.
- 16 Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C coinfecting patients. *Hepatology* 1999;30:1054–8.
- 17 Soriano V, Rodriguez-Rosado R, Garcia-Samaniego J. Management of chronic hepatitis C in HIV-infected patients *AIDS* 1999;13:539–46.
- 18 Keeffe EB, Marcellin P. New and emerging treatment of chronic hepatitis B. *Clin Gastroenterol Hepatol* 2007;5(3):285–94.
- 19 Strasser SI, McCaughan GW. Therapies for chronic hepatitis B: emerging roles for nucleoside analogues. *Aust NZ J Med* 2000;30:556–8.
- 20 Torresi J, Locarnini S. Antiviral chemotherapy for the treatment of hepatitis B infection. *Gastroenterology* 2000;118 (suppl):S83–S103.
- 21 Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, Häussinger D. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med* 1996;334:1422–7.
- 22 Perrillo RP, Schiff ER, Davis GL, Bodenheimer HC, Lindsay K, Payne J, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. The Hepatitis Interventional Therapy Group. *N Engl J Med* 1990;323:295–301.
- 23 Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R et al. Peginterferon alfa-2a Alone, Lamivudine Alone, and the Two in Combination in Patients with HBeAg-Negative Chronic Hepatitis B [Multicenter Study. Randomized Controlled Trial]. *N Engl J Med* 2004;351(12):1206–17.
- 24 Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, et al. Peginterferon Alfa-2a, Lamivudine, and the Combination for HBeAg-Positive Chronic Hepatitis B [Multicenter Study. Randomized Controlled Trial]. *N Engl J Med* 2005;352(26):2682–95.
- 25 Schiff ER, Lai CL, Hadziyannis S, Neuhaus P, Terrault N, Colombo M, et al. Adefovir Dipovoxil Study 435 International Investigators Group. Adefovir dipovoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. *Hepatology* 2003;38:1419–27.
- 26 Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. *Hepatology* 2007;45(2):307–13.

## 11 Primary care management of chronic viral hepatitis

- 27 Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao Y-C, et al. for the BEHoLD A1463022 Study Group. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006;354(10):1001–10.
28. Lai CL, Shouval D, Lok AS, Chang T-T, Cheinquer H, Goodman Z, et al. for the BEHoLD A1463027 Study Group. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006;354(10):1011–20.
- 29 Schmutz G, Nelson M, Lutz T, Sheldon J, Bruno R, von Boemmel F, et al. Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection. *AIDS* 2006;20(15):1951–4.