Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016

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Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016

The Consensus Statement was prepared by an expert panel representing the Gastroenterological Society of Australia (Australian Liver Association), the Australasian Society for Infectious Diseases, the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, the Australasian Hepatology Association, Hepatitis Australia and the Royal Australian College of General Practitioners.

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Introduction

Chronic hepatitis C virus (HCV) infection is a major public health challenge for Australia, affecting approximately 230 000 people who are at risk of progressive liver fibrosis leading to cirrhosis, liver failure and hepatocellular carcinoma (HCC). HCV infection is the most common cause of liver disease requiring liver transplantation in Australia. The burden of liver disease due to HCV is projected to triple by 2030. However, HCV infection is curable, and viral eradication is associated with multiple clinical benefits, including improvement in quality of life, loss of infectivity, regression of cirrhosis, lower risk of liver failure and HCC, and reduction in mortality. Until recently, the treatment of HCV involved interferon therapy, which had limited efficacy and was poorly tolerated. The introduction of direct-acting antiviral (DAA) therapies for HCV that are highly effective and well tolerated is a major medical advance. All Australians living with HCV should now be considered for antiviral therapy. DAAs may be prescribed by specialists experienced in treating HCV or by general practitioners in consultation with one of these specialists, meaning that treatment can occur in the community.

This document presents the *Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016*. This is a living document that will be updated as new data emerge. Grading of the levels of evidence for the recommendations is described in Section 14.

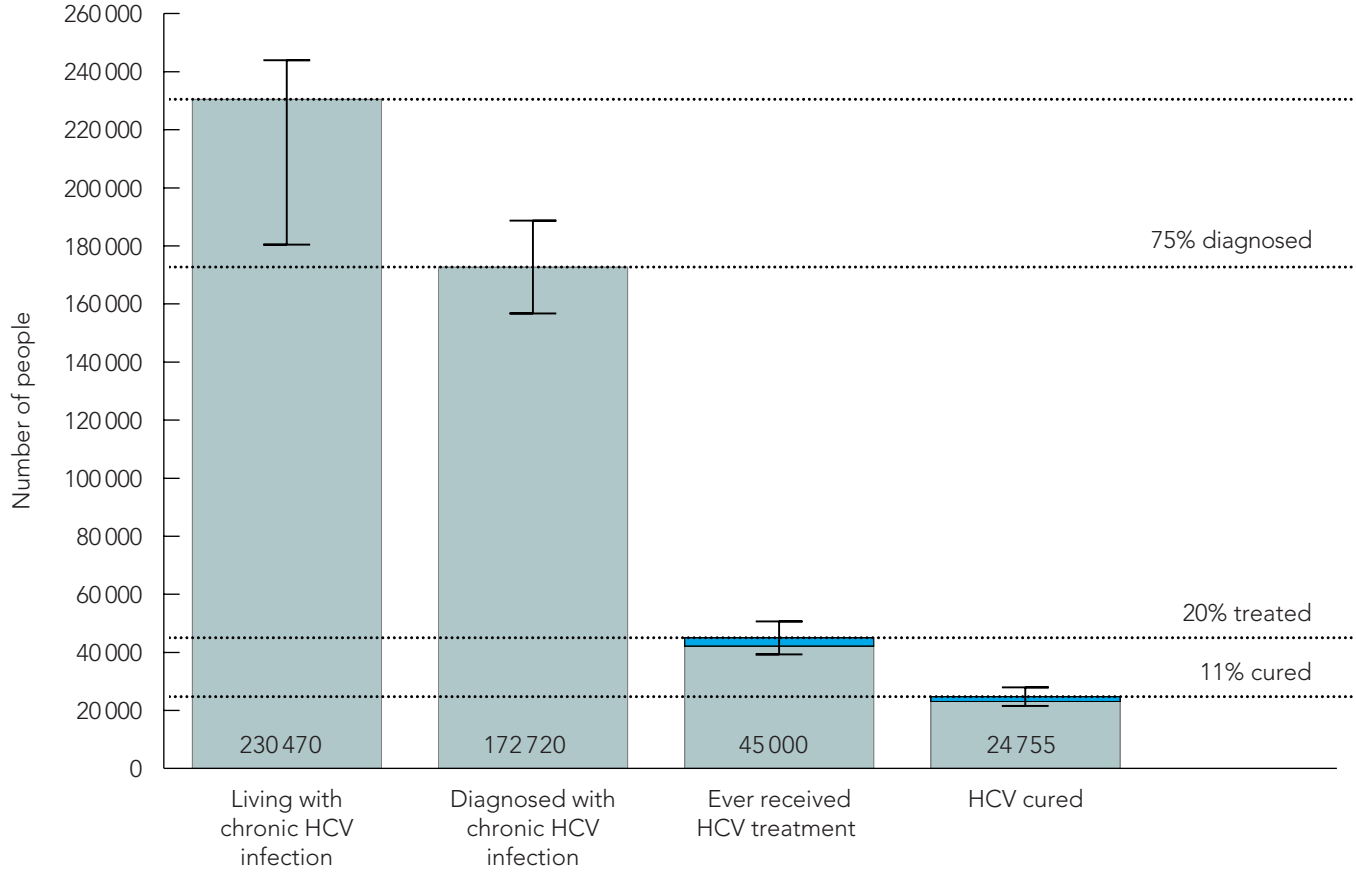
1. The epidemiology of HCV in Australia

Hepatitis C virus (HCV) infection is a major public health challenge for Australia. Acute infection progresses to chronic disease in up to 75% of cases, and these people are at risk of progressive liver fibrosis leading to cirrhosis, liver failure and hepatocellular carcinoma (HCC). Around 20%–30% of people with chronic HCV infection will develop cirrhosis, generally after 20–30 years of infection.

In Australia, the diagnosis of HCV infection has required mandatory notification since the early 1990s. HCV notifications by jurisdictions are forwarded to the National Notifiable Diseases Surveillance System, with recording of information including age, sex and year of diagnosis. Total HCV notifications and estimates of HCV incidence and prevalence in at-risk populations, particularly among people who inject drugs (PWID), indicate that a high proportion (75%–85%) of people with HCV infection have been diagnosed.[1,2] In Australia, the anti-HCV antibody prevalence among adults is estimated at 1.7% (range, 1.2%–1.8%) or 314 000 people (range, 227 000–349 000). The prevalence of detectable HCV RNA (indicating viraemic or chronic HCV prevalence) is approximately 1.2% (range, 0.9%–1.4%) or 230 470 people (range, 180 490–243 990).[2]

The incidence of new HCV infections in Australia has declined since 2000, related to both a reduction in the prevalence of injecting drug use and improved harm reduction measures (eg, needle and syringe programs and opioid substitution treatment uptake) among PWID. The proportion of new HCV cases in young adults (aged 20–39 years) provides the best

Figure 1. Estimates of the cascade of care for people with chronic hepatitis C virus (HCV) infection in Australia



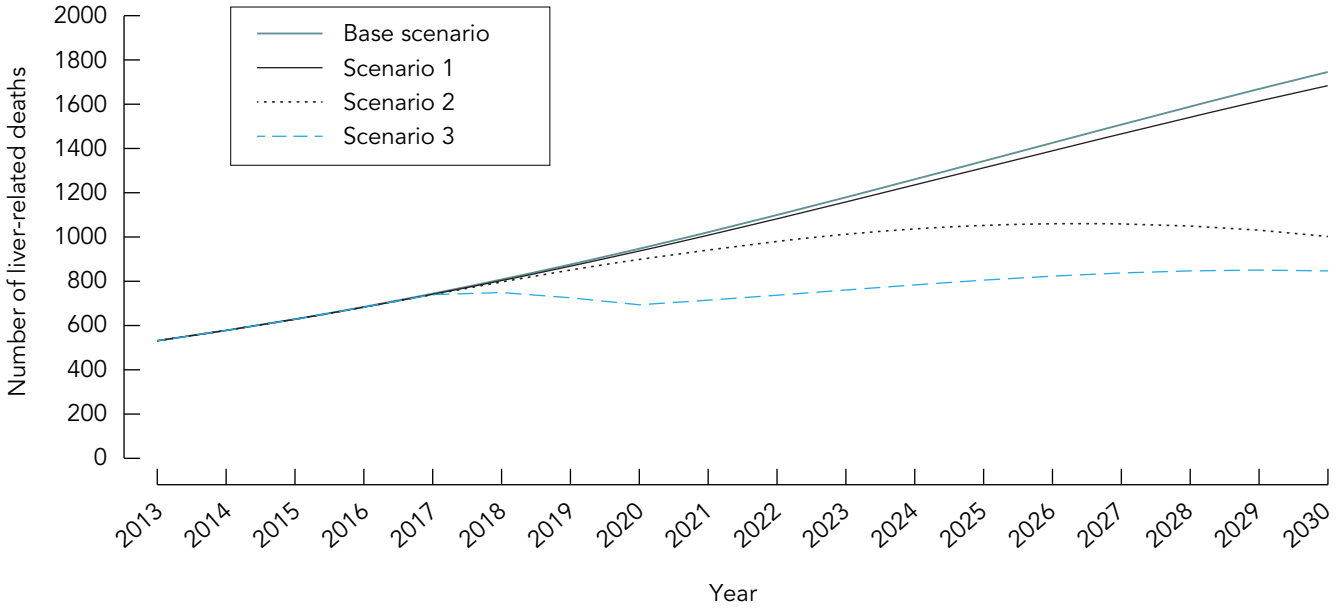
Source: Hajarizadeh B, et al. *Global Antiviral Journal* 2015; 11 Suppl 3: 85-86.[2]

estimate of incident cases. Modelling suggests that the incidence of HCV infection peaked at 14 000 new infections in 1999 and had declined to 8500–9000 new infections in 2013.[1,3,4] Despite this decline in HCV incidence, prevalence is increasing and the overall burden of liver disease continues to increase, due to the ageing of the population with chronic HCV infection and suboptimal HCV treatment uptake and outcomes. The increasing liver disease burden is reflected in escalating rates of end-stage liver disease, including HCC and liver failure, as well as HCV-related liver transplantation.

Despite one of the highest HCV diagnosis rates in the world, treatment uptake in Australia remains low (2000–4000 people/year, or 1%–2% of the infected population) (**Figure 1**). This low rate likely reflects the toxicity of interferon (IFN)-based antiviral therapy, inadequate treatment infrastructure and insufficient linkage to care due to social marginalisation of the populations at greatest risk of infection. In addition, the low cure rates in people with cirrhosis using IFN-alfa-based regimens have not altered the growing burden of advanced liver disease.

Recent modelling of the Australian HCV epidemic examined strategies to reduce projected HCV-related morbidity and mortality with the planned availability of well tolerated and highly effective direct-acting antiviral (DAA) agents.[5] In 2013, most people living with HCV were estimated to have mild liver fibrosis, and only 6% (13 850) to have compensated cirrhosis. However, without an increase in treatment uptake or efficacy, the number of people with compensated cirrhosis will almost triple to 38 000 by 2030, with concomitant increases in the number of people with HCC (n = 2040) and liver-related death (n = 1740). The modelling showed that increasing rates of sustained virological response at least 12 weeks after treatment (SVR) AND increasing the number of people treated each year will be necessary to effect a substantial reduction in HCV prevalence and HCV-related mortality (**Figure 2**).[5]

Figure 2. Projected burden of disease: liver-related deaths, 2013–2030



Model inputs for scenarios:

Scenario 1: increase sustained virological response (SVR) only, with no increase in annual treated population and treatment eligibility not restricted by fibrosis stage.

Scenario 2: increase SVR and annual treated population, with treatment eligibility not restricted by fibrosis stage.

Scenario 3: increase SVR and annual treated population, restricted to fibrosis stage ≥ F3 in 2015–2017, then unrestricted (all stages ≥ F0) from 2018.[5]

These scenarios illustrate that it will be necessary to increase both treatment efficacy AND treatment uptake rates to reduce the projected burden of liver-related deaths due to HCV infection in Australia by 2030.

In addition to efforts that increase the number of people treated overall, strategies that target populations with high HCV transmission risk could accelerate HCV elimination by preventing new infections ("treatment as prevention"). A modelling study by Martin and colleagues recently showed that increasing treatment in PWID would have a dramatic effect on reducing HCV prevalence.[6] Using a baseline HCV prevalence of 50% among PWID in Melbourne, they predicted that increasing the annual treatment rate to 40 per 1000 PWID would decrease HCV prevalence among PWID by 50% in 15 years.[6] An increase to 80 per 1000 PWID would decrease prevalence in PWID by > 90%, essentially eliminating HCV infection from the Australian population of PWID. Clinical trials examining treatment as prevention in PWID have recently commenced in Australia.

Armed with a detailed understanding of the epidemiology of HCV infection and the unrestricted access to highly effective and well tolerated oral DAAs through the Pharmaceutical Benefits Scheme (PBS), it is very likely that the onward transmission of the virus can be halted and that HCV can be eliminated as a major public health issue in Australia.

2. Models of care for the treatment of HCV infection in Australia

The reasons why the health care system has failed to effectively deal with the HCV epidemic are multifactorial and include the toxicity of IFN-based-antiviral therapy, insufficient linkage to tertiary hospital-based care for socially marginalised individuals, capacity constraints in tertiary care and a lack of alternative models of care. The introduction of new DAA regimens is a major advance for HCV therapy.[5] Their high efficacy, short duration and excellent tolerability mean that most people will now be suitable for treatment, that most people who start treatment will be cured, and that treatment will be possible in the community as well as in specialist centres.

The PBS listing allows the new HCV medicines to be prescribed by gastroenterologists, hepatologists or infectious diseases physicians who are experienced in treating chronic HCV infection, as well as general practitioners who are eligible to prescribe under the PBS in consultation with one of these specialists. PBS authority approval from the Department of Human Services (Medicare) — via written or telephone channels — will be required for each prescription; the medicines will not be available under streamlined authority. "In consultation with" means that a GP must consult with one of the specified specialists by phone, fax, mail, email or videoconference in order to meet the prescriber eligibility requirements. The new HCV medicines will be available through the PBS General Schedule (Section 85), as well as the Section 100 Highly Specialised Drugs (HSD) Program. This means that it will be possible for approved pharmacists in the community to dispense the new HCV medications. The S100 listing makes provision for treatment of prisoners through the HSD Program.

The S85 provision for community dispensing of DAA therapy by GPs is intended to increase capacity to allow upscaling of treatment rates to the desired level for reducing population burdens of HCV and secondary liver disease. The development of new models of care for HCV treatment will be necessary. Suggested models of care for this new era are outlined below.

2.1 Tertiary centre-led models of care

Tertiary care clinics led by gastroenterologists, hepatologists or infectious diseases physicians have traditionally been the main sites for HCV clinical referral, assessment and treatment. Tertiary treatment centres should continue to be the main treatment sites for people with chronic HCV infection who have cirrhosis, complex comorbidities or other types of liver disease, or in whom first-line DAA therapy has failed. Tertiary treatment centres will continue to provide treatment for people with all stages of liver disease. Tertiary centres will also be required to support, up-skill and facilitate treatment by non-specialists in non-hospital settings.

2.2 Treatment by general practitioners in primary care

The PBS listing of DAA medicines enables GPs to initiate HCV therapy in primary care, with the goal of substantially increasing the HCV treatment workforce. GPs will be eligible to prescribe the new HCV medicines provided this is done in consultation with an experienced gastroenterologist, hepatologist or infectious diseases physician. The consultation removes the need for formal accreditation for GPs. For people living with HCV, receiving treatment in familiar environments with their trusted, accessible, long-term doctors removes an important barrier to treatment and will improve the cascade of care. Evidence from the IFN era supports the efficacy of GP-led treatment with remote specialist supervision.[7,8] Primary care-based treatment is suitable for most people living with HCV, in particular those with mild–moderate liver fibrosis. To support this, the availability and interpretation of simple tools for liver fibrosis assessment in the community will be very important. People with cirrhosis, complex comorbidities or other types of liver disease, or in

whom first-line DAA therapy has failed, should still be referred for specialist care.

2.3 Nurse-led models of care

In collaboration with a medical specialist, appropriately qualified and experienced hepatology nurses are involved in educating, supporting and clinically managing people with liver disease during their treatment journey. Several Australian state governments have already committed significant investment to deliver nurse-led models of care for clinical assessment and management of HCV infection, with clinics staffed by advanced practice nurses or nurse practitioners.[9,10] Such models involve supervised practice within well defined clinical protocols, including education, clinical assessment, performance of diagnostic tests such as transient elastography, and monitoring of treatment. Nurse-led HCV outreach clinics appear to be a cost-effective way of decentralising care and increasing HCV treatment capacity. They have been used to expand HCV education and treatment into a variety of HCV high-prevalence community settings including prison populations, opioid substitution centres, primary health services for PWID, and remote regions described below.[10,11]

2.4 Models of care in custodial settings

Prison populations in Australia have a high prevalence of HCV infection, estimated at 30%,[12] which reflects the close relationship between injecting drug use, HCV infection and incarceration. Although treatment uptake in custodial settings across Australia remains extremely low, incarceration presents a unique opportunity for HCV therapy due to improved direct access to health care and stable accommodation. Both Australian and international studies have demonstrated the safety, feasibility and acceptability of nurse-led models of IFN-based HCV treatment in prison populations,[7,13,14] supported by specialist teleconferencing. With newer DAA regimens, the ease of treatment will be considerably enhanced in this setting. Treatment of prisoners is a priority to reduce the incidence of HCV transmission.

2.5 Models of care for people who inject drugs and for opioid substitution treatment centres

Approximately 80% of people infected with HCV in Australia have acquired the infection through sharing unsterile injecting equipment, and new infections almost exclusively occur in PWID. Although some practitioners previously excluded current PWID from treatment, there is clear evidence of equivalent treatment outcomes, albeit with a low risk of reinfection.[15] Holistic care therefore includes harm reduction strategies such as opioid substitution therapy, together with access to needle and syringe programs. In addition, treating PWID may reduce HCV transmission (treatment as prevention), making this group a high priority for HCV treatment.[16] Engagement with PWID and their injecting networks is recommended. The integration of HCV therapy with addiction therapy in opioid substitution treatment centres represents an opportunity to enhance HCV treatment uptake. Successful Australian models have been described, demonstrating feasibility and cost-effectiveness.[17-20] Education and training of clinical staff at opioid substitution treatment centres to integrate HCV therapy with addiction therapy is therefore an important priority.

2.6 Models of care in rural and remote settings

Uneven distribution of health care resources is a contributing factor to poor treatment uptake in rural and remote regions of Australia. Successful models of care using a nurse practitioner and telehealth clinics supported by tertiary care specialists have been described in Australia and overseas.[7,21] Real-time videoconferencing involving both patients and local clinical staff is designed to increase treatment uptake and build local capacity. Results from this and other similar models appear equivalent to traditional face-to-face clinics in tertiary care centres[7,21] and have been associated with high levels of patient satisfaction.

2.7 Models of care for Aboriginal and Torres Strait Islander people

Aboriginal and Torres Strait Islander people are another currently under-served population with a high prevalence rate of HCV. Models of care that

are centred in facilities close to home, involve local trusted providers and provide culturally competent care using best-practice protocols are likely to increase HCV treatment uptake in this population. Education and training of local clinicians with linkage to expert providers is an important priority.

2.8 Models of care for migrant populations

Migrants from high-prevalence regions (Egypt, Pakistan, the Mediterranean and Eastern Europe, Africa and Southern Asia) also represent a population that is currently under-served. Again, models of care that are centred in facilities close to home, involve local trusted providers, and provide culturally appropriate care using best-practice protocols are likely to increase HCV treatment uptake. Such care should include access to interpreting and translating services. Education and training of local clinicians with linkage to expert providers is an important priority.

Consensus recommendations	Grade
HCV treatment uptake in Australia must be substantially increased in order to limit HCV-related liver disease and deaths and to reduce ongoing transmission of HCV. This will require new models of care.	A1
Tertiary care centres must continue to have a major role in managing people with HCV who have cirrhosis or complex care needs.	A1
Hepatology nurse practitioners and advanced practice nurses linked to specialist care centres are a safe and effective way of increasing HCV treatment capacity in a range of health care environments and should have a critical role in the expansion of treatment uptake.	B1
GP-led HCV care should be a major driver of increased HCV treatment uptake. Treatment should occur in consultation with an experienced specialist.	B2
Specific models of care for high-prevalence but under-served populations (PWID, including those attending primary health care services and opioid substitution treatment centres; prisoners; rural and remote populations; Aboriginal and Torres Strait Islander people; and migrant communities) must be developed to reduce barriers to treatment and increase HCV treatment uptake.	B1

3. Screening and diagnosis

Transmission of HCV infection is associated with identifiable risk factors (**Table 1**), and most diagnoses result from screening of at-risk populations. All individuals with a risk factor for HCV infection should be tested. The appropriate screening test for HCV is serology (HCV antibodies), which indicates exposure to HCV, either current or past infection.

Current HCV infection should be confirmed by a polymerase chain reaction (PCR) assay for HCV RNA. Approximately 25% of acute HCV infections will clear spontaneously within 6 months; these individuals continue to be HCV antibody-positive but do not have detectable HCV RNA in plasma. Criteria for PBS eligibility require evidence of chronic infection documented by repeated HCV antibody positivity and HCV RNA positivity. The clinical definition of chronic HCV infection is duration longer than 6 months. People with confirmed chronic HCV infection should be tested for HCV genotype. There are seven different HCV genotypes (Gt 1–7). The common genotypes in Australia are Gt 1 (50%–55%; 1a:1b = 2:1) and Gt 3 (35%–40%).[22] As approved treatment regimens for HCV infection are genotype-specific, HCV genotyping is necessary before treatment initiation.

Annual HCV serological testing is recommended for seronegative individuals with ongoing risk factors for HCV transmission. For individuals who are seropositive but have undetectable HCV RNA (indicating past infection), annual HCV RNA testing is recommended only in the setting of ongoing risk factors for HCV transmission.

Table 1. High-risk populations for hepatitis C virus (HCV) infection

- People who inject drugs or who have ever injected drugs
- Sex workers
- People in custodial settings
- People with tattoos or body piercing
- People who received a blood transfusion or organ transplant before 1990
- Children born to HCV-infected mothers
- Sexual partners of an HCV-infected person
- People infected with human immunodeficiency virus or hepatitis B virus
- People with evidence of liver disease (persistently elevated alanine aminotransferase level)
- People who have had a needlestick injury
- Migrants from high-prevalence regions (Egypt, Pakistan, Mediterranean and Eastern Europe, Africa and Asia)

Consensus recommendations	Grade
HCV seronegative people with risk factors for HCV transmission should be screened annually for HCV infection.	A1
The appropriate screening test for HCV infection is HCV serology (HCV antibodies).	A1
If HCV antibodies are detected, current infection should be confirmed by testing for HCV RNA using a sensitive PCR assay.	A1
Chronic HCV infection is defined by repeated HCV antibody positivity and HCV RNA positivity with a duration of infection longer than 6 months.	A1
All individuals with chronic HCV infection should be tested for HCV genotype.	A1

4. Pre-treatment assessment

All people living with HCV infection should be considered for treatment, except those with limited life expectancy (< 12 months) due to non-liver-related or non-HCV-related comorbidities. It is important that all people considered for treatment undergo a comprehensive pre-treatment assessment (**Table 2**). This assessment provides the foundation for a successful virological outcome by establishing a therapeutic and collaborative relationship.

Key elements of the pre-treatment assessment are:

- Perform a virological evaluation to:
  - confirm the diagnosis of chronic HCV infection
  - identify the genotype of HCV infection
  - document the HCV treatment history
- Consider whether there are coexisting liver diseases present
- Evaluate for the presence of cirrhosis
- Consider concomitant medications for risk of drug–drug interactions, including over-the-counter preparations and recreational substances.

4.1 Perform a virological evaluation

4.1.1 Confirm the diagnosis of chronic HCV infection

In an individual who is repeatedly HCV antibody-positive, current HCV infection should be confirmed by a PCR assay for HCV RNA. Quantitative PCR is recommended as part of the pre-treatment assessment because HCV RNA level can identify people who are eligible for a short treatment duration with certain regimens.

4.1.2 Identify the genotype of HCV infection

Approved treatment regimens for HCV are genotype-specific, and the HCV genotype must be documented in the patient's history to meet PBS criteria for the new HCV medicines. Therefore, HCV genotyping is necessary before treatment initiation. HCV genotyping is now a routine laboratory test.

4.1.3 Document the HCV treatment history

It is important to document any prior treatment for HCV infection. Key information includes treatment regimen, duration, adherence and response. These may influence the choice of treatment regimen and/or treatment duration (see Section 5).

4.2 Consider whether there are coexisting liver diseases present

It is important to consider whether another liver disease is present as this increases the risk of cirrhosis being present, and will need ongoing management after viral eradication. Common comorbidities include excessive alcohol consumption, diabetes, obesity and non-alcoholic fatty liver disease. Coinfection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) is more common in people with HCV infection than in the general population. It is therefore important to perform a targeted assessment in all patients, including calculation of body mass index and measurement of blood pressure, waist circumference, fasting glucose level and lipid levels, as well as HBV and HIV serology. All people with chronic HCV infection should be vaccinated against hepatitis A virus (HAV) and HBV if seronegative. Testing for other causes of liver disease, including haemochromatosis, autoimmune hepatitis, primary biliary cholangitis, Wilson disease and alpha-1-antitrypsin deficiency, can be reserved for individuals whose liver function test results do not normalise once HCV infection has been cured, or in whom there is a high index of clinical suspicion. For people aged > 50 years in whom it is planned to use ribavirin-containing regimens, it is important to consider the complications of anaemia and screen for cardiovascular disease with directed history plus an electrocardiogram. For people with cardiovascular disease, a regimen that does not involve ribavirin may be most suitable.

Table 2. Pre-treatment assessment of people with chronic hepatitis C virus (HCV) infection

History	• Estimated duration of HCV infection • Previous HCV treatment experience — date, regimen and response • Cofactors for liver disease progression: alcohol intake, marijuana use, virological cofactors (HIV, HBV), diabetes, obesity • For those planned to receive ribavirin, note history of ischaemic heart disease or cardiovascular risk factors • Vaccinations against HBV and HAV • Physical and psychiatric comorbidities • Ongoing risk factors for viral transmission and reinfection • Social issues — potential barriers to medication adherence
Medication	• Concomitant medications (prescription, over-the-counter, illicit)
Physical examination	• Features of cirrhosis: hard liver edge, spider naevi, leukonychia • Features of decompensation or portal hypertension: jaundice, ascites, oedema, bruising, muscle wasting, encephalopathy • Body weight and body mass index
Virology	• HCV genotype and subtype • HCV RNA level (quantitative) • HBV (HBsAg, anti-HBc, anti-HBs), HIV, HAV serology

Investigations	• Full blood examination, liver function tests, urea and electrolytes, eGFR, INR
	• Pregnancy test for women of childbearing potential
	• Liver fibrosis assessment, eg:
	  ▸ Elastography (FibroScan, ARFI, SWE)
	  ▸ Serum biomarker (APRI, Hepascore, ELF test, FibroGENE*)
	• Liver ultrasound should be performed in people with cirrhosis to exclude hepatocellular carcinoma
	• Electrocardiogram should be performed if ribavirin therapy is planned and patient is > 50 years of age or has cardiac risk factors

HIV = human immunodeficiency virus. HBV = hepatitis B virus. HAV = hepatitis A virus. HBsAg = hepatitis B surface antigen. anti-HBc = hepatitis B core antibody. anti-HBs = hepatitis B surface antibody. eGFR = estimated glomerular filtration rate. INR = international normalised ratio. ARFI = acoustic radiation force impulse. SWE = shear wave elastography. APRI = aspartate aminotransferase to platelet ratio index. ELF = Enhanced Liver Fibrosis. * Online calculator available at: http://www.fibrogene.com/viral_hepatitis.html.

4.3 Evaluate for the presence of cirrhosis

Once a diagnosis of chronic HCV infection has been established, further investigation should be directed toward assessing for the presence or absence of cirrhosis. Although all people with chronic HCV infection are eligible for treatment, regardless of liver fibrosis stage, the presence of cirrhosis influences treatment duration and regimen (see Section 5), and a person's cirrhosis status must be provided at the time of seeking PBS authority to write a prescription for the new HCV medicines. The presence of cirrhosis also identifies people who

require lifelong surveillance for HCC and portal hypertension.

Clinical risk factors for cirrhosis include male sex, older age at infection, prolonged duration of HCV infection (> 20 years) and comorbidities including excessive alcohol consumption, diabetes, the metabolic syndrome and coinfection with HBV or HIV. Clues to the presence of advanced liver disease include peripheral stigmata of chronic liver disease (eg, leukonychia, spider naevi) and markers of portal hypertension, including splenomegaly and thrombocytopaenia. Low albumin levels, raised bilirubin levels and a raised international normalised ratio (INR) are markers of reduced liver functional reserve and decompensated liver disease.

Formal evaluation for cirrhosis with a non-invasive test is recommended for all individuals with chronic HCV infection. Evaluation of liver fibrosis stage should be performed before commencing treatment. None of the non-invasive tests have been validated for diagnosing cirrhosis after SVR, and there is a risk of false negative results when performed after treatment. Transient elastography, or FibroScan (EchoSens, Paris), measures liver stiffness and is the most common method used for diagnosing cirrhosis. It has been extensively evaluated and validated in people with chronic HCV infection[23] and outperforms serum biomarkers for detecting cirrhosis.[24] FibroScan is available in most metropolitan centres. A liver stiffness of > 12.5 kPa measured using FibroScan is a reasonable threshold for identifying people with cirrhosis for treatment decision making.[25,26] Alternative elastography methods for measuring liver stiffness include shear wave elastography and acoustic radiation force impulse (ARFI) technology. These techniques can be offered as an add-on to liver ultrasound using many machines, but have been less well validated for the assessment of fibrosis stage in the setting of chronic HCV infection.

Serum biomarkers for liver fibrosis have also been developed, such as the APRI (aspartate aminotransferase [AST] to platelet ratio index), Hepascore, FibroGENE, Enhanced Liver Fibrosis (ELF) test and FibroTest. The APRI is a simple biochemical marker that can be calculated from routine blood test results. Hepascore and the ELF test are alternative serum fibrosis markers that are available in Australia but not currently reimbursed. FibroGENE is a biomarker panel based on age, biochemical markers and IL28B genotype. FibroTest is not yet available in Australia. Serum biomarkers may be used to exclude the presence of cirrhosis in settings where other tools, such as transient elastography, are not accessible in a timely fashion. **Supplementary Table 1** presents further information and key clinical thresholds for excluding the presence of cirrhosis in people using the serum biomarkers for liver fibrosis that are available in Australia.

It is important to remember that none of the methods for non-invasive assessment of liver fibrosis are perfectly accurate, and the results must be interpreted in the context of the pre-test probability based on other clinical information. For example, a 50-year-old obese man with a 30-year duration of HCV infection, a past history of heavy alcohol consumption, spider naevi evident on examination and a platelet count of 90×10^9/L is very likely to have cirrhosis, even if the liver stiffness measures 9.0 kPa using FibroScan. If there is concern about the accuracy of the liver fibrosis assessment, referral for further assessment for the presence of cirrhosis by a specialist with experience in assessing liver disease severity and managing patients with advanced liver disease is recommended. There is no routine role for liver biopsy. Liver biopsy is generally reserved for people in whom there is uncertainty about the underlying cause of liver disease, or where there is uncertainty about the liver fibrosis stage. Liver histology is not required for accessing antiviral therapy.

All individuals with cirrhosis should have a liver ultrasound to examine for features of portal hypertension (splenomegaly, reversal of portal vein flow) and to exclude HCC. Guidelines recommend gastroscopy for all people with cirrhosis to exclude the presence of clinically significant oesophageal varices before commencing therapy. Bone densitometry is recommended to screen for osteoporosis. Performance of these tests should not delay treatment for HCV infection, but may be scheduled simultaneously or after treatment.

In the setting of cirrhosis, it is also important to evaluate for markers of hepatic decompensation. Two key groups among those with cirrhosis are: i) people with Child–Pugh A cirrhosis who have a low albumin level (< 35 g/L) and/or platelets < 100×10^9/L (NS3 protease inhibitors should be avoided in these people due to concerns about increased intrahepatic drug concentrations and secondary toxicity); and ii) people with true decompensated liver disease — this group should be considered a special population (see Section 8). All individuals with decompensated liver disease should be assessed by a specialist with experience in managing chronic liver disease and, where appropriate, referred to a liver transplant centre. Indications for assessment by a liver transplant centre include Child–Pugh score ≥ B7, Model for End-Stage Liver Disease (MELD) score ≥ 13 or one of the following clinical events: refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, recurrent or chronic hepatic encephalopathy, small HCC or severe malnutrition (**Supplementary Table 2**[27]).

Due to the complexity of managing cirrhosis, it is recommended that these people are referred for assessment by a specialist who is an expert in the care of patients with chronic liver disease, and that they are treated in active collaboration with HCV treatment experts.

4.4 Consider concomitant medications for risk of drug–drug interactions

The pre-treatment assessment must also include an evaluation for potential drug–drug interactions between HCV DAAs and concomitant medications, including over-the-counter and recreational drugs. The University of Liverpool's Hepatitis Drug Interactions website (www.hep-druginteractions.org) is a very useful resource and contains regularly updated information.

4.5 Adherence to treatment

Adherence to treatment is important, and managing any condition or circumstance that may affect adherence to treatment is recommended before commencing DAA therapy for HCV. People with stable psychiatric conditions and/or stable injecting drug use are candidates for DAA treatment. People with no cirrhosis may continue to drink alcohol at low risk levels during treatment (no more than two standard drinks on any day[28]). Complete abstinence from alcohol is recommended for people with cirrhosis or people with alcohol dependence. People with high-risk alcohol use should be considered for management for alcohol dependence before DAA therapy.

Consensus recommendations	Grade
Assessment of comorbid conditions and liver disease cofactors should occur before commencing DAA therapy, and these conditions should be addressed before or concurrent with DAA therapy.	A1
Assessment of HCV RNA level (quantitative PCR) and HCV genotype should occur before making decisions regarding HCV therapy.	A1
Past HCV treatment experience should be documented, including regimen and response.	A1
Detecting cirrhosis is essential to identify people requiring long-term management of chronic liver disease, and also determines treatment duration for a number of DAA regimens.	A1
A non-invasive assessment of liver fibrosis is suitable for the majority of people.	A1
People with cirrhosis should be screened for complications including: • HCC (liver ultrasound) • oesophageal varices (gastroscopy) • osteoporosis (bone densitometry)	A1
All people with cirrhosis should be referred to, and managed in consultation with, a specialist familiar with the management of this condition.	A1
Vaccination against HVA and HVB is recommended for all susceptible individuals with HCV infection.	A1
All concomitant medications must be assessed for potential drug–drug interactions.	A1
Men and women of childbearing potential should be cautioned to avoid pregnancy while receiving DAA treatment.	B1
Men and women of childbearing potential should be cautioned to avoid pregnancy while receiving ribavirin-containing antiviral regimens, and for up to 6 months after stopping.	A1

5. Treatment for chronic hepatitis C

5.1 Goal of treatment

The goal of treatment is cure, or SVR, defined as undetectable plasma HCV RNA at least 12 weeks after treatment has ceased. SVR is associated with multiple clinical benefits, including improvement in quality of life, loss of infectivity, regression of liver fibrosis and cirrhosis, reduction in the risk of liver failure and HCC, and reduction in the risk of liver-related and all-cause mortality.

5.2 Indications for treatment

All people living with HCV should be considered for treatment, except those with limited life expectancy (< 12 months) due to non-liver or non-HCV-related comorbidities. Urgent consideration for treatment should be given to those with advanced liver fibrosis or cirrhosis.

5.3 Direct-acting antiviral agents

DAA agents that target multiple steps in the HCV replication life cycle have been developed and are highly effective, safe and require a short treatment duration. Virtually all patients are suitable for DAA therapy, including those previously intolerant of or ineligible for IFN therapy. Multiple DAAs have been approved by the Therapeutic Goods Administration (TGA) in Australia, including the NS3 protease inhibitor paritaprevir (ritonavir-boosted); the NS5B nucleotide inhibitor sofosbuvir; the NS5B non-nucleotide inhibitor dasabuvir; and the NS5A inhibitors ledipasvir, ombitasvir and daclatasvir. Several IFN-free regimens combining these DAAs have been PBS-listed for the treatment of people with Gt 1, 2 and 3 HCV and those with decompensated liver disease. The regimens are genotype-specific and each genotype will be considered individually. At the time of writing, treatment for Gt 4, 5 and 6 HCV continues to involve peginterferon-alfa (pegIFN) plus ribavirin. The treatment for HCV is evolving rapidly, and this Consensus Statement will be updated as new data emerge.

5.4 Regimens for chronic infection with genotype 1 HCV

As of 1 March 2016, there are two IFN-free DAA regimens that are available for PBS prescription for the treatment of Gt 1 HCV (**Table 3**):

i) sofosbuvir + ledipasvir

ii) sofosbuvir + daclatasvir ± ribavirin

A third IFN-free DAA regimen has been TGA-approved and is expected to be available for PBS prescription for the treatment of Gt 1 HCV before mid 2016. Although the exact date of PBS availability was not available at the time of writing, this regimen has been included in the Consensus Statement:

iii) paritaprevir (ritonavir-boosted) + ombitasvir + dasabuvir ± ribavirin

These three well tolerated regimens have efficacy ≥ 95% across all patient groups, including people with cirrhosis and those who have not responded previously to pegIFN plus ribavirin therapy.

There are other IFN-free DAA regimens that are currently under consideration by the TGA/Pharmaceutical Benefits Advisory Committee (PBAC) for the treatment of Gt 1 HCV. The timelines for PBS availability of these regimens remain unclear, and they will be included in updated versions of this Consensus Statement once available.

5.4.1 Sofosbuvir plus ledipasvir

Sofosbuvir plus ledipasvir is a coformulated, once-daily, single-pill regimen. The recommended treatment duration is 12 weeks, except for people with cirrhosis who have not responded to pegIFN therapy, who should receive treatment for 24 weeks (**Table 3**).[25,26] Rates of SVR ≥ 95% are achieved in all patient groups, including those with cirrhosis and non-responders to first-generation protease inhibitor therapy (**Table 3**).[25,26] Response rates are similar for Gt 1a and Gt 1b HCV. A shortened treatment duration of 8 weeks may be considered in treatment-naive people with no cirrhosis who have

Table 3. Treatment protocols for people with compensated liver disease and hepatitis C virus (HCV) genotype (Gt) 1 infection, including people with HCV–HIV coinfection

		Treatment duration				
		No cirrhosis		Cirrhosis		
Regimen	HCV Gt	Treatment-naive	Treatment-experienced*	Treatment-naive	Treatment-experienced*	Efficacy (SVR)
Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily	1a/b	8 weeks OR 12 weeks‡	12 weeks§	12 weeks	24 weeks§	≥ 95%
Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily† ± Ribavirin 1000/1200 mg, orally, daily (weight-based)††	1a/b	12 weeks	12 weeks OR 24 weeks¶	12 weeks + ribavirin OR 24 weeks (no ribavirin)	12 weeks + ribavirin OR 24 weeks (no ribavirin)¶	≥ 95%
Paritaprevir–ritonavir (150 mg/100 mg), orally, daily + Ombitasvir 25 mg, orally, daily + Dasabuvir 250 mg, orally, twice daily ± Ribavirin 1000/1200 mg, orally, daily (weight-based)††	1a	12 weeks + ribavirin	12 weeks + ribavirin	12 weeks + ribavirin	12 or 24 weeks + ribavirin**	≥ 95%
	1b	12 weeks	12 weeks	12 weeks	12 weeks	

HIV = human immunodeficiency virus. SVR = sustained virological response at least 12 weeks after treatment. PBS = Pharmaceutical Benefits Scheme. pegIFN = peginterferon-alfa. PrOD = paritaprevir (ritonavir-boosted) + ombitasvir + dasabuvir.

* Treatment experience may include a number of different treatment regimens; PBS eligibility and recommended duration for specific regimens varies according to the treatment history.

† Daclatasvir dose modification is required when used in combination with specific antiretroviral therapies for HIV (see Section 10.3.3).

‡ 8 weeks may be considered if HCV RNA level is $< 6 \times 10^6$ IU/mL in people with no cirrhosis who are treatment-naive.

§ Sofosbuvir + ledipasvir can be used to treat people in whom either pegIFN + ribavirin dual therapy or protease inhibitor + pegIFN + ribavirin triple therapy has failed.

¶ Sofosbuvir + daclatasvir (no ribavirin) for 12 weeks is recommended for people with no cirrhosis in whom pegIFN + ribavirin or sofosbuvir + ribavirin has previously failed; 24 weeks (no ribavirin) is recommended for people with cirrhosis in whom pegIFN + ribavirin has previously failed; 24 weeks (no ribavirin) is recommended for all people in whom a protease inhibitor + pegIFN + ribavirin has failed.

** The recommended treatment duration for PrOD plus ribavirin in people with Gt 1a HCV and cirrhosis who have had a previous null response to pegIFN and ribavirin therapy is 24 weeks. PrOD therapy is not recommended for people who did not respond to previous therapy that included an HCV protease inhibitor or an NS5A inhibitor.

†† Ribavirin dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg.

Notes: For Gt 1 HCV patients in whom treatment with a protease inhibitor + pegIFN + ribavirin has failed, the preferred treatment is sofosbuvir + ledipasvir or sofosbuvir + daclatasvir. Sofosbuvir is not recommended for patients with an estimated glomerular filtration rate < 30 mL/min/1.73 m^2. At the time of writing, the combination of PrOD ± ribavirin was approved by the Therapeutic Goods Administration but not yet available for prescription under the PBS. Dose reduction or dose interruption of direct-acting antiviral therapy is not recommended. Dose reduction of ribavirin for the management of symptomatic anaemia according to the product information is appropriate and will not reduce the likelihood of SVR.

baseline HCV RNA levels < 6×10^6 IU/mL.[29] Baseline HCV RNA levels ≥ 6×10^6 IU/mL are associated with higher relapse rates with 8 versus 12 weeks of treatment (10% v 1%).[29] Caution is recommended when considering an 8-week treatment course in those who are eligible but have other adverse prognostic factors, particularly advanced (stage F3) liver fibrosis. In people with cirrhosis who have not responded to pegIFN-based therapy, recent data suggest that outcomes are similar when comparing 24 weeks of treatment with sofosbuvir plus ledipasvir versus 12 weeks with sofosbuvir plus ledipasvir plus ribavirin.[30] Note that the combination of sofosbuvir, ledipasvir and ribavirin is not currently available on the PBS. Combination sofosbuvir and ledipasvir is safe even with decompensated cirrhosis (see Section 8). Fatigue, headache and nausea are the most common adverse effects, but are uncommon and typically mild.[25,26,29] Sofosbuvir, and its main metabolite GS-331007, are renally excreted. As safety data are lacking in people with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, sofosbuvir is not recommended in this setting (see Section 12.2).

5.4.2 Sofosbuvir plus daclatasvir, with or without ribavirin

Sofosbuvir plus daclatasvir therapy is available for PBS prescription as a first-line treatment for HCV Gt 1 HCV.[31,32] SVR rates are ≥ 95%. The recommended treatment duration is 12 weeks for people with no cirrhosis who are treatment-naive, or in whom treatment with pegIFN and ribavirin has previously failed (**Table 3**). People with cirrhosis are harder to cure and should be treated with either sofosbuvir plus daclatasvir plus ribavirin for 12 weeks, or sofosbuvir plus daclatasvir (no ribavirin) for 24 weeks. Sofosbuvir plus daclatasvir (no ribavirin) for 24 weeks is the recommended treatment for people with or without cirrhosis who have not responded to prior treatment with a protease inhibitor plus pegIFN and ribavirin (**Table 3**). Sofosbuvir plus daclatasvir is well tolerated, with low (≤ 1%) discontinuation rates due to adverse events. The most common treatment-related adverse effects are fatigue, headache and nausea; again, these are typically infrequent and mild. Addition of ribavirin increases the frequency of adverse reactions, as outlined in Section 5.4.4.

5.4.3 Paritaprevir–ritonavir, ombitasvir and dasabuvir ± ribavirin

The regimen of paritaprevir (ritonavir-boosted), ombitasvir and dasabuvir (PrOD) in combination is used with ribavirin for HCV Gt 1a, or without ribavirin for HCV Gt 1b (**Table 3**).[33-37] At the time of writing, this regimen was not yet available for prescription under the PBS. Treatment is for 12 weeks, except for Gt 1a patients with cirrhosis and prior null response to pegIFN plus ribavirin; this group should receive treatment for 24 weeks. SVR rates ≥ 95% are observed in all groups treated according to the label. PrOD therapy is not recommended for prior non-responders to protease inhibitor therapy due to concern about reduced efficacy of paritaprevir. The regimen should be used with caution in people with compensated cirrhosis and is contraindicated in patients with decompensated cirrhosis and/or prior history of liver decompensation. Caution is recommended because of the unlikely but real possibility of drug-induced liver injury associated with this regimen. No dosage adjustment of any components of this regimen is required in patients with renal impairment. However, ribavirin dose adjustment is required for patients with renal impairment (see Section 12).

PrOD is well tolerated, with low (≤ 1%) discontinuation rates.[33] The most commonly reported adverse effects are nausea, pruritus and insomnia; these are uncommon and mild in most people. Serum alanine aminotransferase (ALT) level rises of > 5 times the upper limit of normal (ULN) are observed in approximately 1% of patients and typically occur during the first 4 weeks of therapy. Rises in ALT level are more common in women taking ethinyl estradiol-containing medication, and this should be stopped before starting treatment. Alternative contraceptive agents (eg, progestin-only contraception) or methods (eg, non-hormonal contraceptive method) are recommended. ALT level elevations generally occur without bilirubin elevation and resolve with ongoing treatment. Around 2% of patients receiving this treatment (15% in those taking concomitant

ribavirin) have developed transient hyperbilirubinaemia > 2 × ULN, due to paritaprevir-induced inhibition of biliary transporters. Bilirubin elevations typically occur early (peak, Weeks 1–2), are not associated with serum ALT elevations and generally resolve with ongoing therapy. Elevation of ALT above baseline and/or elevation of bilirubin > 2 × ULN during treatment should prompt close monitoring of liver function test results, and specialist opinion.

5.4.4 Ribavirin-related adverse events

Adverse events associated with ribavirin therapy include anaemia, rash, cough, dyspnoea, insomnia and anxiety. The mean reduction in haemoglobin level associated with PrOD plus ribavirin is 2.4 g/dL. It is important that ribavirin is started at the full recommended starting dose according to eGFR. Dose reduction of ribavirin in the setting of symptomatic anaemia is appropriate according to the product information and will not reduce the likelihood of SVR.

Ribavirin is teratogenic and therefore both women and men should be counselled about the risks of pregnancy. Both women and men should be counselled that two forms of contraception are recommended while taking ribavirin and for 6 months after treatment. As noted, ethinyl estradiol-containing contraceptives should not be used in combination with PrOD; alternative contraceptive agents or methods are recommended. Ribavirin is renally excreted and dose adjustment is required according to eGFR (see Section 12).

5.4.5 Peginterferon-containing regimens

Treatment of Gt 1 HCV with an NS3 protease inhibitor (simeprevir, telaprevir or boceprevir) combined with pegIFN plus ribavirin is no longer standard-of-care, and these treatment regimens are actively discouraged because of the lower rates of efficacy, longer treatment duration and higher toxicity profile (see Section 5.8). Treatment with sofosbuvir plus pegIFN plus ribavirin for 12 weeks' duration is also available for prescription under the PBS, but is not recommended as a first-line treatment. Although there are no head-to-head comparisons with IFN-free DAA treatments, the SVR rates observed in clinical trials evaluating sofosbuvir plus pegIFN plus ribavirin were lower than those observed in studies that evaluated the TGA-approved IFN-free treatments for Gt 1 HCV.[38]

5.5 Regimens for chronic infection with genotype 2 HCV

5.5.1 Sofosbuvir plus ribavirin

The IFN-free treatment regimen for HCV Gt 2 available for prescription under the PBS is sofosbuvir plus ribavirin for 12 weeks (**Table 4**). This regimen is highly effective in people with no cirrhosis, with overall cure rates of 90%–95%.[38-41] The optimal treatment duration for people with cirrhosis remains unclear, with current evidence suggesting treatment extension to at least 16 weeks may increase SVR rates. Evidence for this comes from data for treatment-experienced people with Gt 2 HCV and cirrhosis, in whom treatment extension from 12 to 16 weeks improved SVR rates from 60% to 78%.[39] A subsequent study in the same population demonstrated a non-significant trend for higher SVR rates with treatment extension to 24 weeks (16 v 24 weeks: SVR, 87% v 100%).[41] However, although extending treatment duration to 24 weeks in people with cirrhosis may increase SVR rates, treatment duration for longer than 12 weeks is not currently available under the PBS. Treatment is well tolerated, with the adverse event profile typical for ribavirin.

5.6 Regimens for chronic infection with genotype 3 HCV

Genotype 3 HCV is harder to cure than Gt 1 or 2 HCV using DAA therapy, particularly in people with cirrhosis and prior non-responders to pegIFN plus ribavirin. The IFN-free treatment regimens available for prescription under the PBS for Gt 3 HCV include sofosbuvir plus daclatasvir for 12 or 24 weeks, and sofosbuvir plus ribavirin for 24 weeks (**Table 4**).[40,42,43] Ledipasvir is less effective against Gt 3 HCV, so is not recommended in this setting. Sofosbuvir is also available for prescription under the PBS in combination with pegIFN plus ribavirin as a 12-week treatment regimen.

5.6.1 Sofosbuvir plus daclatasvir

Combination therapy with sofosbuvir and daclatasvir for 12 weeks in people with Gt 3 HCV infection and no cirrhosis is very effective, with SVR rates of 94%–97%.[43] Lower SVR rates of 58%–69% are observed in those with cirrhosis, regardless of treatment history.[43] Therefore, for people with Gt 3 HCV and cirrhosis, it is recommended that treatment

Table 4. Treatment protocols for people with compensated liver disease and hepatitis C virus (HCV) genotype (Gt) 2 or 3 infection, including people with HCV–HIV coinfection

		Treatment duration				
		No cirrhosis		Cirrhosis		
Regimen	HCV Gt	Treatment-naive	Treatment-experienced*	Treatment-naive	Treatment-experienced*	Efficacy (SVR)
Sofosbuvir 400 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily (weight-based)**	2	12 weeks	12 weeks§	12 weeks	12 weeks§	> 90%
Sofosbuvir 400 mg, orally, daily + Daclatasvir, 60 mg, orally, daily†	3	12 weeks	12 weeks¶	24 weeks	24 weeks¶	> 85%
Sofosbuvir 400 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily (weight-based)**	3	24 weeks	24 weeks§	24 weeks	24 weeks§	58%–95%‡
Sofosbuvir 400 mg, orally, daily + PegIFN, subcutaneously, weekly + Ribavirin 1000/1200 mg, orally, daily (weight-based)**	3	12 weeks	12 weeks	12 weeks	12 weeks	> 85%

SVR = sustained virological response at least 12 weeks after treatment. PBS = Pharmaceutical Benefits Scheme. pegIFN = peginterferon-alfa.

* Treatment experience may include a number of different treatment regimens; PBS eligibility and recommended duration for specific regimens varies according to the treatment history.

† Daclatasvir dose modification is required when used in combination with specific antiretroviral therapies for human immunodeficiency virus (HIV; see text).

‡ SVR rates vary from 90%–95% for treatment-naive individuals with no cirrhosis to 58%–76% for treatment-experienced individuals with cirrhosis.

§ Sofosbuvir + ribavirin can be used to treat people with Gt 2 or Gt 3 HCV in whom pegIFN + ribavirin dual therapy has failed.

¶ Sofosbuvir + daclatasvir (no ribavirin) for 12 weeks is recommended for people with no cirrhosis in whom pegIFN + ribavirin or sofosbuvir + ribavirin has previously failed; 24 weeks (no ribavirin) is recommended for people with cirrhosis in whom pegIFN + ribavirin or sofosbuvir + ribavirin has previously failed.

** Ribavirin dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg.

Notes: Dose reduction or dose interruption of direct-acting antiviral therapy is not recommended. Dose reduction of ribavirin for the management of symptomatic anaemia according to the product information is appropriate and will not reduce the likelihood of SVR.

be extended to 24 weeks (**Table 4**). Evidence supporting treatment extension comes from a French multicentre compassionate access program, which reported an SVR rate of 86% in patients with Gt 3 HCV infection and cirrhosis who were treated for 24 weeks with sofosbuvir plus daclatasvir.[44] Recent data suggest that sofosbuvir plus daclatasvir plus ribavirin for 12 weeks may have similar efficacy in people with cirrhosis. The ALLY-3+ Study reported an overall SVR rate of 90% in people with advanced fibrosis or cirrhosis treated for 12 or 16 weeks with sofosbuvir plus daclatasvir plus ribavirin.[45] The SVR rate in the cirrhosis subgroup was 86%. SVR rates were similar with 12 or 16 weeks' treatment duration. Note that the combination of sofosbuvir plus daclatasvir plus ribavirin is not currently available on the PBS for the treatment of Gt 3 HCV (**Table 4**).

5.6.2 Sofosbuvir plus ribavirin

Sofosbuvir plus ribavirin combination therapy for 24 weeks is also PBS-approved for the treatment of Gt 3 HCV infection. In large Phase III studies, treatment with this regimen for 24 weeks achieved superior SVR rates to those with 12 or 16 weeks' therapy.[39,40] SVR rates after 24 weeks of sofosbuvir plus ribavirin are 90%–95% in treatment-naive people with no cirrhosis, and 58%–76% in treatment-experienced people with cirrhosis.[40,41] Thus, this is not the preferred regimen for people with Gt 3 HCV and cirrhosis, particularly those who are treatment-experienced.

5.6.3 Sofosbuvir plus peginterferon-alfa plus ribavirin

Data from a prospective, randomised Phase III trial demonstrate that triple therapy with sofosbuvir plus pegIFN plus ribavirin for 12 weeks is very effective for the treatment of Gt 3 HCV. This regimen is more effective than 16 or 24 weeks of sofosbuvir plus ribavirin, including among treatment-experienced people with cirrhosis, but it is associated with pegIFN-related toxicity.[41] This triple regimen is likely to be most useful as salvage therapy for the minority of people with Gt 3 HCV in whom first-line DAAs fail (**Table 4**).

5.7 Regimens for chronic infection with genotypes 4, 5 and 6 HCV

The treatment regimen for HCV Gt 4, 5 and 6 that is currently available for prescription under the PBS is the combination of sofosbuvir plus pegIFN and ribavirin for 12 weeks (**Table 5**). In a Phase III study of treatment-naive individuals, this regimen was associated with SVR rates of 96%–100% in a relatively small number of patients with Gt 4, 5 and 6 HCV infection.[38]

There are no IFN-free treatment regimens for Gt 4–6 HCV currently available on the PBS in Australia. The combinations of sofosbuvir plus ribavirin, and sofosbuvir plus ledipasvir are effective for Gt 4,[46-48] while the combination of sofosbuvir plus ledipasvir is effective for Gt 6 HCV.[49] Paritaprevir–ritonavir plus ombitasvir plus ribavirin is also effective for Gt 4 HCV.[50] It is likely that these regimens will be approved in Australia in the future.

5.8 Peginterferon-alfa-related adverse events

Peginterferon-alfa-based therapy is associated with considerable morbidity, resulting in many people being pegIFN-ineligible or intolerant, or unwilling to use it. Intensive on-treatment monitoring is required. The most common adverse effects of pegIFN include influenza-like symptoms (fevers, lethargy and myalgia), fatigue, bone marrow suppression, mood disturbance and alopecia. Less frequently, severe cytopaenia, major depression and psychosis may occur. PegIFN is contraindicated in people with: untreated major depression or psychosis; significant immune-mediated disease (eg, inflammatory arthritis, lupus, ulcerative colitis); and decompensated liver disease (Child–Pugh B and C). PegIFN-based treatment may precipitate hepatic decompensation in people with advanced liver disease; a platelet count $< 100 \times 10^9$/L and albumin level < 35 g/dL identify those at highest risk.[51] Thus, treatment should only be considered within a specialised centre. Despite the significant adverse event profile, the discontinuation rate among patients treated with 12 weeks of sofosbuvir plus pegIFN and ribavirin was only 2%,[38] similar to that reported for IFN-free regimens.

Table 5. Treatment protocols for people with compensated liver disease and hepatitis C virus (HCV) genotype (Gt) 4, 5 or 6 infection, including people with HCV–HIV coinfection

		Treatment duration				
		No cirrhosis		Cirrhosis		
Regimen	HCV Gt	Treatment-naive	Treatment-experienced*	Treatment-naive	Treatment-experienced*	Efficacy (SVR)
Sofosbuvir 400 mg, orally, daily + Peginterferon-alfa, subcutaneously, weekly + Ribavirin 1000/1200 mg, orally, daily (weight-based)‡	4, 5, 6	12 weeks	12 weeks	12 weeks	12 weeks	> 90%†

HIV = human immunodeficiency virus. SVR = sustained virological response at least 12 weeks after treatment.

* Treatment-experienced refers to prior peginterferon-alfa + ribavirin dual therapy.

† Of 35 treatment-naive patients with Gt 4, 5 or 6 HCV enrolled in the NEUTRINO study, 34 (97%) achieved SVR.[38] Treatment-experienced patients were not enrolled in the NEUTRINO study.

‡ Ribavirin dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg.

Notes: Dose reduction or dose interruption of direct-acting antiviral therapy is not recommended. Dose reduction of ribavirin for the management of symptomatic anaemia according to the product information is appropriate and will not reduce the likelihood of SVR.

5.9 Drug–drug interactions

Drug–drug interactions are a potential issue for all IFN-free treatment regimens. Important drugs to consider for potential interactions with DAAs include proton pump inhibitors, statins, St John's wort, antimicrobials, anti-epileptic agents, amiodarone, immunosuppressive agents including cyclophilin inhibitors and mammalian target of rapamycin (mTOR) inhibitors, and antiretroviral agents. Notably, the combination of sofosbuvir with a second DAA for the treatment of HCV is contraindicated with concomitant use of amiodarone due to the risk of severe symptomatic bradycardia. It is strongly recommended that concomitant medications be reviewed before starting treatment for any person, using the University of Liverpool's Hepatitis Drug Interactions website (www.hep-druginteractions.org). We recommend working with an experienced pharmacist to confirm the safety of concomitant medications before starting DAA regimens. Patients should be advised to seek advice before starting any new medication during DAA therapy.

5.10 Pregnancy, breastfeeding and children

There are no safety data for the use of any DAA regimen during pregnancy, with all PBS-listed DAA regimens classed as Category B (sofosbuvir, B1; ledipasvir, B1; daclatasvir, B3; PrOD, B3) for their risk in pregnancy. Treatment of pregnant women with DAA therapy is therefore not recommended. All DAA regimens are contraindicated in pregnancy when combined with ribavirin (Category X), with or without pegIFN. As noted, ribavirin requires contraceptive precautions. People treated with ribavirin should be counselled about the risk of teratogenicity and the importance of not becoming pregnant during treatment or for 6 months after treatment. The safety of the listed DAA regimens during lactation has not yet been established, and treatment of women who are breastfeeding is therefore not recommended. Children under the age of 18 years are not currently eligible for treatment with the new HCV medications under the PBS. Studies in paediatric populations are ongoing. People under the age of 18 years should be referred to a paediatrician

who is experienced in the treatment of HCV for discussion about therapy.

5.11 Direct-acting antivirals and drug resistance

Resistance-associated variants (RAVs) have been identified in vitro for all of the DAAs approved for clinical use. NS3 and NS5A RAVs may arise spontaneously due to the error-prone HCV RNA polymerase and therefore are present before DAA therapy. NS3 and NS5A RAVs are selected during DAA therapy and enriched in people in whom treatment fails with NS3 and NS5A inhibitor-containing regimens, respectively. NS5B RAVs have been reported but are very rare. Despite this, there is currently no clinical role for baseline HCV resistance testing in treatment-naive people or prior non-responders to either pegIFN-based therapy or protease inhibitor-based triple therapy, because high SVR rates are achieved with all the approved DAA regimens. Resistance testing for NS3, NS5B and NS5A RAVs should be considered following failure of combination DAA treatment, to guide salvage therapy. Resistance testing involves direct sequencing of the HCV genome and is available through specialised laboratories. HCV sequencing may also identify cases of reinfection. Patients in whom combination DAA therapy fails should be managed in specialist centres.

5.12 Salvage therapy

5.12.1 People with Gt 1 HCV who did not respond to treatment with a protease inhibitor plus peginterferon-alfa plus ribavirin

The preferred regimen for people with Gt 1 HCV who did not respond to treatment with a protease inhibitor plus pegIFN plus ribavirin is the combination of sofosbuvir plus ledipasvir, or the combination of sofosbuvir plus daclatasvir (**Table 3**). Response rates are similar to those observed in treatment-naive individuals.

5.12.2 Non-responders to interferon-free therapy

The combination of sofosbuvir plus daclatasvir can be prescribed for treating people with Gt 3 HCV in whom previous treatment with sofosbuvir plus ribavirin has failed. In people with no cirrhosis, the recommended treatment duration is 12 weeks; in people with cirrhosis, the recommended treatment duration is 24 weeks. The combination of sofosbuvir plus pegIFN plus ribavirin for 12 weeks can also be used to treat people with Gt 3 HCV (with or without cirrhosis) who did not respond to previous treatment. For other situations, current PBS restrictions do not prohibit patients receiving retreatment with a different IFN-free regimen. However, the evidence to support the use of regimens currently available under the PBS for salvage treatment of Gt 1 HCV is limited, and it is recommended that all individuals in whom first-line DAA therapy fails be referred to a specialist centre where there is greater access to evolving salvage treatment strategies and HCV resistance testing to help guide the choice of therapy.

Consensus recommendations	Grade
All individuals with chronic HCV infection should be considered for antiviral therapy.	A1
Choice of treatment regimen should be based on: • HCV genotype and subtype • the presence or absence of cirrhosis • the presence or absence of liver decompensation • prior treatment history • the potential for drug–drug interactions • comorbidities	A1
First-line treatment regimens for chronic Gt 1 HCV infection and compensated liver disease include (see Table 3): • sofosbuvir + ledipasvir for 8 or 12 or 24 weeks • sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks • paritaprevir–ritonavir + ombitasvir + dasabuvir ± ribavirin for 12 or 24 weeks*	A1
The first-line treatment regimen for chronic Gt 2 HCV infection and compensated liver disease is (see Table 4): • sofosbuvir + ribavirin for 12 weeks	A1
First-line treatment regimens for chronic Gt 3 HCV infection and compensated liver disease include (see Table 4): • sofosbuvir + daclatasvir for 12 or 24 weeks • sofosbuvir + ribavirin for 24 weeks • sofosbuvir + pegIFN + ribavirin for 12 weeks (second-line)	A1
The current first-line treatment for chronic Gt 4–6 HCV infection and compensated liver disease is (see Table 5): • sofosbuvir + pegIFN + ribavirin for 12 weeks	B1
Dose reduction or dose interruption of DAA therapies is not recommended.	A1
Dose reduction of ribavirin for the management of symptomatic anaemia according to the product information is appropriate and will not reduce the likelihood of SVR.	A1
DAA therapies for HCV should not be used in combinations other than those that have demonstrated efficacy in prospective clinical trials.	B1
People in whom first-line DAA therapy fails should be referred to a specialist centre for consideration of salvage therapy.	B1

* At the time of writing, the combination of paritaprevir–ritonavir + ombitasvir + dasabuvir ± ribavirin was TGA-approved but not yet available for prescription on the PBS (anticipated to be available for prescription on the PBS before mid 2016).

6. On-treatment monitoring

In contrast to IFN-based treatment regimens, intense monitoring of people undergoing DAA therapy is usually unnecessary. This simplification recognises the high efficacy of these regimens, the lack of a role for response-guided therapy, and the considerably improved side effect profile. During treatment, follow-up intervals need to be established on a case-by-case basis to optimise adherence, assess adverse events and potential drug–drug interactions, and monitor blood test results necessary for patient safety (**Table 6**). All patients should be provided with contact details for a clinician to contact if problems arise in between appointments. For many people, one assessment at Week 4 of treatment will be sufficient during an 8-week or 12-week treatment course. Patients treated with ribavirin require monitoring of haemoglobin levels. More intensive monitoring is warranted for people in whom adherence is a concern, those with risk factors for ribavirin intolerance (eg, cardiac disease) or who develop ribavirin-induced anaemia, or people with advanced liver disease (portal hypertension or hepatic decompensation). In this setting, repeat liver function tests at Week 2 and Week 4 of therapy are advisable to monitor for medication adherence and early evidence of hepatic decompensation related to drug reaction. Calculation of MELD and Child–Pugh scores, as well as measurement of body weight, is useful for detecting deteriorating liver function or ascites in people with cirrhosis.

Almost all people treated with DAA regimens attain undetectable HCV RNA levels during therapy. There are no response-guided DAA treatment protocols. Therefore, routine on-treatment and end-of-treatment virological assessments are not required, but may be considered if there are concerns regarding adherence to therapy or in people who have had prior DAA exposure. Note that low levels of plasma HCV RNA at Week 4 of treatment can be detected in up to 20% of people using sensitive PCR assays, but this does not predict for treatment failure, nor does it require treatment extension. Failure to achieve an SVR with DAA therapy is rare but may be due to poor adherence to therapy, viral relapse or, rarely, post-treatment reinfection.

Consensus recommendations	Grade
On-treatment monitoring for medication adherence, side effects and hepatic function should be performed.	A1
Routine on-treatment HCV PCR testing is not required as it is unlikely to change management. Quantitative HCV PCR testing should be considered if there are concerns about DAA adherence or viral resistance.	B1
Qualitative HCV PCR testing at the end of treatment is reasonable to confirm an end-of-treatment response; however, given the high efficacy of DAA therapy, such monitoring is not mandated in all individuals.	C2

Table 6. Monitoring of patients receiving antiviral therapy for hepatitis C virus (HCV) infection: (A) on-treatment and post-treatment monitoring for virological response; and (B) monitoring after SVR

A. On-treatment and post-treatment monitoring for virological response	
Routine monitoring for a 12-week treatment regimen:	
Week 0	• FBE, urea and electrolytes, LFTs, INR, HCV RNA level (quantitative)
Week 4	• FBE, LFTs
Week 12 ± 24 (EOT)	• FBE, LFTs, HCV PCR (qualitative)
	• At each on-treatment visit, assess for: ▸ medication adherence ▸ treatment adverse effects ▸ drug–drug interactions
Week 12 after EOT (SVR)	• FBE, LFTs, HCV PCR (qualitative)

- Routine on-treatment HCV RNA testing is not mandated but may be considered where there is a clinical concern about non-adherence to treatment, especially in people with cirrhosis.
- The need for increased frequency of review should be individualised.
- Patients taking ribavirin may require FBE at Week 2 and Week 4 and then every 4 weeks.
- Patients with cirrhosis require monitoring every 4 weeks, including FBE, LFTs and assessment for hepatic decompensation. Measurement of quantitative HCV RNA level is recommended at Weeks 4, 12 ± 24 on-treatment in patients with cirrhosis.
- Patients with decompensated liver disease require close monitoring, with review every 2–4 weeks.

B. Monitoring after SVR

SVR, no cirrhosis and normal LFT results (males, ALT < 30 U/L; females, ALT < 19 U/L):

- Patients who are cured do not require clinical follow-up for HCV

SVR and abnormal LFT results (males, ALT ≥ 30 U/L; females, ALT ≥ 19 U/L):

- Patients with persistently abnormal LFT results require evaluation for other liver diseases and should be referred for gastroenterology review. Investigations to consider include: fasting glucose level, fasting lipid levels, iron studies, ANA, ASMA, anti-LKM antibodies, total IgG and IgM, AMA, coeliac serology, copper level, caeruloplasmin level and α-1-antitrypsin level

SVR, cirrhosis:

- Patients with cirrhosis require long-term monitoring and should be enrolled in screening programs for:
  - hepatocellular carcinoma — liver ultrasound ± serum α-fetoprotein level
  - oesophageal varices — gastroscopy
  - osteoporosis — dual emission x-ray absorptiometry

EOT = end of treatment. SVR = sustained virological response at least 12 weeks after treatment (cure). FBE = full blood examination. LFT = liver function test. INR = international normalised ratio. PCR = polymerase chain reaction. ALT = alanine aminotransferase. ANA = anti-nuclear antibodies. ASMA = anti-smooth muscle antibodies. LKM = liver–kidney microsome. AMA = anti-mitochondrial antibody.

7. Post-treatment follow-up

7.1 Confirm SVR

Successful viral eradication is defined as undetectable plasma HCV RNA using a highly sensitive PCR assay 12 weeks after completion of DAA therapy (SVR). This time point has shown excellent correlation with the previously used SVR24.[52] Late relapse after SVR is very uncommon (< 0.5%), and the reappearance of HCV after this time point is most frequently due to reinfection. People who do not have cirrhosis and who have normal liver function test results after SVR (males, ALT < 30 U/L; females, ALT < 19 U/L) have no further need of specialist liver services and can be medically managed as if they never had HCV infection. There is no reason to repeat anti-HCV serological tests. It should be reiterated to all people who have achieved an SVR that persistence of anti-HCV antibodies is expected and that this does not represent active infection, nor does it confer immunity to reinfection.

Those who fail to achieve an SVR should be assessed for explanations for treatment failure (especially adherence, drug resistance and reinfection). Retreatment should be considered as appropriate. In this setting, referral to an expert treatment centre is advisable.

7.2 Long-term management of liver disease

Individuals whose liver function test results remain abnormal should be assessed by a specialist for alternative causes of liver disease (**Table 6**). All people with cirrhosis need to enter appropriate surveillance programs for HCC and oesophageal varices as recommended by existing guidelines.[53-55] In addition, complications of chronic liver disease, including malnutrition and osteoporosis, should be addressed.

Consensus recommendations	Grade
HCV qualitative PCR should be performed 12 weeks after cessation of DAA therapy.	A1
People with cirrhosis should continue in long-term variceal and HCC surveillance programs.	A1
People with no cirrhosis who achieve SVR and normal liver function test results should be medically managed as individuals who have never had HCV infection.	B1
People with persistently abnormal liver function test results after SVR should undergo further assessment and monitoring for alternative causes of liver disease.	A1

8. Special populations: treatment of decompensated liver disease

All individuals with decompensated liver disease must be assessed and managed in specialist centres. Typical clinical presentations of liver decompensation include variceal haemorrhage, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, hepatopulmonary syndrome and jaundice. All predict a poor prognosis. Multiple scoring systems have been proposed to predict prognosis for people with chronic liver disease, the most well known being the Child–Pugh score (based on degree of ascites, encephalopathy, serum bilirubin level, albumin level and INR) and the MELD score (based on serum bilirubin level, creatinine level and INR) (**Supplementary Table 2**). These scoring systems have clinical utility for predicting short-term mortality and for prioritising individuals on liver transplant waiting lists.

Liver transplantation provides excellent outcomes for patients with decompensated cirrhosis or early-stage HCC. People who are not referred until they have severe liver failure may not be suitable for transplantation, so early referral is advisable. Consider referring people to a transplant team if they have refractory ascites, an episode of spontaneous bacterial peritonitis or hepatorenal syndrome, recurrent or chronic hepatic encephalopathy, small HCCs or significant malnutrition. Additionally, people should be referred to a transplant team if they are eligible for liver transplantation and have a Child–Pugh score ≥ B7 or MELD score ≥ 13.

Contraindications to liver transplantation may include advanced HCC, extrahepatic malignancy, uncontrolled extrahepatic infection, active alcohol or substance misuse, significant coronary or cerebrovascular disease or inadequate social support. For more information about liver transplantation, see the DonateLife website.[56]

In people with decompensated liver disease, the goal of therapy is SVR, with the aim of improving liver function. The eligibility criteria for DAA regimens that have recently been PBS-listed for the treatment of HCV do not distinguish between people with compensated versus decompensated liver disease, with the exception of PrOD, which is contraindicated in the setting of hepatic decompensation (Child–Pugh score B or C). Therefore, people with decompensated liver disease are eligible to have the same treatment regimens prescribed under the PBS, according to HCV genotype and treatment history (**Table 7**). It should be noted, however, that people with decompensated liver disease were not enrolled in the key registration studies used to define the product labels; that data specific to this important population continue to emerge; and that regimens that have been evaluated for this population have not always been identical to those trialled in patients with compensated liver disease. Some of the recommendations for this population are based on expert opinion.

The efficacy of a number of DAA regimens in people with decompensated liver disease has been formally evaluated in recent clinical trials.[57-63] Current data support the combination of sofosbuvir plus ledipasvir plus ribavirin for 12 weeks as the first-line regimen for Gt 1 HCV, with ribavirin started at a low oral dose of 600 mg daily. This regimen was evaluated for 12 versus 24 weeks in the SOLAR-1/2 studies — there was no benefit of extending treatment to 24 weeks.[58] However, the combination of sofosbuvir plus ledipasvir plus ribavirin cannot currently be prescribed under the PBS. Early access programs suggest that treatment with sofosbuvir plus ledipasvir (no ribavirin) for 24 weeks has similar efficacy; this regimen is currently available under the PBS and can be recommended as a reasonable alternative (**Table 7**). Alternative regimens that have demonstrated efficacy for the treatment of Gt 1 HCV include the combination of sofosbuvir plus daclatasvir plus ribavirin for 12 weeks, or sofosbuvir plus daclatasvir (no ribavirin) for 24 weeks, both of which can also be prescribed under the PBS (**Table 7**). The rates of SVR observed using these regimens for

Table 7. Treatment protocols before liver transplantation for hepatitis C virus (HCV) infection in people with decompensated liver disease

HCV Gt	Treatment regimen	Duration	PBS listing
1	Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	The combination of sofosbuvir + daclatasvir with ribavirin is PBS-listed for Gt 1 HCV in people with cirrhosis
1	Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	Ribavirin is not PBS-listed for use in combination with sofosbuvir + ledipasvir
3	Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily + Ribavirin 600 mg, orally, daily*	24 weeks	Ribavirin is not PBS-listed for use in combination with sofosbuvir + daclatasvir for the treatment of Gt 3 HCV
2	Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	The combination of sofosbuvir + daclatasvir with ribavirin is not PBS-listed for the treatment of Gt 2 HCV
4, 6	Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	The combination of sofosbuvir + ledipasvir with ribavirin is not PBS-listed for the treatment of Gt 4 or 6 HCV
4–6	Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	The combination of sofosbuvir + daclatasvir with ribavirin is not PBS-listed for the treatment of Gt 4–6 HCV

Gt = genotype. PBS = Pharmaceutical Benefits Scheme. DAA = direct-acting antiviral. SVR = sustained virological response at least 12 weeks after treatment.

* Ribavirin starting dose should be 600 mg daily, with dose adjustment according to tolerance.

Notes: None of the currently available DAAs in Australia include a specific indication for treating decompensated HCV liver disease. A number of the DAA regimens evaluated in recent studies enrolling subjects with decompensated liver disease have not been submitted to the Therapeutic Goods Administration/Pharmaceutical Benefits Advisory Committee and are therefore not reflected in the PBS listing. All patients should be treated by a specialist experienced in the management of decompensated liver disease. SVR may be associated with improvement in liver function (see text). Recommendations are based on a limited number of studies with small sample sizes. There are insufficient clinical data available to support treatment recommendation for patients with Gt 4, 5 or 6 HCV infection; these recommendations are expert opinion based on in vitro data and small numbers of patients enrolled in clinical trials. Paritaprevir–ritonavir + ombitasvir + dasabuvir and peginterferon-alfa are both contraindicated in people with decompensated liver disease.

Gt 1 HCV in the setting of Child–Pugh B cirrhosis were 85%–95%.[49,58,61,64] Only small numbers of patients with Child–Pugh C scores have been included in studies to date; data suggest SVR may be lower (observed SVR, 56%–87%[49,58,61,64]) than in those with Child–Pugh B scores. Patients with Gt 3 HCV and decompensated liver disease are harder to cure.[62] Although data are limited, we recommend treatment with sofosbuvir plus daclatasvir plus ribavirin for 24 weeks' duration in this group (**Table 7**). There are very limited clinical data available to support treatment recommendations for patients with Gt 2, 4-6 HCV infection and decompensated liver disease; recommendations in **Table 7** represent expert opinion. When used, ribavirin should be started at the lower dose of 600 mg daily in this population. If a patient does not tolerate ribavirin, treatment duration should be extended to 24 weeks regardless of HCV genotype. People with Child–Pugh C cirrhosis are at highest risk for ribavirin-related toxicity, especially anaemia; treatment for 24 weeks' duration with no ribavirin may be most suitable for this group. Note that important exclusion criteria for the Phase II SOLAR-1/2 studies that evaluated ribavirin-containing regimens included a haemoglobin level < 10 g/dL, platelet count < 20×10^9/L, bilirubin level > 170 µmol/L (with the exception of those with fibrosing cholestatic hepatitis [FCH]; see Section 9.4) and serum creatinine level > 2.5 × ULN.

People with decompensated liver disease should not be treated with PrOD or pegIFN. These agents are contraindicated in people with decompensated liver disease, as there is a risk of causing further deterioration in liver function.

Early data based on short-term follow-up indicate that SVR may lead to improvement of liver function in some, but not all, people. The severity of baseline liver disease appears to determine the likelihood of clinical improvement. Three distinct groups are emerging: i) people with a MELD score < 15 and Child–Pugh score B; ii) those with a MELD score of 15–20 or Child–Pugh C cirrhosis; and iii) those with a MELD score > 20.

People with a MELD score < 15 and Child–Pugh B cirrhosis are most likely to benefit from eradication of HCV and should start treatment immediately. In people with a MELD score of 15–20, or Child–Pugh C cirrhosis, liver function may improve with achievement of SVR, and some people may even be delisted for liver transplantation. However, predictive factors are yet to be determined and it must be noted that improvement in MELD score may result in prolonging the waiting time for transplantation in those who do not improve sufficiently to be delisted. Until predictive factors can be identified, it appears reasonable to treat and closely monitor the progress of patients on the liver transplant waiting list with MELD scores of 15–20. Longer term assessment of clinical outcomes after SVR in this population are needed to determine the impact on liver synthetic function, portal hypertension and HCC risk. People with a MELD score > 20 are unlikely to benefit sufficiently from SVR to be delisted.[62,64] Antiviral therapy may be started with the intent of suppression and prevention of post-transplant HCV recurrence (see Section 9.1). Alternatively, these individuals may be best served with HCV treatment after transplantation. DAA therapy after liver transplantation results in higher SVR rates than in the pre-transplant population with decompensated liver disease (see Section 9.3), which minimises the risk of selecting for drug-resistant variants. Finally, among people who are not candidates for liver transplantation, it is reasonable to consider DAA therapy regardless of MELD score.

Consensus recommendations	Grade
Indications for assessment by a liver transplant centre include a Child–Pugh score ≥ B7, MELD score ≥ 13 or one of the following clinical events: refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, recurrent or chronic hepatic encephalopathy, small HCC or severe malnutrition.	A1
People with decompensated HCV cirrhosis, Child–Pugh score B and MELD score < 15 should be assessed by an expert hepatologist for consideration of treatment as soon as possible, as they are at risk of further decompensation and liver-related complications and death, which may be prevented by eradicating HCV.	B2
People with decompensated HCV cirrhosis, Child–Pugh score B or C and MELD score > 15 (who are NOT liver transplant candidates) should be assessed by an expert hepatologist for consideration of treatment where there is an anticipated benefit from such treatment.	B1
People with decompensated HCV cirrhosis, Child–Pugh score B or C and MELD score > 15 (who ARE liver transplant candidates) should be assessed by a liver transplant physician to consider the individual benefit and risks of treatment before transplantation.	B2
When making treatment decisions, decompensated liver disease should be defined by a Child–Pugh score ≥ B7.	A1
First-line treatment regimens for chronic Gt 1 HCV infection and decompensated liver disease include (see Table 7):	
• sofosbuvir + ledipasvir ± ribavirin for 12 or 24 weeks	B1
• sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks	B1
The first-line treatment regimen for chronic Gt 3 HCV infection and decompensated liver disease is (see Table 7):	
• sofosbuvir + daclatasvir + ribavirin for 24 weeks	B1
A first-line treatment regimen for chronic Gt 2, 4–6 HCV infection in the setting of decompensated liver disease is (see Table 7):	
• sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks	C2
A first-line treatment regimen for chronic Gt 4 or 6 HCV infection in the setting of decompensated liver disease is (see Table 7):	
• sofosbuvir + ledipasvir ± ribavirin for 12 or 24 weeks	C2
The combination of paritaprevir–ritonavir, ombitasvir and dasabuvir should NOT BE USED in people with decompensated liver disease.	A1
PegIFN should NOT BE USED in people with decompensated liver disease.	A1
Notes: None of the currently available DAAs in Australia include a specific indication for the treatment of decompensated HCV liver disease. Recommended or preferred treatment regimens may not be eligible for prescription on the PBS, reflecting the dynamic nature of this area (see Table 7).	

9. Special populations: treatment of HCV after liver transplantation

Chronic hepatitis C is the leading indication for adult liver transplantation in Australia, accounting for about 40% of transplants.[65] Recurrence of hepatitis C after liver transplantation is universal and is a major clinical problem. Recurrent HCV pursues a more aggressive course after transplantation, with up to 80% of patients developing chronic hepatitis and 30% of patients progressing to cirrhosis within 5 years.[66] Furthermore, in the setting of immunosuppression, 2%–5% of patients develop FCH within 6 months of transplantation.[67] FCH is associated with very high-level viraemia, which is directly cytotoxic, causing rapid progression to jaundice, liver failure and death. Mortality rates of 80% are reported. Finally, although recurrent HCV infection is a major cause of allograft dysfunction after transplantation, it is not the only cause, and discrimination from other causes, including acute cellular rejection, biliary and vascular complications and drug hepatotoxicity, is challenging.

Treatment with DAAs offers the opportunity to clear HCV either before transplantation (preventing recurrence) or after transplantation (treating recurrence). Where possible, treatment should be initiated early after transplantation to prevent fibrosis progression; however, treatment is also indicated in people with established recurrence, including cirrhosis. People with FCH should be identified and treated immediately to prevent rapid progression to allograft failure.

9.1 Preventing recurrent HCV after transplantation: treatment of people on the transplant waiting list

Some people, such as those with HCC or very advanced liver failure, require liver transplantation regardless of whether hepatitis C is present or not, and receiving treatment while on the waiting list is unlikely to impact the timing or outcome of liver transplantation. A decision as to whether to treat a patient on the waiting list, or wait until after transplantation, should be made on a case-by-case basis by a liver transplant physician. Treatment regimen and duration should be chosen according to recommendations for treatment of compensated cirrhosis (for patients with HCC) or decompensated cirrhosis (see Sections 5 and 8).

If a decision is made to treat a person while awaiting liver transplantation, a period of at least 30 days with undetectable HCV RNA during treatment is associated with a very low risk of recurrence of HCV after transplantation.[59] People treated for ≥ 12 weeks, with a period of undetectable serum HCV RNA of ≥ 8 weeks, can have antiviral treatment stopped at transplantation. For people treated for < 12 weeks before transplant, treatment should continue after transplantation until a total treatment duration of 12 weeks has been achieved. The development of severe acute kidney injury may lead to an interruption of dosing if the person is taking a sofosbuvir-containing regimen. Potential drug–drug interactions in the post-transplant setting should be considered.

9.2 Treatment of HCV and compensated liver disease after transplantation

Recommendations for the treatment of HCV after liver transplantation are based on clinical trial data where available. We have tried to avoid extrapolation from studies performed in non-liver transplant patients, given the complexity associated with post-transplant immunosuppression. Therefore, treatment recommendations may differ from those for the non-transplant population, and may differ from the treatment regimens currently eligible for prescription under the PBS (**Table 8**). None of the currently available DAAs in Australia include a specific indication for treating HCV after liver transplantation.

Clinical trial data are limited. In the SOLAR-1 study, treatment with sofosbuvir plus ledipasvir plus 1000/1200 mg of ribavirin daily for 12 or 24 weeks was studied in 162 post-transplant patients with HCV Gt 1 (31% with Child–Pugh A cirrhosis).[57] SVR was observed in 96%–98% (157/162) and there was no significant difference between 12 and 24 weeks

of treatment. Similar SVR results were found for the combination of sofosbuvir and daclatasvir plus ribavirin for 12 weeks in patients with HCV Gt 1 and post-transplant HCV recurrence in the ALLY-1 study.[68] This regimen was also effective in 10 of 11 patients (91%) with Gt 3 and is the only currently available regimen suitable for people with Gt 3 HCV. It is therefore recommended for post-transplant patients with HCV Gt 3. Treatment was well tolerated in these studies and there were no clinically significant drug–drug interactions between sofosbuvir plus ledipasvir or sofosbuvir plus daclatasvir and calcineurin inhibitors or mTOR inhibitors.

The combination of PrOD and ribavirin for 24 weeks' duration was evaluated for the treatment of post-transplant Gt 1 HCV recurrence in 34 individuals with no or minimal fibrosis in an open-label, prospective, multicentre study.[69] All those enrolled had received their transplant more than 12 months previously. SVR was achieved in 97%. The majority of patients received 600–800 mg of ribavirin daily. Treatment was well tolerated, and no one developed allograft rejection. This regimen is associated with drug–drug interactions that require dose modification of calcineurin inhibitors; use in combination with mTOR inhibitors is not recommended.

There are limited data on treatment of post-transplant patients with HCV Gt 2, 4, 5 or 6. Until such data are available, we recommend treatment with sofosbuvir plus ledipasvir plus ribavirin for 12 weeks for people with Gt 4 or 6, or sofosbuvir plus daclatasvir plus ribavirin for 12 weeks for those with Gt 2–6.

9.3 Treatment of decompensated HCV after transplantation

The treatment of decompensated liver disease due to recurrent HCV after liver transplantation has been evaluated in a multicentre, prospective study in which 52 patients with Gt 1 or 4 HCV were treated with sofosbuvir plus ledipasvir plus ribavirin for 12 versus 24 weeks (SOLAR-1).[57] The ribavirin starting dose was 600 mg; increased dosing on-treatment was rare. SVR was observed in 85%–88% of patients (45/52) with Child–Pugh B cirrhosis and 60%–75% (6/9) with Child–Pugh C cirrhosis. Response rates were similar with 12 and 24 weeks of treatment. No study has examined a ribavirin-free regimen in post-transplant patients. There are no prospective clinical trial data that specifically evaluate treatment of post-transplant HCV in people with decompensated cirrhosis and HCV Gt 2, 3, 5 or 6. Until such data are available, we recommend treatment with sofosbuvir plus daclatasvir plus ribavirin 600 mg daily for 12 weeks, or sofosbuvir plus daclatasvir for 24 weeks if ribavirin is not tolerated (**Table 8**). In people with decompensated cirrhosis and HCV Gt 3 after liver transplantation, we recommend treatment with sofosbuvir plus daclatasvir plus ribavirin 600 mg for 24 weeks.

9.4 Treatment of fibrosing cholestatic hepatitis C

Diagnosis of FCH should be made according to established criteria.[70] Treatment with DAAs results in rapid clinical improvement and high rates of SVR (**Table 8**). In 23 people with FCH, sofosbuvir with daclatasvir or ribavirin for 24 weeks resulted in rapid clinical improvement and survival in all.[71] Post-treatment relapse occurred in one individual with HIV coinfection treated with sofosbuvir and daclatasvir. Six people with HCV Gt 1 and FCH were enrolled in Group 7 of the SOLAR-1 study of ledipasvir plus sofosbuvir plus ribavirin for 12 or 24 weeks and all had rapid clinical improvement and achieved SVR.[57]

Table 8 (A). Treatment protocols after liver transplantation for hepatitis C virus (HCV) infection in people with compensated liver disease

HCV Gt	Treatment regimen	Duration	PBS listing
1, 4, 6	Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily (weight-based)*	12 weeks (24 weeks if ribavirin-intolerant)	The combination of sofosbuvir + ledipasvir is only PBS-listed for the treatment of Gt 1 HCV 24-week treatment duration is only PBS-listed for the treatment of Gt 1 HCV in people with cirrhosis who are treatment-experienced Ribavirin is not PBS-listed for use in combination with sofosbuvir + ledipasvir
1–6	Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily (weight-based)*	12 weeks (24 weeks if ribavirin-intolerant)	The combination of sofosbuvir + daclatasvir is only PBS-listed for the treatment of Gt 1 and 3 HCV 24-week treatment duration is PBS-listed for people with Gt 1 or 3 HCV and cirrhosis, or people with Gt 1 HCV and no cirrhosis who have not responded to previous treatment with a protease inhibitor + pegIFN + ribavirin Ribavirin is PBS-listed for use in combination with sofosbuvir + daclatasvir for the treatment of Gt 1 HCV only
1a, 1b plus prior non-response to pegIFN plus ribavirin	Paritaprevir–ritonavir (150 mg/100 mg), orally, daily† + Ombitasvir 25 mg, orally, daily + Dasabuvir 250 mg, orally, twice daily + Ribavirin 600–800 mg, orally, daily	24 weeks	PrOD + ribavirin is PBS-listed for 24 weeks' treatment duration only for people with Gt 1a HCV with cirrhosis and prior null response to pegIFN plus ribavirin PBS listing for other situations is for 12 weeks
1b plus treatment-naive or prior relapse to pegIFN plus ribavirin	Paritaprevir–ritonavir (150mg/100 mg), orally, daily† + Ombitasvir 25 mg, orally, daily + Dasabuvir 250 mg, orally, twice daily	24 weeks	PrOD ± ribavirin is PBS-listed for 12 weeks' treatment duration only for Gt 1b HCV

Gt = genotype. PBS = Pharmaceutical Benefits Scheme. pegIFN = peginterferon-alfa. PrOD = paritaprevir–ritonavir + ombitasvir + dasabuvir. mTOR = mammalian target of rapamycin.

* Ribavirin dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg.

† PrOD is associated with drug–drug interactions that require dose modification of calcineurin inhibitors; use in combination with mTOR inhibitors is not recommended.

Table 8 (B). Treatment protocols after liver transplantation for hepatitis C virus (HCV) infection in people with decompensated liver disease

HCV Gt	Treatment regimen	Duration	PBS listing
Decompensated liver disease			
1	Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	The combination of sofosbuvir + daclatasvir with ribavirin is PBS-listed for the treatment of Gt 1 HCV in people with cirrhosis
1	Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	Ribavirin is not PBS-listed for use in combination with sofosbuvir + ledipasvir
3	Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily + Ribavirin 600 mg, orally, daily*	24 weeks	Ribavirin is not PBS-listed for use in combination with sofosbuvir + daclatasvir for the treatment of Gt 3 HCV
2	Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	The combination of sofosbuvir + daclatasvir with ribavirin is not PBS-listed for the treatment of Gt 2 HCV
4, 6	Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	The combination of sofosbuvir + ledipasvir with ribavirin is not PBS-listed for the treatment of Gt 4 or 6 HCV
4–6	Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	The combination of sofosbuvir + daclatasvir with ribavirin is not PBS-listed for Gt 4-6 HCV

Table 8 (B). Treatment protocols after liver transplantation for hepatitis C virus (HCV) infection in people with decompensated liver disease *(continued)*

Fibrosing cholestatic hepatitis (FCH)			
1–6	Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily (weight-based)†	24 weeks	Sofosbuvir + daclatasvir is PBS-listed for: • 12 weeks in Gt 1 and 3 HCV in people with no cirrhosis, or • 24 weeks in Gt 1 and 3 HCV in people with cirrhosis, or • 24 weeks in Gt 1 HCV in people with no cirrhosis in whom treatment with a protease inhibitor + pegIFN + ribavirin has previously failed
1, 4, 6	Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily + Ribavirin 600 mg, orally, daily*	12 weeks (24 weeks if ribavirin-intolerant)	Ribavirin is not PBS-listed for use in combination with sofosbuvir + ledipasvir The combination of sofosbuvir + ledipasvir is not PBS-listed for the treatment of Gt 4 or 6 HCV

Gt = genotype. PBS = Pharmaceutical Benefits Scheme. pegIFN = peginterferon-alfa. SVR = sustained virological response at least 12 weeks after treatment.

* Where ribavirin starting dose is 600 mg daily, consider dose adjustment according to tolerance.

† Ribavirin dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg.

Notes: None of the currently available direct-acting antivirals (DAAs) in Australia include a specific indication for treating decompensated HCV liver disease. A number of the DAA regimens evaluated in recent studies enrolling subjects with decompensated liver disease have not been submitted to the Therapeutic Goods Administration/Pharmaceutical Benefits Advisory Committee and are therefore not reflected in the PBS listing. All patients should be treated by a specialist experienced in the management of decompensated liver disease. SVR may be associated with improvement in liver function (see text). Recommendations are based on a limited number of studies with small sample sizes. There are insufficient clinical data available to support treatment recommendation for patients with Gt 4, 5 or 6 HCV infection; these recommendations are expert opinion based on in vitro data and small numbers of patients enrolled in clinical trials. PegIFN and paritaprevir–ritonavir + ombitasvir + dasabuvir are both contraindicated in people with decompensated liver disease.

Consensus recommendations	Grade
People with post-transplant HCV infection should be treated as soon as possible, as they are at risk of severe complications.	A1
Optimal timing of initiation of treatment has not been established. For people with newly transplanted livers, initiation of treatment at 3–6 months after transplantation is recommended.	B1
Preferred treatment options for chronic HCV infection and compensated liver disease after transplantation include (see Table 8):	
Gt 1 HCV:	
• sofosbuvir + ledipasvir ± ribavirin for 12 or 24 weeks	A1
• sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks	B1
• paritaprevir–ritonavir, ombitasvir, dasabuvir ± ribavirin for 24 weeks	B1
Gt 2, 3 HCV:	
• sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks	B2
Gt 4, 6 HCV:	
• sofosbuvir + ledipasvir ± ribavirin for 12 or 24 weeks	B2
• sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks	B2
Preferred treatment options for chronic HCV infection and decompensated liver disease after transplantation include (see Table 8):	
Gt 1 HCV:	
• sofosbuvir + ledipasvir ± ribavirin for 12 or 24 weeks	A1
• sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks	B1
Gt 2 HCV:	
• sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks	B2
Gt 3 HCV:	
• sofosbuvir + daclatasvir + ribavirin for 24 weeks	B2
Gt 4, 6 HCV:	
• sofosbuvir + ledipasvir ± ribavirin for 12 or 24 weeks	B2
• sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks	B2
Preferred treatment options for FCH after transplantation include (see Table 8):	
Gt 1, 4, 6 HCV:	
• sofosbuvir + ledipasvir ± ribavirin for 12 or 24 weeks	B1
Gt 1–6 HCV:	
• sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks	B1
Treatment with sofosbuvir + ledipasvir, sofosbuvir + daclatasvir or sofosbuvir + ribavirin does not require dose adjustment of calcineurin inhibitors or mTOR inhibitors.	A2
Treatment with paritaprevir–ritonavir, ombitasvir, and dasabuvir requires dose modification of calcineurin inhibitors; use in combination with mTOR inhibitors is not recommended.	A2
Notes: None of the currently available DAAs in Australia include a specific indication for the treatment of HCV infection after transplantation. Recommended or preferred treatment regimens may not be eligible for prescription on the PBS, reflecting the dynamic nature of this area (see Table 8).	

10. Special populations: treatment of HCV in the setting of HIV coinfection

Simultaneous infection with HIV and HCV is associated with an increased rate of progression to liver cirrhosis, increased risk of HCC and increased mortality,[72] even in those achieving full HIV virological suppression with antiretroviral treatment (ART) for HIV.[73,74] Eradication of HCV can prevent these complications, and people with HCV–HIV coinfection should be prioritised for treatment of HCV. In contrast to IFN-containing regimens, IFN-free DAA regimens for HCV are just as effective in the setting of HCV–HIV coinfection as they are in HCV monoinfection.[75-80] Drug–drug interactions, cumulative drug toxicities and increased pill burden are the main considerations when planning HCV treatment in people living with HIV. It is also important to note that thrombocytopaenia may occur secondary to HIV infection rather than portal hypertension; this may influence interpretation of APRI and FIB-4 serum markers for liver fibrosis staging. Serum bilirubin levels may be elevated by ARTs that inhibit biliary transporters. People with HIV–HCV coinfection should be cared for by a multidisciplinary team with experience in managing both viral infections.

10.1 Prevention and screening tests for HCV in people who are HIV-positive

HCV and HIV share common routes of acquisition. The risk of sexual (permucosal) transmission of HCV in people with HIV is increased, and the majority of sexual transmission of HCV occurs in HIV-positive people, particularly in men who have sex with men (MSM). High-risk practices include fisting, sharing sex toys, group sex and concurrent use of recreational drugs, particularly drugs absorbed through the mucosa.[81] Unprotected anal intercourse alone has been associated with an increased risk of HCV transmission.

Education and discussion about harm reduction strategies to prevent parenteral or sexual transmission of HCV are important. HIV pre-exposure prophylaxis has no efficacy in preventing the transmission of HCV. Those wishing to minimise their exposure risk of HCV should be advised of safer sex practices, including condom use. Access to peer and social support; psychological, alcohol and drug counselling; and information about preventing transmission of HIV and HCV by parenteral and sexual routes and avoidance of HCV reinfection should be provided.

All people who are infected with HIV should be tested for HCV,[82] and all HCV-positive people should be tested for HIV. It is recommended that people who are HIV-positive should be screened with HCV serological testing annually.[83] Those who are at high risk of HCV acquisition should be rescreened using 3–6-monthly liver function tests, with HCV RNA PCR performed in the setting of an unexplained rise in transaminase levels. HIV-positive individuals who achieve SVR after DAA therapy remain at risk of reinfection with HCV, and should continue to be screened with annual HCV RNA PCR and 3–6-monthly liver function test monitoring.

10.2 Antiretroviral treatment in people with HIV–HCV coinfection

ART is now recommended for all people with HIV irrespective of CD4+ cell count.[84] HIV ART-naive people with HIV–HCV coinfection should have an ART regimen selected that will minimise drug–drug interactions with HCV medications and minimise potential liver toxicity. HIV should be controlled before HCV treatment, particularly in those with advanced HIV immunosuppression (CD4+ count, < 200 cells/mm^3). HIV-related opportunistic infections should be treated before initiation of HCV treatment. Treatment of people with a CD4+ cell count greater than 500 cells/mm^3 may be deferred until HCV treatment is completed, to avoid drug–drug interactions. ART should not be switched for people who are on a stable regimen unless an unavoidable and unmanageable drug–drug interaction is identified, because switching ART in HIV virologically suppressed patients has a risk of HIV virological failure.[85]

10.3 HCV treatment in people with HIV–HCV coinfection

The treatment regimens for HCV in people with HIV are the same as those used for HCV mono-infection and, as noted, the response rates are equivalent.[75-80] Selection of DAA therapy for people with HIV–HCV coinfection should be as for HCV mono-infection, with the important caveat that ART increases the likelihood of clinically significant drug–drug interactions. A careful assessment of potential drug–drug interactions between DAAs and ART and drugs prescribed to manage HIV-related complications and comorbidities should be made before commencing HCV treatment, using the University of Liverpool's Hepatitis Drug Interactions website (www.hep-druginteractions.org). Caution is warranted even for combinations of HIV ART and HCV DAAs where a specific drug–drug interaction issue is not expected or reported, as further information on interactions is likely to emerge. Due to extensive drug–drug interactions, tipranavir should be avoided with concurrent HCV DAA therapy.

10.3.1 Sofosbuvir

Drug interaction studies of sofosbuvir with antiretroviral drugs (including efavirenz, tenofovir, emtricitabine, rilpivirine, ritonavir-boosted darunavir, and raltegravir) in uninfected individuals have not identified any clinically significant interactions.[86] Sofosbuvir is not recommended for use with tipranavir because of the potential of tipranavir to induce P-glycoprotein.

10.3.2 Ledipasvir

Tenofovir exposure is increased when coadministered with ledipasvir, particularly when the ART regimen also includes efavirenz–emtricitabine or rilpivirine–emtricitabine. The effect may be further amplified when the ART regimen also includes elvitegravir–cobicistat or an HIV protease inhibitor boosted with ritonavir. Caution should be exercised with the combination of tenofovir and ledipasvir, with frequent monitoring for tenofovir-associated kidney injury.

10.3.3 Daclatasvir

Daclatasvir is available in both 60 mg and 30 mg formulations to manage drug–drug interactions. When administered concurrently with efavirenz, the dose of daclatasvir should be increased to 90 mg daily. Etravirine and nevirapine also decrease daclatasvir levels, requiring an increased dose, but as the effect has not been studied, these combinations should be avoided where possible. No daclatasvir dose adjustment is needed with rilpivirine. HIV protease inhibitors used without pharmacological "boosting" by ritonavir generally do not require dose adjustment of daclatasvir. However, when atazanavir, fosamprenavir, indinavir or saquinavir are used in combination with ritonavir, the daclatasvir dose should be reduced to 30 mg daily. The dose of daclatasvir should also be decreased to 30 mg daily when used with cobicistat. There is no need for daclatasvir dose adjustment when used with lopinavir–ritonavir or darunavir–ritonavir.

10.3.4 Ombitasvir–paritaprevir–ritonavir–dasabuvir

Given extensive drug–drug interactions, the combination of ombitasvir–paritaprevir–ritonavir–dasabuvir should be avoided in those whose ART regimen includes non-nucleoside reverse transcriptase inhibitors or HIV protease inhibitors apart from atazanavir, in which case ritonavir should be omitted from the ART regimen. Further, due to the inclusion of ritonavir in the DAA regimen, all people treated with this combination should be receiving suppressive HIV therapy.

10.3.5 Ribavirin

Ribavirin-containing regimens should be avoided in people treated with zidovudine, stavudine or didanosine and may have increased risk of toxicity when used with abacavir and atazanavir.

Consensus recommendations	Grade
People with HCV–HIV coinfection should be cared for by a clinician who is experienced in managing both viral infections.	B1
All people living with HCV should be tested for HIV.	A1
All HCV-negative people living with HIV should be tested for HCV annually if they have risk factors for HCV exposure.	A1
HIV should be controlled before HCV treatment.	B1
ART should not be switched for people who are on a stable regimen, unless an unavoidable and unmanageable drug–drug interaction is identified.	B1
The treatment regimens for chronic HCV infection in people living with HIV should be the same as those used for HCV mono-infection, because DAA regimens for the treatment of HCV are just as effective in the setting of HIV coinfection.	A1
A careful assessment of potential drug–drug interactions between DAAs and ART and drugs prescribed to manage HIV-related complications and comorbidities should be performed and used to guide the selection of an appropriate DAA regimen for HCV.	A1
HIV-positive individuals who achieve SVR after DAA therapy and who remain at risk of reinfection with HCV should continue to be screened with annual HCV RNA PCR and 3–6-monthly liver function test monitoring.	C2

11. Special populations: treatment of HCV in the setting of HBV coinfection

People with HCV–HBV coinfection have a greater risk of significant liver fibrosis and should be prioritised for treatment. People with HCV–HBV coinfection should be treated for HCV using the same treatment regimens, and the same treatment durations, as people with HCV mono-infection. Although there have been no studies specifically evaluating efficacy in HCV–HBV-coinfected patients, it is expected that the approved IFN-free DAA regimens will have similar efficacy in this population. People with HCV–HBV coinfection and low-level HBV DNA levels should be monitored for HBV reactivation after eradication of HCV. Antiviral therapy for HBV infection is indicated in the setting of clinically significant HBV replication.[87] The potential for drug–drug interactions should be considered before treating HCV and HBV concurrently. People with HCV–HBV coinfection should be cared for by a clinician who is experienced in managing both viral infections.

Consensus recommendations	Grade
All people living with HCV infection should be tested for HBV.	A1
People with HCV–HBV coinfection should be treated for HCV with the same treatment regimen and same treatment duration as people with HCV mono-infection.	B1
People with HCV–HBV coinfection should be monitored for HBV reactivation during and after treatment for HCV infection.	B1
If HBV replicates at clinically significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated.	B1

12. Special populations: treatment of HCV in people with renal impairment

Hepatitis C is associated with intrinsic renal disease, including cryoglobulinaemia and glomerulonephritis.[88] People with renal impairment should be investigated to determine the underlying cause and managed appropriately. Those with severe acute vasculitic manifestations may require immunosuppressive therapy, including anti-CD20 antibody therapy and/or plasma exchange. In addition, the prevalence of anti-HCV antibodies is higher in patients requiring haemodialysis compared with the general population.

Management of HCV in individuals with renal impairment is complicated by renal clearance of drugs including sofosbuvir and ribavirin, as well as the complications and treatment of the intrinsic renal disease, including drug–drug interactions.[89,90] People with moderate–severe renal impairment (eGFR < 50 mL/min/1.73 m^2) should be referred to specialist centres for consideration of antiviral therapy.

12.1 People with mild–moderate renal impairment (eGFR, 30–80 mL/min/1.73 m^2)

For people with mild to moderate renal impairment (eGFR, 30–80 mL/min/1.73 m^2), no dose adjustment is required for sofosbuvir, ledipasvir, paritaprevir–ritonavir, ombitasvir, dasabuvir or daclatasvir. Ribavirin is renally excreted and cannot be removed by dialysis. Ribavirin accumulates in the setting of renal impairment with creatinine clearance < 50 mL/min and can cause severe anaemia.[91] The product information recommends that ribavirin should not be used in individuals with an eGFR < 50 mL/min/1.73 m^2. In specialist centres, ribavirin-containing regimens may be considered for those with an eGFR < 50 mL/min/1.73 m^2. In this setting, ribavirin therapy should be started at a low dose, with close monitoring of haemoglobin levels. Recommended ribavirin dose according to eGFR is: > 50 mL/min/1.73 m^2, no dose adjustment; 30–50 mL/min/1.73 m^2, alternating doses of 200 mg and 400 mg every other day; < 30 mL/min/1.73 m^2, 200 mg daily; haemodialysis, 200 mg pre-dialysis.

12.2 People with severe renal impairment (eGFR < 30 mL/min/1.73 m^2 or haemodialysis)

Drugs that are primarily metabolised by the liver can be used in people with severe renal impairment and in those receiving haemodialysis; drugs excreted by the kidneys should be avoided or the dose regimen modified. Paritaprevir–ritonavir, ombitasvir and dasabuvir are all cleared by hepatic metabolism and can be used in individuals with severe renal disease. The efficacy of this regimen was demonstrated in the RUBY-1 study, a small, open-label, Phase IIIb study that enrolled 20 patients with Gt 1 HCV and no cirrhosis with an eGFR < 30 mL/min/1.73 m^2 (including patients receiving haemodialysis).[92] All patients had a baseline haemoglobin level > 100 g/L. People with Gt 1a HCV infection (n = 13) were treated with PrOD plus ribavirin (200 mg daily for patients not on haemodialysis; 200 mg 4 hours before dialysis for patients on haemodialysis), and people with Gt 1b HCV infection (n = 7) were treated with PrOD alone. Of 19 patients with post-treatment data, 18 (95%) achieved SVR. Overall, treatment was well tolerated, but ribavirin dose interruption was required for management of anaemia in most patients receiving ribavirin 200 mg daily.

Daclatasvir[93] is also hepatically cleared, but is used in combination with sofosbuvir and therefore cannot be recommended. Sofosbuvir is renally excreted and there are limited safety data on its use in people with severe renal impairment. The registration studies for sofosbuvir-containing regimens excluded patients with an eGFR < 30 mL/min/1.73 m^2. Pharmacokinetic studies of a single 400 mg dose of sofosbuvir resulted in an increased area under the curve of 171% for sofosbuvir and 451% for its inactive metabolite (GS-331007), which is excreted exclusively by the kidneys. Studies in people with

severe renal impairment or receiving haemodialysis are ongoing to determine dosing recommendations.

Clearance of pegIFN is reduced and overall exposure increased in proportion to the degree of renal dysfunction. Haemodialysis has little effect on clearance. In patients with an eGFR < 30 mL/min/1.73 m^2 or receiving haemodialysis, the dose of peginterferon alfa-2a should be reduced to 135 µg weekly and further reduced to 90 µg weekly if adverse events occur.

The treatment of HCV continues to evolve. A number of sofosbuvir-free and ribavirin-free regimens are in clinical development for the treatment of people with moderate to severe renal impairment. The combination of the NS3 protease inhibitor grazoprevir and the NS5A inhibitor elbasvir has recently completed Phase III development. Both drugs are hepatically cleared. The C-SURFER study enrolled patients with Gt 1 HCV who had severe renal impairment (Stage 4 or 5), including 17% in whom treatment with pegIFN plus ribavirin had previously failed. A small number of people with cirrhosis were enrolled (n = 14 [6%]). SVR was 99% (115/116, modified full analysis set), and treatment was well tolerated.[94] A TGA/PBAC application for this regimen has been submitted, and it is expected it will be listed on the PBS late in 2016. It is reasonable to consider deferring therapy pending the availability of this regimen for patients who would otherwise require treatment with a ribavirin-containing regimen.

Consensus recommendations	Grade
Renal function must be evaluated in all individuals before initiating antiviral therapy for HCV infection.	A1
All people with chronic HCV infection and renal impairment (eGFR < 50 mL/min/1.73 m^2) should be referred to a specialist for assessment and management of HCV as well as their renal disease.	A1
In people with mild–moderate renal impairment (eGFR, 30–80 mL/min/1.73 m^2), no dose adjustment is required for: • sofosbuvir • sofosbuvir + ledipasvir • sofosbuvir + daclatasvir • paritaprevir–ritonavir + ombitasvir + dasabuvir	A1
Ribavirin should be used with caution in people with an eGFR < 50 mL/min/1.73 m^2; treatment should be supervised by a specialist experienced in the treatment of HCV.	A1
In people with severe renal impairment (eGFR < 30 mL/min/1.73 m^2 or haemodialysis): • sofosbuvir cannot be recommended, pending further studies • paritaprevir–ritonavir + ombitasvir + dasabuvir can be used to treat Gt 1b HCV • paritaprevir–ritonavir + ombitasvir + dasabuvir + ribavirin can be used to treat Gt 1a HCV • low-dose ribavirin should be used with close monitoring of haemoglobin levels (eg, ribavirin 200 mg daily for patients not on haemodialysis; ribavirin 200 mg pre-dialysis for patients on haemodialysis)	 B1 B1 B1 B1

13. Special populations: treatment of people with acute HCV infection

Acute HCV infection refers to the 6-month period after infection acquisition, though definitions vary[95] and the distinction between acute and early chronic infection is somewhat arbitrary. In Australia, it is estimated that approximately 8500–9000 new infections occur each year.[1,3] While in some cases acute HCV infection may develop after discrete exposure (eg, a needlestick injury in a health care worker), detection of acute HCV infection is often hampered by its asymptomatic or non-specific presentation, lack of specific diagnostic tests and the inherent difficulties in identifying and following individuals at highest risk of transmitting and acquiring HCV, including PWID. Another high-risk group for HCV transmission is HIV-positive MSM, in whom sexual or permucosal transmission has become increasingly common.[81,96,97] Risk factors for sexual transmission include, but are not limited to, traumatic sexual practices, recreational non-injecting drug use, group sex and the presence of a coexistent sexually transmitted infection.[98]

Acute HCV infection is characterised by the appearance of HCV RNA in blood within 2–14 days of exposure, elevation of liver-associated enzyme levels (particularly ALT), and development of HCV antibodies within 30–60 days of exposure. Up to 80% of acute HCV infections are asymptomatic, making detection and estimation of duration of infection difficult if seroconversion cannot be documented. Clinical features suggestive of acute infection include significant elevation of ALT level or an acute illness manifest by jaundice. However, only 15%–30% of those infected develop a symptomatic illness, and elevation of ALT level is non-specific. Acute infection should be suspected if the clinical signs and symptoms are compatible with acute hepatitis C — such as serum ALT level > 10 × ULN and jaundice in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent source of transmission is identifiable. The preferred criteria for diagnosis of acute HCV infection are: i) positive anti-HCV IgG and a documented negative anti-HCV IgG in the previous 12 months; or ii) positive serum HCV RNA test and a documented negative serum HCV RNA test and negative anti-HCV IgG in the previous 12 months. Alternative, less stringent criteria are the presence of positive serum HCV RNA regardless of anti-HCV IgG and with: i) an acute rise in ALT level > 10 × ULN; *or* ii) an acute rise in ALT level > 5 × ULN, with documented normal ALT level within the past 12 months; *or* iii) in individuals with a previously high ALT level, an acute rise to 3.5 times the baseline ALT level; *and* in the absence of serological evidence of HAV or HBV infection or other causes of acute hepatitis. Documentation of seroconversion is difficult in the absence of routine serological testing, but monitoring of at-risk populations, including PWID[99] and HIV-positive MSM, may be beneficial. There is no single definitive laboratory test to distinguish acute from chronic HCV infection.

13.1 Monitoring during acute infection

Individuals presenting with acute HCV infection should be monitored using HCV RNA, transaminase (ALT, AST) levels, bilirubin level and INR every 2–6 weeks for the first 6 months or until parameters have stabilised and spontaneous clearance has either occurred or is deemed unlikely.[100] Management is predominantly supportive, and admission to hospital is rarely required unless symptoms are uncontrolled or there is concern about rising bilirubin levels and/or INR. Acute liver failure is rare (< 1%) but may be indicated by a rising INR. Any person with an INR > 1.5 or signs of acute liver failure should be referred urgently to a liver transplant centre. Paracetamol and alcohol should be avoided during the period of acute HCV infection. Antiviral treatment during acute liver failure following HCV infection should only be considered by experienced clinicians and in conjunction with a liver transplant specialist.

13.2 Spontaneous clearance

Spontaneous clearance after acute HCV infection occurs in 20%–25% of individuals.[101] Predictors of spontaneous clearance include jaundice, elevated ALT level, female sex, younger age and host genetic polymorphisms (including *IL28B*), although none of these factors can be used to predict clearance at the individual level. In most cases, clearance occurs within the first 6 months after infection, although late clearance has been demonstrated in a small proportion of individuals[102] Fluctuating viraemia is common in the first few months after infection, with variable patterns.[103] A single HCV RNA test result below the limit of detection should not be taken as an indication of clearance; at least two undetectable HCV RNA test results, a minimum of 1 month apart, are required before clearance can be confirmed. Conversely, indicators of likely chronicity include a failure of reduction in HCV viral load of > 1 $\log_{10}$ IU/mL at 4 weeks, or a detectable HCV RNA test result at 12 weeks after initial presentation.[104]

13.3 Treatment of acute HCV infection

The optimal timing and regimen for acute hepatitis C treatment is currently unclear due to a lack of data with IFN-free DAA therapies. In the setting of IFN-based therapy, acute HCV infection can be treated with shorter and simpler therapeutic regimens, to give a similar or even greater SVR than in chronic HCV infection.[105,106] This paradigm is unproven in the setting of IFN-free DAA therapies and is currently the subject of ongoing research studies. If spontaneous clearance has not occurred by 6 months after presentation, the person can be considered to have chronic HCV infection and treated according to current DAA treatment guidelines. Treatment can be considered earlier in specific situations, including occupationally infected health care workers. Further, there may be a population-level benefit from treating early to prevent ongoing transmission events, particularly in communities such as HIV-positive MSM. In the situation where a decision has been made to commence therapy early, within the first 6 months after infection, it is still recommended to hold treatment by monitoring HCV RNA for 12–16 weeks to determine that spontaneous clearance is unlikely. If treatment with DAA-based therapy is considered in the first 6 months after HCV infection, a standard duration of 8–12 weeks should be applied, or the patient entered into a research study pending further data. There is no place for the use of post-exposure prophylaxis with antiviral therapy after HCV exposure. Following acute HCV infection, all individuals should undergo risk behaviour education and discussion regarding the possibility of reinfection risk after spontaneous or treatment-induced clearance.

Consensus recommendations	Grade
There is no place for the use of post-exposure prophylaxis with antiviral therapy after HCV exposure.	B1
A single HCV RNA level below the limit of detection should not be taken as an indication of clearance; at least two undetectable HCV RNA test results, a minimum of 1 month apart, are required before clearance can be confirmed.	A1
If spontaneous clearance has not occurred by 6 months after presentation, a person can be considered to have chronic HCV infection and treated according to current DAA treatment guidelines.	B1
The optimal timing and regimen for acute hepatitis C treatment is currently unclear due to a lack of data with IFN-free DAA therapies.	B2
In the situation where a decision has been made to commence therapy early, within the first 6 months after infection, it is still recommended to hold treatment by monitoring HCV RNA for 12–16 weeks to determine that spontaneous clearance is unlikely.	B1
If treatment with DAA-based therapy is considered in the first 6 months after HCV infection, treatment regimens in line with recommendations for chronic HCV infection should be used.	B1
Following acute HCV infection, all individuals should undergo risk behaviour education and discussion regarding the possibility of reinfection risk after spontaneous or treatment-induced clearance.	B1

14. Methodology

This consensus statement presents a synthesis of evidence from the published literature and scientific abstract presentations available at the time of writing, relevant to the Australian PBS listing for HCV medications at the time of writing. Levels of evidence for recommendations have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[107] The quality of the evidence in the recommendations has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2).

Evidence quality	Notes	Grade
High	Further research is very unlikely to change our confidence in the estimate of effect.	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	B
Low	Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate. Any change of estimate is uncertain.	C
Recommendation	**Notes**	**Grade**
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes and cost.	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or higher resource consumption.	2

Abbreviations

ALT	alanine aminotransferase
ARFI	acoustic radiation force impulse
APRI	aspartate aminotransferase to platelet ratio index
ART	antiretroviral treatment
AST	aspartate aminotransferase
DAA	direct-acting antiviral
eGFR	estimated glomerular filtration rate
ELF	Enhanced Liver Fibrosis
FCH	fibrosing cholestatic hepatitis
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Gt	genotype
HAV	hepatitis A virus
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IFN	interferon
INR	international normalised ratio
LFT	liver function test
MSM	men who have sex with men
MELD	Model for End-Stage Liver Disease
mTOR	mammalian target of rapamycin
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCR	polymerase chain reaction
pegIFN	peginterferon-alfa
PrOD	paritaprevir (ritonavir-boosted), ombitasvir and dasabuvir
PWID	people who inject drugs
RAV	resistance-associated variant
HSD	Highly Specialised Drugs
SVR	sustained virological response at least 12 weeks after treatment (cure)
TGA	Therapeutic Goods Administration
ULN	upper limit of normal

Supplementary Table 1. Non-invasive serum markers for assessing liver fibrosis stage currently available in Australia

Method	Formula	Key threshold for excluding cirrhosis*
APRI	APRI = (AST [IU/L] ÷ AST ULN [IU/L] × 100) ÷ platelet count (× 10^9/L) Online calculator: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri	APRI < 1.0
Hepascore	Patented formula combining bilirubin, GGT, hyaluronate, α-2-macroglobulin, age and sex	Hepascore < 0.80
FibroGENE	Patented formula based on age, platelet count, AST, GGT and *IL28B rs12979860* genotype Online calculator: http://www.fibrogene.com/viral_hepatitis.html	Threshold not published but online calculator available
ELF test	Patented formula combining age, hyaluronate, MMP-3 and TIMP-1	ELF < 9.8

APRI = AST to platelet ratio index. AST = aspartate aminotransferase. ULN = upper limit of normal. GGT = gamma-glutamyl transferase. ELF = Enhanced Liver Fibrosis. MMP-3 = matrix metalloproteinase-3. TIMP-1 = tissue inhibitor of metalloproteinase-1.

* These thresholds have good performance characteristics for excluding the presence of cirrhosis. Patients in whom results exceed these thresholds should be referred for further assessment for the presence of cirrhosis by a specialist with experience in assessing liver disease severity and managing patients with advanced liver disease. These thresholds alone should not be used to diagnose cirrhosis.

Note that the performance of Hepascore and APRI for predicting the presence of cirrhosis may be less accurate in people with HIV coinfection than in people with HCV mono-infection (be aware of false positive results due to HIV-induced thrombocytopaenia with APRI, or antiretroviral treatment-related hyperbilirubinaemia with Hepascore).

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Supplementary Table 2. Child–Pugh and Model for End-Stage Liver Disease (MELD) scoring systems for predicting prognosis in people with decompensated liver disease

A. Child–Pugh score

	Points		
Clinical measure	**1**	**2**	**3**
Albumin (g/dL)	> 35	28–35	< 28
Bilirubin (µmol/L)	< 34	34–51	> 51
INR	< 1.7	1.7–2.3	> 2.3
Ascites	Nil	Slight	Moderate
Encephalopathy	Nil	Grade 1–2	Grade 3-4

Interpretation

Classification	**1-year mortality**	**Consider transplant centre referral**
Class A (5–6 points)	0	No
Class B (7–9 points)	20%	Yes*
Class C (10+ points)	55%	

B. MELD score

MELD = 10 × ((0.957 × Log_e (creatinine/88.4)) + (0.378 × Log_e (bilirubin/17.1)) + (1.12 × Log_e (INR))) + 6.43

Online calculators are available.

Classification	**3-month mortality**	**Consider transplant centre referral**
MELD < 10	1.9%	No
MELD 10–19	6.0%	Yes if MELD ≥ 13*
MELD 20–29	19.6%	
MELD 30–39	52.6%	
MELD 40+	71.3%	

INR = international normalised ratio.

* Indications for assessment by a liver transplant centre include Child–Pugh score ≥ B7, MELD score ≥ 13 or one of the following clinical events: refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, recurrent or chronic hepatic encephalopathy, small hepatocellular carcinoma or severe malnutrition.

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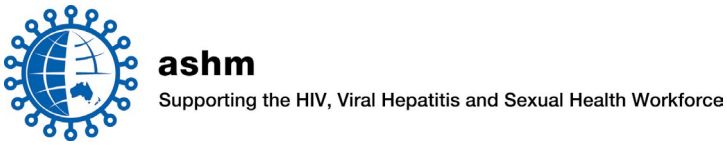
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