

# Australian recommendations for the management of hepatitis C virus infection: a consensus statement (June 2020)



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The consensus statement was prepared by an expert panel representing the Gastroenterological Society of Australia (Liver Faculty), 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

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Chronic hepatitis C virus (HCV) infection is a major public health challenge for Australia, affecting about 200 000 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. 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 was a major medical advance. All Australian adults living with HCV should now be considered for antiviral therapy. DAAs may be prescribed by any medical practitioner or nurse practitioner experienced in treating HCV, or in consultation with a specialist experienced in the treatment of HCV, 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* (June 2020). 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 15.

## What's new?

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This version of the consensus statement includes the following important updates.

### Prescribing by nurse practitioners

Prescribing rights have been extended to authorised nurse practitioners under the Highly Specialised Drugs Program (Section 100), as well as the PBS General Schedule (prescribing rights for nurse practitioners were previously restricted to the General Schedule) (Section 2).

### Removal of the PBS requirement to document HCV genotype before prescribing pan-genotypic treatment regimens for hepatitis C

The PBS *General Statement for Drugs for the Treatment of Hepatitis C* has been amended to remove the requirement for documenting HCV genotype to determine patient eligibility for subsidisation of hepatitis C treatment under the PBS (Section 4.1.2). Rather, it is now recommended that, where possible, evidence of the HCV genotype be documented in the patient's medical record. HCV genotype must still be documented for regimens that are not pan-genotypic (Section 5).

### PBS listing of sofosbuvir plus velpatasvir plus voxilaprevir

Sofosbuvir plus velpatasvir plus voxilaprevir is a pan-genotypic regimen that was listed on the PBS in April 2019 for the treatment of people who had failed therapy with a regimen including an NS5A

inhibitor (Section 5.4.3). Details of the previous NS5A inhibitor-containing treatment regimen are now required at the time of application to the PBS for sofosbuvir plus velpatasvir plus voxilaprevir.

### Removal of the PBS requirement that patients be aged 18 years or older before prescribing treatment for hepatitis C

Children under the age of 18 years can now be prescribed HCV treatment that is listed on the PBS (Section 5.8). Treatment regimens that have been evaluated in children under the age of 18 years include sofosbuvir plus velpatasvir, glecaprevir plus pibrentasvir and sofosbuvir plus ledipasvir (for Gt 1 HCV). Children under the age of 18 years should be referred to a paediatrician who is experienced in the treatment of HCV for discussion about therapy. A document providing specific guidance on the treatment of HCV infection in children aged under 18 years is in development.

### TGA approves the first point-of-care assay for hepatitis C

The first point-of-care test for HCV RNA was approved by the Australian TGA in May 2020. The Xpert<sup>®</sup> HCV viral load assay (Cepheid) measures HCV RNA from a finger-prick blood sample (100 µL) and provides a real-time result in less than 60 minutes. The availability of this assay may promote screening for hepatitis C, as well as the development of "test-and-treat" models of care in high-risk populations (Section 2).

# 1. The epidemiology of HCV in Australia

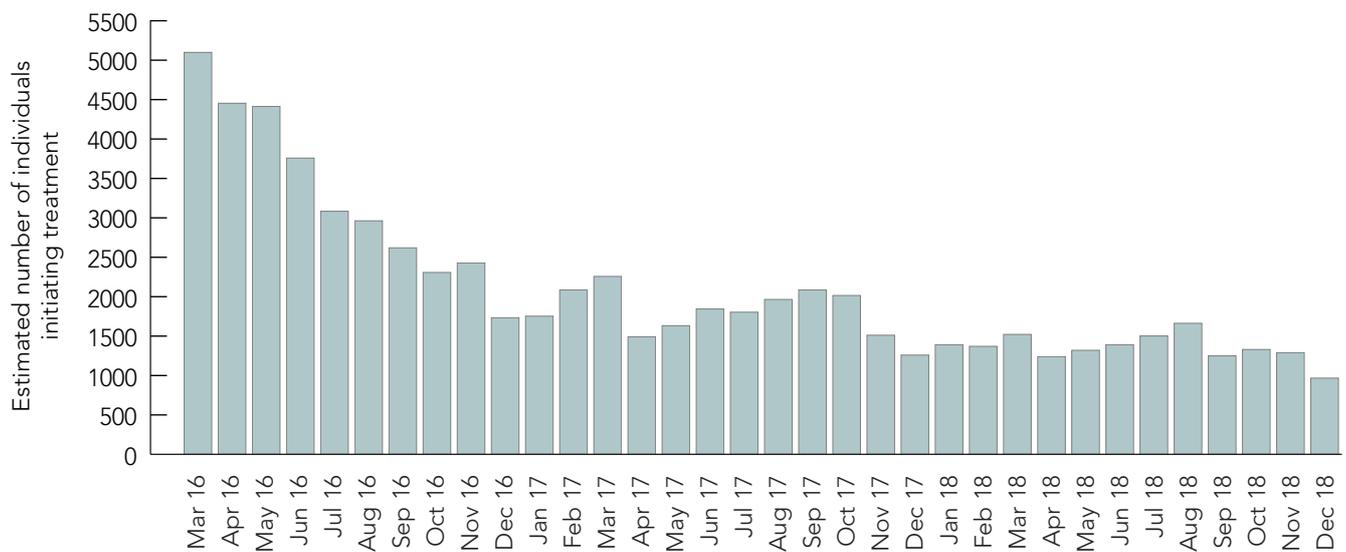
Hepatitis C virus (HCV) infection is a major public health challenge for Australia. Acute infection progresses to chronic disease in about 75% of cases, and these people are at risk of progressive liver fibrosis leading to cirrhosis, liver failure and hepatocellular carcinoma (HCC). About 20%–30% of 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 (80%) of people with HCV infection have been diagnosed.<sup>1–3</sup> At the end of 2017, it was estimated that there were 182 144 people in Australia living with chronic hepatitis C.<sup>4</sup>

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 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.<sup>1,3</sup> There is some evidence of further declines in the incidence of HCV infection since the unrestricted availability of direct-acting antiviral (DAA) therapy in 2016.<sup>4</sup>

Despite one of the highest HCV diagnosis rates in the world, treatment uptake in Australia was low (2000–4000 people/year, or 1%–2% of the infected population) before the DAA era. In contrast, since interferon (IFN)-free DAA regimens were listed on the Pharmaceutical Benefits Scheme (PBS) in March 2016, about 70 260 people have received HCV treatment (Figure 1).<sup>5</sup>

**Figure 1. Estimated number of people initiating direct-acting antiviral treatment each month in Australia, 2016–2018**



Source: The Kirby Institute.<sup>5</sup>

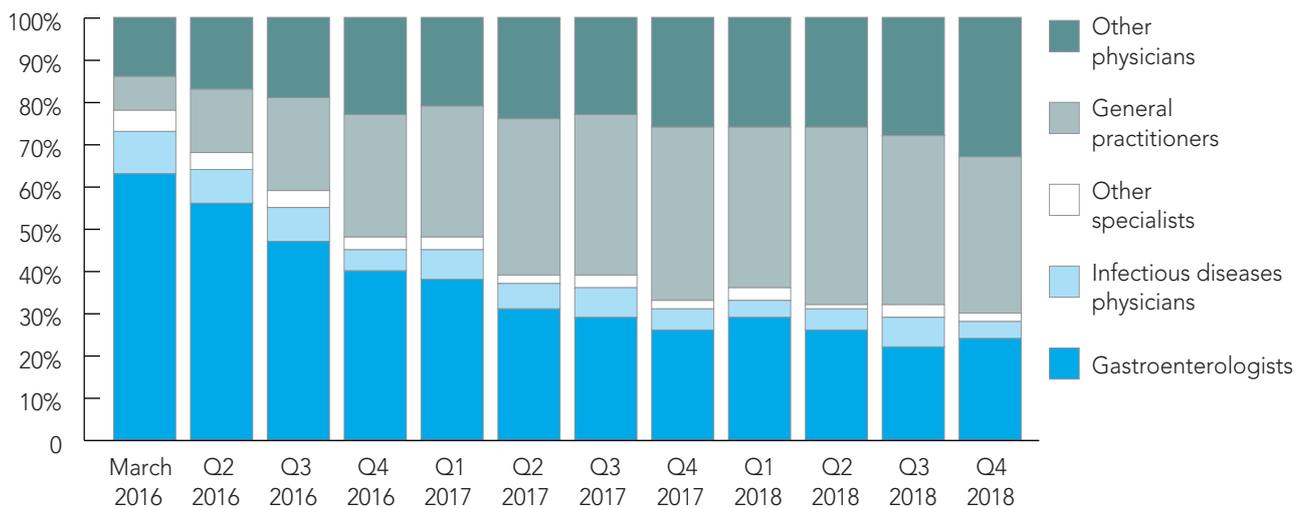
A key feature of the Australian HCV treatment landscape since the DAA program commenced has been the involvement of non-specialists in prescribing. Although the overall numbers of DAA treatment initiations per month have declined since March 2016, the contribution from general practitioners has increased (Figure 2).<sup>5</sup>

In addition to efforts to increase the number of people treated overall, strategies that target populations with high HCV transmission risk will be required to facilitate HCV elimination by preventing new infections (“treatment as prevention”). A modelling study by Martin and colleagues showed that increasing treatment in PWID would have a dramatic effect on reducing HCV prevalence.<sup>6</sup> Using a baseline HCV prevalence of 50% among PWID in Melbourne, they predicted that increasing the annual treatment rate to 4% of PWID (8% of PWID with chronic HCV

infection) would decrease HCV prevalence among PWID by 50% in 15 years.<sup>6</sup> An increase to 8% of PWID (16% of PWID with chronic HCV infection) would decrease prevalence in PWID by > 90% within a decade, essentially eliminating HCV infection from the Australian population of PWID. Clinical trials examining treatment as prevention in PWID and prison populations are ongoing in Australia.

Ongoing efforts will be required to sustain DAA treatment uptake, particularly among highly marginalised populations. Enhanced DAA access in drug and alcohol services, community clinics and prison clinics will be needed for HCV to be eliminated as a major public health issue in Australia. Recent data also suggest that a focus on increasing testing rates and linkage with care will be important to maintain adequate levels of treatment.<sup>7</sup>

**Figure 2. Quarterly distribution of prescriber types for people initiating direct-acting antiviral treatment, 2016–2018**



Other physicians include supervised medical officers (e.g. interns, resident medical officers and registrars), public health physicians, temporary resident doctors, other/unclassified non-specialised and undefined.

Source: The Kirby Institute.<sup>5</sup>

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

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The reasons why the health care system has previously 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 was a major advance for HCV therapy.<sup>8</sup> Their high efficacy, short duration and excellent tolerability mean that most people are now suitable for treatment, most people who start treatment will be cured, and treatment is possible in the community as well as in specialist centres.

The PBS listing allowed DAA medicines to be prescribed by a medical practitioner experienced in the treatment of chronic HCV infection, or in consultation with a gastroenterologist, hepatologist or infectious diseases physician experienced in treating chronic HCV infection. This means that general practitioners are eligible to prescribe under the PBS in consultation with one of these specialists. “In consultation with” means that a GP must consult with one of the specified specialists by phone, fax, mail, email or videoconference to meet the prescriber eligibility requirements. Once GPs are experienced in treating chronic HCV infection, they may prescribe independently (see Section 2.2). The Pharmaceutical Benefits Advisory Committee (PBAC) has also expanded the criteria for prescribing DAA treatments to include authorised nurse practitioners experienced in the treatment of chronic HCV infection. This initiative will increase the timely, affordable and equitable access to treatment in Australia.

The DAA medicines are available through the PBS General Schedule (Section 85), as well as the Section 100 Highly Specialised Drugs (HSD) Program. This means that approved pharmacists in the community can dispense DAA medications for HCV. The S100 listing makes provision for treatment of prisoners through the HSD Program. The S85 provision for community dispensing of DAA therapy

prescribed by GPs or nurse practitioners 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 and for achieving the ambitious target set by the World Health Organization of HCV elimination by 2030.<sup>9</sup> The development of new models of care for HCV treatment will be necessary to achieve these goals. 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. A useful tool has been developed for GPs and nurses to facilitate remote consultations with tertiary care specialists and initiation of HCV therapy (available at: [www.gesa.org.au/resources/hepatitis-c-treatment/](http://www.gesa.org.au/resources/hepatitis-c-treatment/)).

### 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. As noted above, GPs who are experienced in the treatment of chronic HCV infection may prescribe independently. GPs who are not experienced in the treatment of HCV are eligible to prescribe the new HCV medicines provided this is done in consultation with an experienced gastroenterologist, hepatologist

or infectious diseases physician. The consultation process promotes GP prescribing and experience without the need for formal accreditation. The PBAC has not defined “experienced”. It should include all practitioners who have previously been accredited as prescribers for HCV medicines. For interested practitioners who do not have experience in treating HCV, we recommend participation in a formal education session. Links to useful and complementary online resources are given in **Box 1**. Clinical experience should be gained by providing treatment in consultation with a doctor who is experienced in the treatment of hepatitis C. Ideally, the treatments prescribed in consultation should occur with one specialist, to develop an ongoing working relationship. The PBS does not require formal accreditation. The important role of GPs in prescribing DAA therapy is supported by local data showing superior cost-effectiveness and net monetary benefit associated with a GP model of care.<sup>10</sup>

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.<sup>11,12</sup> Primary care-based treatment is suitable for most people living with HCV, particularly those with mild–moderate liver fibrosis. To support this, the availability and interpretation of simple tools for liver fibrosis assessment in the community is 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.

Prescribing by GPs is increasing. The proportion of HCV treatments prescribed by GPs increased from 14.6% in 2016 to 36.8% in 2017, and GP prescribers were the main providers of DAA treatment in all states except New South Wales and Victoria.<sup>13,14</sup> Continued promotion of GP prescribing, particularly in areas of low specialist concentration, will be a key model of care required to achieve HCV elimination targets.

### **Box 1. Resources containing useful information about assessment, treatment, monitoring and adherence**

- [learn.nps.org.au/mod/page/view.php?id=7278](https://learn.nps.org.au/mod/page/view.php?id=7278)
- [www.ashm.org.au/HCV/training](https://www.ashm.org.au/HCV/training)
- [www.racgp.org.au/education/professional-development/online-learning/webinars/hiv-and-hepatitis/hepatitis-c-cure-chronic-disease](https://www.racgp.org.au/education/professional-development/online-learning/webinars/hiv-and-hepatitis/hepatitis-c-cure-chronic-disease)
- [www.hepatologyassociation.com.au](https://www.hepatologyassociation.com.au)

### 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. Shared care between specialists and nurses has shown cost-effectiveness and net monetary benefits relative to traditional specialist-alone models of care.<sup>10</sup> 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.<sup>15,16</sup> Such models involve supervised practice within well-defined clinical protocols, including education, patient support, 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 treatment centres, primary health services for PWID, and remote regions, described below.<sup>16,17</sup>

Nurse practitioners can prescribe DAAs independently. The PBAC has now expanded the criteria for prescribing DAA treatments through the S100 HSD Program to include authorised nurse practitioners experienced in the treatment of chronic HCV infection. Medicines for the treatment of HCV were previously only listed for prescribing by authorised nurse practitioners under the General Schedule.

## 2.4 Models of care in custodial settings

Prison populations in Australia have a high prevalence of HCV infection, estimated at 30%,<sup>18</sup> which reflects the close relationship between injecting drug use, HCV infection and incarceration. Although treatment uptake in custodial settings across Australia was extremely low before March 2016, 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 shown the safety, feasibility and acceptability of nurse-led models of IFN-based HCV treatment in prison populations,<sup>11,19-22</sup> supported by specialist teleconferencing. With newer DAA regimens, the ease of treatment has been considerably enhanced in this setting. Treatment of prisoners is a priority to reduce the incidence of HCV transmission.<sup>23</sup>

All prisoners entering the prison system in Australia are offered screening for blood-borne viruses, including hepatitis C, but testing rates remain suboptimal. In May 2020, a point-of-care assay for HCV RNA was approved by the Australian Therapeutic Goods Administration (TGA). The Xpert<sup>®</sup> HCV viral load assay (Cepheid) measures HCV RNA from a finger-prick blood sample (100 µL) and provides a real-time result in less than 60 minutes. This assay may promote testing and treatment within the correctional system.

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

About 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.<sup>24</sup> Holistic care therefore includes harm reduction strategies, such as opioid substitution therapy, together with access to needle and syringe programs and education on safer injecting practices. In addition, treating PWID may reduce HCV transmission (treatment as prevention), making this group a high priority for HCV treatment.<sup>25</sup> 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.<sup>26-28</sup> Education and training of clinical staff at opioid substitution treatment centres to integrate HCV therapy with addiction therapy is therefore an important priority. Nurses can play a major and increasing role in this integration, through championing and facilitating HCV treatment in opioid substitution treatment centres and acting as an educational resource for medical practitioners prescribing HCV treatment in this setting.

As noted, a point-of-care assay for HCV RNA has now been approved by the TGA (May 2020). The Xpert<sup>®</sup> HCV viral load assay (Cepheid) measures HCV RNA from a finger-prick blood sample (100 µL) and provides a real-time result in less than 60 minutes. This assay will promote the development of hepatitis C “test-and-treat” models of care, which may simplify the treatment cascade, particularly for marginalised people.

## 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. A recent HCV mapping study has highlighted that rural and remote settings are frequently areas of high HCV prevalence but low treatment uptake.<sup>13,14</sup> Providing adequate resources and training for GPs and clinicians in these settings is therefore an important priority. Successful models of care using a nurse practitioner and telehealth clinics supported by tertiary care specialists have been described in Australia and overseas.<sup>11,29</sup> 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<sup>11,29</sup> 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

higher 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.

### 2.9 Models of care for people with mental illness

People diagnosed with mental illness are more likely to have risk factors for HCV transmission, and the prevalence of HCV is higher in this population than in the general community. A recent multicentre Australian study described an HCV seroprevalence of 11% among patients admitted urgently to psychiatric inpatient facilities.<sup>30</sup> When treatment was commenced, it was completed in all patients, with sustained virological response (SVR) able to be documented in 88% of treated patients. DAA treatment is not associated with the mental health side effects associated with IFN-based therapy. It is important to raise awareness of HCV testing and treatment among professionals and patients in the mental health community. HCV testing and treatment should be incorporated into models of care for people with mental illness.

Consensus recommendations	Grade
HCV treatment uptake in Australia must be substantially increased 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
GP-led HCV care should be a major driver of increased HCV treatment uptake. GPs and other primary care physicians who are experienced in the treatment of HCV can prescribe HCV medicines. Those who are not experienced in the treatment of HCV should provide treatment in consultation with an experienced specialist.	B2
For GPs and other primary care physicians, "experienced" should include all practitioners who have previously been accredited as prescribers for HCV medicines, as well as interested practitioners who have participated in a formal education session and completed treatments in consultation with an experienced specialist.	B2
Hepatology 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
Authorised nurse practitioners experienced in the treatment of chronic HCV can prescribe HCV medicines, and this will increase timely, affordable and equitable access to treatment in Australia.	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; people with mental illness; 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, and most diagnoses result from screening of at-risk populations (**Box 2**). 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. About 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.

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. Patients with prior positive HCV serological test results do not require repeated serological testing, as most people will have detectable HCV antibodies for life regardless of antiviral treatment.

#### Box 2. Populations to consider for a hepatitis C virus (HCV) screening test

- People who inject drugs or who have ever injected drugs
- People in custodial settings
- People with tattoos or body piercing
- People who received a blood transfusion or organ transplant before 1990
- People with coagulation disorders who received blood products or plasma-derived clotting factor treatment products before 1993
- Children born to HCV-infected mothers
- People infected with human immunodeficiency virus (HIV) or hepatitis B virus
- Sexual partners of an HCV-infected person (individuals at higher risk of sexual transmission include men who have sex with men and people with HCV–HIV coinfection)
- People with evidence of liver disease (persistently elevated alanine aminotransferase level)
- People who have had a needle-stick 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 initial 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
HCV seropositive people with undetectable HCV RNA (either spontaneous or after treatment) and with ongoing risk factors for HCV transmission should be screened annually for HCV infection with HCV RNA (PCR).	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 1**). This assessment provides the foundation for a successful virological outcome by establishing a therapeutic and collaborative relationship. Access to peer and social support; psychological, alcohol and drug counselling; and information about preventing transmission of HCV and avoidance of HCV reinfection should be provided.

Key elements of the pre-treatment assessment are to:

- Perform a virological evaluation to:
  - ▶ confirm the diagnosis of chronic HCV infection
  - ▶ where possible, identify the genotype of HCV infection
  - ▶ document the HCV treatment history
- Evaluate for the presence of cirrhosis
- Evaluate for the presence of hepatitis B virus (HBV) or human immunodeficiency virus (HIV) coinfection
- Consider whether coexisting liver diseases are present
- Consider concomitant medications for risk of drug–drug interactions, including ethinylloestradiol-containing oral contraceptives, over-the-counter preparations and recreational substances
- Discuss the need for contraception
- Discuss the importance of treatment adherence.

### 4.1 Perform a virological evaluation

#### 4.1.1 Confirm the diagnosis of chronic HCV infection

In an individual who is HCV antibody-positive, current HCV infection should be confirmed by a

PCR assay for HCV RNA. Quantitative PCR may be considered as part of the pre-treatment assessment because HCV RNA level can identify people who are eligible for a short treatment duration with sofosbuvir plus ledipasvir (see Section 5). As noted, the first point-of-care test for HCV RNA was approved by the TGA in May 2020. The Xpert<sup>®</sup> HCV viral load assay (Cepheid) measures HCV RNA from a finger-prick blood sample (100 µL) and provides a real-time result in less than 60 minutes. This assay will promote the development of hepatitis C “test-and-treat” models of care to increase screening and treatment rates.

#### 4.1.2 Consider testing to identify the genotype of HCV infection

The introduction of pan-genotypic treatment regimens for HCV infection means that it is no longer mandatory to determine HCV genotype before prescribing treatment. HCV genotype is not required by the PBS criteria before prescribing: sofosbuvir plus velpatasvir (first-line, treatment-naive); glecaprevir plus pibrentasvir (first-line, treatment-naive); and sofosbuvir plus velpatasvir plus voxilaprevir (NS5A inhibitor-experienced).

However, where possible, it is recommended that HCV genotype be documented in the patient’s medical record. Documenting HCV genotype is useful for people at high risk of reinfection, where genotype switch can differentiate reinfection from relapse. HCV genotype is also still relevant to decision making regarding sofosbuvir plus velpatasvir for people with cirrhosis, and for glecaprevir plus pibrentasvir in people who are treatment-experienced (see Section 5). HCV genotyping is a routine laboratory test and is reimbursed on the Medicare Benefits Schedule (MBS).

It is particularly important to document HCV genotype before prescribing DAA treatment regimens that are genotype-specific. Elbasvir plus grazoprevir and sofosbuvir plus ledipasvir are both genotype-specific treatment regimens, and HCV genotype should be determined before prescribing either regimen.

**Table 1. Pre-treatment assessment of people with chronic hepatitis C virus (HCV) infection**

<b>History</b>	<ul style="list-style-type: none"> <li>• Estimated duration of HCV infection</li> <li>• Previous HCV treatment experience — date, regimen and response</li> <li>• Cofactors for liver disease progression: alcohol intake, marijuana use, virological cofactors (HIV, HBV), diabetes, obesity</li> <li>• For those planned to receive ribavirin, note history of ischaemic heart disease or cardiovascular risk factors</li> <li>• Vaccinations against HBV and HAV</li> <li>• Physical and psychiatric comorbidities</li> <li>• Ongoing risk factors for viral transmission and reinfection</li> <li>• Social issues — potential barriers to medication adherence</li> </ul>
<b>Medication</b>	<ul style="list-style-type: none"> <li>• Concomitant medications (prescription, over-the-counter, illicit)</li> </ul>
<b>Physical examination</b>	<ul style="list-style-type: none"> <li>• Features of cirrhosis: hard liver edge, spider naevi, leukonychia</li> <li>• Features of decompensation or portal hypertension: jaundice, ascites, oedema, bruising, muscle wasting, encephalopathy</li> <li>• Body weight and body mass index</li> </ul>
<b>Virology</b>	<ul style="list-style-type: none"> <li>• HCV PCR</li> <li>• HCV genotype (where possible)*</li> <li>• HBV (HBsAg, anti-HBc, anti-HBs†), HIV, HAV serology</li> </ul>
<b>Investigations</b>	<ul style="list-style-type: none"> <li>• Full blood examination, liver function tests, urea and electrolytes, eGFR, INR</li> <li>• Pregnancy test for women of childbearing potential</li> <li>• Liver fibrosis assessment, eg:                             <ul style="list-style-type: none"> <li>▶ Elastography (FibroScan®, ARFI, SWE)</li> <li>▶ Serum biomarker (APRI, Hepascore, ELF test, FibroGENE‡)</li> </ul> </li> <li>• Liver ultrasound should be performed in people with cirrhosis to exclude hepatocellular carcinoma (within 3 months before starting DAAs)</li> </ul>
<p>anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; APRI = aspartate aminotransferase to platelet ratio index; ARFI = acoustic radiation force impulse; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; ELF = Enhanced Liver Fibrosis; HAV = hepatitis A virus; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; INR = international normalised ratio; PBS = Pharmaceutical Benefits Scheme; PCR = polymerase chain reaction; SWE = shear wave elastography.</p> <p>* HCV genotype is no longer required by the PBS criteria for pan-genotypic regimens: sofosbuvir + velpatasvir (first-line, treatment-naive); glecaprevir + pibrentasvir (first-line, treatment-naive); and sofosbuvir + velpatasvir + voxilaprevir (NS5A inhibitor-experienced). Genotype is important before prescribing elbasvir + grazoprevir or sofosbuvir + ledipasvir.</p> <p>† All three tests for HBV may be requested if the clinical notes indicate acute or chronic hepatitis.</p> <p>‡ Online calculator available at: <a href="http://www.fibrogene.com/viral_hepatitis.html">www.fibrogene.com/viral_hepatitis.html</a>.</p> <p><b>Note:</b> People living with hepatitis C can receive information, support and referral from community services, including:</p> <ul style="list-style-type: none"> <li>• Hepatitis Australia: <a href="http://www.hepatitisaustralia.com">www.hepatitisaustralia.com</a></li> <li>• Hepatitis Information Line: 1800 437 222</li> <li>• Australian Injecting &amp; Illicit Drug Users League: <a href="http://www.aivl.org.au">www.aivl.org.au</a></li> </ul>	

#### 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). Patients in whom a previous IFN-free regimen has failed frequently have resistant HCV variants.

#### 4.2 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 DAA 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, obesity, 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 thrombocytopenia. 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<sup>31</sup> and outperforms serum biomarkers for detecting cirrhosis.<sup>32</sup> 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.<sup>33,34</sup> 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, and the cut-offs for identification of cirrhosis are different.

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 IFNL3 genotype.<sup>35</sup> 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  $90 \times 10^9/L$  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  $<100 \times 10^9$ /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  $\geq 7$ , Model for End-Stage Liver Disease (MELD) score  $\geq 13$  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**<sup>36</sup>).

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.

#### 4.3 Consider whether there is HBV or HIV coinfection or coexisting liver disease present

Coinfection with HBV or HIV is more common in people with HCV infection than in the general population. 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. 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. HBV serology should include HBsAg, anti-HBc and anti-HBs (all three tests for HBV may be requested if the clinical notes indicate acute or chronic hepatitis). 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.

#### 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 alternative medicines (including traditional Chinese medicine and St John's wort), as well as recreational drugs. The University of Liverpool's Hepatitis Drug Interactions website

([www.hep-druginteractions.org](http://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. So too, with appropriate support, are people experiencing homelessness. People with no cirrhosis may continue to drink alcohol at low-risk levels during treatment (no more than two standard drinks on any day<sup>37</sup>). Complete abstinence from alcohol is recommended for people with cirrhosis or with alcohol dependence. For people with high-risk alcohol use, management

of alcohol dependence should be considered before DAA therapy.

The Australasian Hepatology Association (AHA) has developed the *AHA consensus guidelines for the provision of adherence support to patients with hepatitis C on direct acting antivirals*.<sup>38</sup> The guidelines consist of 24 consensus recommendations that promote a patient-centred approach, asserting that all patients are at risk of medication non-adherence. “Treatment readiness” is a pivotal concept that influences subsequent adherent behaviour. The AHA guidelines recommend supporting DAA adherence through implementing interventions focused on the patient, such as identifying memory triggers and hooks; and linguistic advice for health professionals, including using non-confrontational and non-judgemental language. See the AHA website ([www.hepatologyassociation.com.au](http://www.hepatologyassociation.com.au)) for further information.<sup>39</sup>

Consensus recommendations	Grade
Assessment of comorbid conditions and liver disease cofactors, including HBV and HIV infection, should occur before commencing DAA therapy, and these conditions should be addressed before or concurrent with DAA therapy.	A1
Where possible, HCV genotype should be documented in the patient’s medical record before prescribing 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 some DAA regimens.	A1
A non-invasive assessment of liver fibrosis is suitable for most people.	A1
People with cirrhosis should be screened for complications including: <ul style="list-style-type: none"> <li>• HCC (liver ultrasound)</li> <li>• oesophageal varices (gastroscopy)</li> <li>• osteoporosis (bone densitometry).</li> </ul>	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 HAV and HBV is recommended for all susceptible individuals with HCV infection.	A1
All concomitant medications must be assessed for potential drug–drug interactions.	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, a reduction in the risk of liver failure and HCC, and a 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 (<12 months) life expectancy 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

The DAA agents target multiple steps in the HCV replication life cycle, are highly effective and 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 TGA in Australia, including the NS3 protease inhibitors glecaprevir, grazoprevir and voxilaprevir; the NS5B nucleotide inhibitor sofosbuvir; and the NS5A inhibitors velpatasvir, pibrentasvir, elbasvir and ledipasvir. Several IFN-free regimens combining these DAAs have been PBS-listed for the treatment of people with HCV infection, including people with compensated and decompensated liver disease.

There are now three pan-genotypic DAA regimens listed on the PBS: sofosbuvir plus velpatasvir, glecaprevir plus pibrentasvir, and sofosbuvir plus velpatasvir plus voxilaprevir (**Table 2**). Other DAA regimens are all genotype-specific (**Table 3**). The treatment for HCV will continue to evolve, and this consensus statement will be updated as new data emerge.

### 5.4 Pan-genotypic regimens for chronic infection with genotypes 1–6 HCV

Pan-genotypic regimens are now recommended as first-line treatment for people with chronic hepatitis C infection (**Table 2**).

#### 5.4.1 Sofosbuvir plus velpatasvir

The first pan-genotypic regimen for the treatment of genotypes 1–6 HCV was the combination of sofosbuvir plus velpatasvir.<sup>40,41</sup> Sofosbuvir (NS5B inhibitor) plus velpatasvir (NS5A inhibitor) is a coformulated, once-daily, single-pill regimen. The recommended treatment duration is 12 weeks for all patients. Rates of SVR  $\geq 95\%$  were reported in clinical trials. Patients with genotype (Gt) 3 HCV who have cirrhosis and/or in whom peginterferon (pegIFN) plus ribavirin has previously failed have been observed to have slightly lower rates of SVR (89%–93%).<sup>41</sup> For this group, consider adding ribavirin to the treatment regimen (**Tables 2 and 3**). Patients with decompensated liver disease should also be treated with sofosbuvir plus velpatasvir plus ribavirin (see Section 8).

The most common adverse events in clinical trials were headache, fatigue, nausea and nasopharyngitis; rates were not significantly different compared with placebo.<sup>40,41</sup> Sofosbuvir and its main metabolite GS-331007 are renally excreted. In view of emerging data supporting the safety of sofosbuvir in people with severe renal impairment, the United States Food and Drug Administration (FDA) has recommended that no dosage adjustment of sofosbuvir-based regimens is required in patients with mild, moderate or severe chronic kidney disease (CKD), including those on dialysis.<sup>42</sup> An update to the Australian product information is anticipated (see Section 12.2). The combination of sofosbuvir plus velpatasvir is safe and well tolerated even in people with decompensated cirrhosis (see Section 8).

#### 5.4.2 Glecaprevir plus pibrentasvir

The combination of glecaprevir (NS3/4A protease inhibitor) plus pibrentasvir (NS5A inhibitor) is the

second pan-genotypic regimen to be approved for treating genotypes 1–6 HCV. Three tablets are taken orally, once daily, with food. Treatment duration varies according to the presence of cirrhosis and IFN-based treatment history (**Tables 2 and 3**). In treatment-naïve individuals, the duration of therapy is 8 weeks for those with no cirrhosis, and 12 weeks for those with cirrhosis. SVR rates >95% have been observed for all genotypes of HCV.<sup>43</sup>

Glecaprevir plus pibrentasvir is also approved for people who did not respond to prior therapy with regimens containing IFN, pegIFN, ribavirin and/or sofosbuvir, as well as those previously treated with an NS5A inhibitor without prior treatment with an NS3/4A protease inhibitor (**Table 3**). Glecaprevir plus pibrentasvir should not be used for people in whom treatment that included both an NS3/4A protease inhibitor and an NS5A inhibitor has previously failed. The recommended treatment duration varies from 8 to 16 weeks according to prior treatment history, HCV genotype and the presence of cirrhosis (**Table 3**). A detailed discussion of the recommended management of non-responders to HCV therapy is presented in Section 5.10.

Glecaprevir plus pibrentasvir was well tolerated in clinical studies. Headache, fatigue and nausea were the most common reported adverse effects but were uncommon and typically mild. Elevations in total bilirubin level of at least two times the upper limit of normal (ULN) were observed in 1% of participants, related to glecaprevir-mediated inhibition of bilirubin transporters and metabolism. Bilirubin elevations were asymptomatic, typically occurred early during treatment and were transient. Bilirubin elevations were predominantly indirect and not associated with alanine aminotransferase (ALT) elevations. Note that coadministration of glecaprevir plus pibrentasvir with ethinyloestradiol-containing products may increase the risk of ALT elevations and is contraindicated. Alternative contraceptive agents (eg, progestin-only contraception) or methods (eg, non-hormonal contraceptive method) are recommended for women in whom treatment with glecaprevir plus pibrentasvir is planned.

Exposure to glecaprevir is increased in the setting of hepatic impairment, and caution is recommended because of the possibility of drug-induced liver

injury. No dose adjustment is required for patients with mild hepatic impairment (Child–Pugh class A). However, glecaprevir plus pibrentasvir is not recommended for patients with moderate hepatic impairment (Child–Pugh class B) and is contraindicated for patients with severe hepatic impairment (Child–Pugh class C).

The major route of elimination of both glecaprevir and pibrentasvir is biliary–faecal, and <1% of the dose is excreted in the urine. No dose adjustment is required for patients with any degree of renal impairment, including patients on dialysis. Glecaprevir plus pibrentasvir is therefore a first-line treatment for people with renal impairment (Section 12).

#### 5.4.3 Sofosbuvir plus velpatasvir plus voxilaprevir

This triple-therapy regimen is the third pan-genotypic regimen for the treatment of HCV. The regimen includes three classes of antiviral agent: an NS5B nucleotide inhibitor (sofosbuvir), NS5A inhibitor (velpatasvir) and NS3 protease inhibitor (voxilaprevir). All three drugs are coformulated into a once-daily, single-pill regimen.

The regimen was specifically developed as a salvage regimen for people who did not respond to previous treatment with a first-line DAA regimen (Section 5.10.1.1). It is listed on the PBS for treating people who did not respond to treatment with a first-line DAA regimen that included an NS5A inhibitor. It is not approved for people who are treatment-naïve. Details of the previous NS5A inhibitor-containing treatment regimen must be provided at the time of application to the PBS.

In clinical trials, SVR rates >95% were observed.<sup>44</sup> SVR rates were high regardless of prior treatment experience (prior NS5A inhibitor, prior regimen that did not involve an NS5A inhibitor), the presence of cirrhosis or HCV genotype. The recommended treatment duration is 12 weeks for all patients (**Tables 2 and 3**). This treatment regimen is discussed in further detail in Section 5.10.1.1.

### 5.5 Genotype-specific treatment regimens for HCV infection

Genotype-specific regimens for the treatment of people with HCV infection are still listed on the PBS.

**Table 2. Recommended pan-genotypic treatment protocols for people with hepatitis C virus (HCV) infection and compensated liver disease, including people with HCV–HIV coinfection\***

		Treatment duration		
Regimen	HCV genotype	Pill burden	No cirrhosis	Cirrhosis
<b>First-line regimens for people who are treatment-naive</b>				
Sofosbuvir 400 mg, orally, daily + Velpatasvir 100 mg, orally, daily	1–6	1 pill daily	12 weeks	12 weeks <sup>†</sup>
Glecaprevir 300 mg, orally, daily + Pibrentasvir 120 mg, orally, daily	1–6	Once daily (3 pills)	8 weeks	12 weeks
<b>Regimen for people who do not respond to first-line therapy due to virological failure</b>				
Sofosbuvir 400 mg, orally, daily + Velpatasvir 100 mg, orally, daily + Voxilaprevir 100 mg, orally, daily	1–6	1 pill daily	12 weeks	12 weeks

HIV = human immunodeficiency virus.  
 \* Note that genotype-specific regimens for the treatment of people with HCV infection are still listed on the Pharmaceutical Benefits Scheme (see text).  
 † Addition of ribavirin may be considered for patients with genotype 3 HCV and compensated cirrhosis. Ribavirin dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg.

Elbasvir plus grazoprevir and sofosbuvir plus ledipasvir are both genotype-specific treatment regimens, and HCV genotype should be determined before prescribing either of these regimens. Both regimens are well tolerated and have efficacy ≥ 95% in people with no cirrhosis, as well as in people with cirrhosis.

Several other genotype-specific regimens for the treatment of HCV infection are no longer marketed in Australia and have been removed from this consensus statement. These include sofosbuvir plus daclatasvir, with or without ribavirin; sofosbuvir plus ribavirin; and paritaprevir (ritonavir-boosted) plus ombitasvir plus dasabuvir (PrOD), with or without ribavirin.

### 5.5.1 Elbasvir plus grazoprevir

The combination of elbasvir plus grazoprevir with or without ribavirin is available under the PBS for the treatment of Gt 1 and Gt 4 HCV. Elbasvir and grazoprevir have been coformulated into a once-daily, single-pill regimen. The recommended treatment regimen differs according to Gt 1 subtype. All

people with Gt 1b HCV infection should be treated with elbasvir plus grazoprevir for 12 weeks. For Gt 1a and Gt 4 HCV, treatment regimen varies according to treatment history (Table 3).<sup>45,46</sup> In people who are treatment-naive, as well as people who have previously relapsed after dual therapy with pegIFN and ribavirin or triple therapy with pegIFN and ribavirin plus boceprevir, simeprevir or telaprevir, the recommended treatment regimen is elbasvir plus grazoprevir for 12 weeks. In people who have previously experienced on-treatment failure during dual therapy with pegIFN and ribavirin or triple therapy with pegIFN and ribavirin plus boceprevir, simeprevir or telaprevir (partial responders and non-responders), the recommended regimen is elbasvir plus grazoprevir plus ribavirin for 16 weeks (see Section 5.10.2 and Table 3).<sup>47</sup> Overall SVR rates ≥ 95% were observed in Phase III studies using the recommended treatment regimens.<sup>45-47</sup>

The regimen should be used with caution in people with compensated cirrhosis and is contraindicated in patients with decompensated cirrhosis and/or a history of liver decompensation. Exposure to all

protease inhibitors on the market is increased in the setting of hepatic impairment, and caution is recommended because of the possibility of drug-induced liver injury.

No dosage adjustment of elbasvir or grazoprevir is required in patients with renal impairment. In patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m<sup>2</sup>) or with end-stage renal disease, including patients receiving dialysis, elbasvir plus grazoprevir should be administered without ribavirin (see Section 12).<sup>48</sup>

Elbasvir plus grazoprevir is well tolerated, and discontinuation rates in the registration studies were less than 1%. Headache, nausea and fatigue were the most common adverse effects, but were typically mild and occurred at the same frequency as in people who were treated with placebo. Typical ribavirin-related adverse events were observed in those who received ribavirin. Elbasvir plus grazoprevir may be associated with biochemical abnormalities. Late rises in serum ALT level have been reported in people treated with grazoprevir. Less than 1% of people (13/1690) treated with elbasvir plus grazoprevir ± ribavirin in clinical trials were reported to experience an elevated ALT level > 5 × ULN, typically at or after Week 8 of treatment. Most of these late elevations in ALT level were asymptomatic and resolved despite ongoing treatment. Cirrhosis was not a risk factor for rise in ALT level, but the frequency was higher in people with higher grazoprevir plasma concentrations, making careful evaluation for possible drug–drug interactions an important pre-treatment assessment. Liver function tests should be performed before therapy and at Week 8 of treatment. For people receiving 16 weeks of therapy, additional liver function tests should be performed at Week 12 of treatment (see Section 6). Elbasvir plus grazoprevir should be discontinued if ALT levels remain persistently > 10 × ULN.

Elevations in serum bilirubin level were also observed in a small proportion of people treated with elbasvir plus grazoprevir. Elevations in bilirubin level > 2.5 × ULN were observed in 6% of patients receiving elbasvir plus grazoprevir with ribavirin, compared with < 1% in those receiving elbasvir plus grazoprevir alone.<sup>49</sup> These increases in bilirubin level

were predominantly indirect. Elevations in bilirubin level were typically not associated with serum ALT level elevations.

Note that ribavirin can cause adverse events, including anaemia, rash, cough, dyspnoea, insomnia and anxiety. Anaemia is more common in patients with decompensated liver disease, and it is recommended that ribavirin be started at a low dose of 600 mg daily for these patients. Ribavirin is renally excreted, and dose adjustment is required according to eGFR (see Section 12). Patients with renal impairment have increased risk of anaemia during ribavirin therapy. Monitoring of haemoglobin levels is recommended every 2–4 weeks during ribavirin therapy in people with decompensated liver disease.

As ribavirin is teratogenic, both women and men should be counselled about the risks of pregnancy and advised that two forms of contraception are recommended while taking ribavirin and for 6 months after treatment.

### 5.5.2 Sofosbuvir plus ledipasvir

Sofosbuvir plus ledipasvir is a coformulated, once-daily, single-pill regimen for the treatment of Gt 1 HCV infection. 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).<sup>33,34</sup> Rates of SVR ≥ 95% are achieved in all patient groups, including those with cirrhosis and non-responders to first-generation protease inhibitor therapy.<sup>33,34</sup> Response rates are similar for Gt 1a and Gt 1b HCV. A shortened treatment duration of 8 weeks should be considered in treatment-naive people with no cirrhosis who have baseline HCV RNA levels < 6 × 10<sup>6</sup> IU/mL.<sup>50</sup> Baseline HCV RNA levels ≥ 6 × 10<sup>6</sup> IU/mL are associated with higher relapse rates with 8 versus 12 weeks of treatment (10% v 1%).<sup>50</sup> 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.<sup>33,34</sup> As noted, sofosbuvir and its main metabolite GS-331007 are renally excreted. In view of emerging data supporting the safety of sofosbuvir in patients with severe renal impairment, the US FDA has recommended that

**Table 3. Recommended treatment protocols for treatment-experienced people with hepatitis C virus (HCV) infection and compensated liver disease, including people with HCV–HIV coinfection**

Salvage regimen (all doses are orally, daily)	Prior treatment history				
	Sofosbuvir + NS5A inhibitor	NS3 PI + NS5A inhibitor ± NS5B inhibitor	Sofosbuvir + RBV <b>or</b> PegIFN + RBV + sofosbuvir	PegIFN + RBV + NS3 PI	PegIFN + RBV
Sofosbuvir 400 mg + Velpatasvir 100 mg + Voxilaprevir 100 mg	Gt 1–6:*^ 12 weeks	Gt 1–6:*^ 12 weeks	Gt 1–6:*^ 12 weeks	†	†
Glecaprevir 300 mg + Pibrentasvir 120 mg	Gt 1 only (PI naive): 16 weeks		Gt 1, 2, 4, 5, 6: No cirrhosis: 8 weeks‡ Cirrhosis: 12 weeks Gt 3: 16 weeks	Gt 1 only (NS5A inhibitor naive): 12 weeks	Gt 1, 2, 4, 5, 6: No cirrhosis: 8 weeks‡ Cirrhosis: 12 weeks Gt 3: 16 weeks
Sofosbuvir 400 mg + Velpatasvir 100 mg			Gt 1b, 2, 4, 5, 6:* 12 weeks§	Gt 1–6: 12 weeks	Gt 1–6: 12 weeks§
Elbasvir 50 mg + Grazoprevir 100 mg ± Ribavirin 1000/1200 mg				Gt 1b: 12 weeks (no RBV) Gt 1a relapser:¶ 12 weeks OTVF: 16 weeks + RBV	Gt 1b: 12 weeks (no RBV) Gt 1a relapser:¶ 12 weeks OTVF: 16 weeks + RBV
Sofosbuvir 400 mg + Ledipasvir 90 mg				Gt 1: No cirrhosis: 12 weeks Cirrhosis: 24 weeks	Gt 1: No cirrhosis: 12 weeks Cirrhosis: 24 weeks

Gt = genotype; HIV = human immunodeficiency virus; OTVF = on-treatment virological failure (null response, partial response, virological breakthrough or rebound, or intolerance to prior treatment); PegIFN = peginterferon; PI = protease inhibitor; RBV = ribavirin.

\* Additional benefit of sofosbuvir + velpatasvir + voxilaprevir over sofosbuvir + velpatasvir has not been demonstrated in adults with Gt 1b, 2, 4, 5 or 6 HCV previously treated with sofosbuvir without an NS5A inhibitor.

^ Sofosbuvir + velpatasvir + voxilaprevir is not yet PBS-listed for the treatment of Gt 1–6 HCV in people in whom DAA therapy has previously failed.

† Sofosbuvir + velpatasvir + voxilaprevir is not PBS-listed for the treatment of non-responders to pegIFN + RBV ± NS3 PI.

‡ Studies in people with no cirrhosis enrolled very few patients with advanced fibrosis, and we recommend 12 weeks' treatment in people with advanced fibrosis (liver stiffness > 9.5 kPa).

§ Addition of RBV may be considered for patients with Gt 3 HCV and compensated cirrhosis. RBV dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg.

¶ Relapser = patient who failed to achieve sustained virological response despite achieving an end-of-treatment response.

no dosage adjustment of sofosbuvir-based regimens is required in patients with mild, moderate or severe CKD, including those on dialysis.<sup>42</sup> An update to the Australian product information is anticipated.

### 5.6 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](http://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.

### 5.7 Pregnancy and breastfeeding

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; velpatasvir, B1; ledipasvir, B1; glecaprevir, B1; pibrentasvir, B1; grazoprevir, B1; elbasvir, B1) 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). 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.

Coadministration of ethinylloestradiol-containing medications, such as combined oral contraceptives,

with glecaprevir and pibrentasvir has been associated with serum ALT elevations. Coadministration is therefore contraindicated. For women using combined oral contraceptives, alternative DAA regimens are recommended.

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.

### 5.8 Children

Clinical trials have recently shown that treatment of HCV infection in children under the age of 18 years is safe and effective. Treatment regimens that have been evaluated in children aged under 18 years include sofosbuvir plus velpatasvir, glecaprevir plus pibrentasvir, and sofosbuvir plus ledipasvir (for Gt 1 HCV).<sup>51–56</sup> HCV treatments listed on the PBS can now be prescribed to children under the age of 18 years. Children aged under 18 years should be referred to a paediatrician who is experienced in the treatment of HCV for discussion about therapy. A document providing specific guidance on the treatment of HCV infection in children under the age of 18 years is in development and will be made available on the GESA and Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine websites.

### 5.9 Direct-acting antivirals and drug resistance

Resistance-associated substitutions (RASs) have been identified in vitro for all of the DAAs approved for clinical use. NS3 and NS5A RASs may arise spontaneously due to the error-prone HCV RNA polymerase and therefore are present before DAA therapy. NS3 and NS5A RASs are selected during DAA therapy and enriched in people in whom treatment fails with NS3 and NS5A inhibitor-containing regimens, respectively. NS5B RASs have been reported but are very rare. For most regimens currently listed on the PBS, there is no clinical role for baseline HCV resistance testing in treatment-naïve people or prior non-responders to either pegIFN-based therapy or protease inhibitor-based triple therapy, because such high SVR rates are achieved.

The frequency of HCV RASs is low in the Australian population (< 5%–10% using population sequencing),<sup>57,58</sup> meaning that the clinical yield from testing is low. Furthermore, RAS testing is not widely available, nor is it currently reimbursed by the government. Given the low frequency of relevant NS5A RASs in the Australian population, we do not recommend routine resistance testing before treatment with DAAs in treatment-naïve people.

Where available, resistance testing for NS3, NS5B and NS5A RASs should be considered after failure of combination DAA treatment. Resistance testing involves direct sequencing of the HCV genome and is available through specialised laboratories. HCV sequencing may also be used as a research tool to differentiate relapse from reinfection and to document transmission. Patients in whom combination DAA therapy fails should be managed in specialist centres.

## 5.10 Salvage therapy

### 5.10.1 Non-responders to interferon-free therapy

Non-response to DAA treatment can be defined simply by detectable serum HCV RNA after treatment. Non-response to a first-line DAA regimen can be due to true virological failure (virological breakthrough during DAA therapy, or virological relapse after treatment in a patient who achieved complete virological suppression during treatment), non-virological failure due to non-adherence, or HCV reinfection. True virological failure is attributable to the emergence of HCV variants that have selected RASs. It is more common in people with cirrhosis, especially advanced cirrhosis, as well as in those with Gt 3 HCV infection.

We suggest that people who do not respond to IFN-free DAA therapy should be referred to a specialist centre with experience in treating HCV infection (including salvage therapy) and advanced liver disease. Details of the first treatment course should be documented. A careful history should be taken to identify treatment adherence, as well as other factors that may have had limited adherence (social factors,

adverse events or possible drug–drug interactions that may have led to inadvertent underdosing). Risk factors for reinfection should be explored. Clinicians should carefully assess for the presence of cirrhosis, which may not have been diagnosed before the first treatment course. Differentiating true virological failure from relapse caused by non-adherence, or from reinfection, may be difficult. True virological failure can be defined by HCV resistance testing; this is useful but, in practice, is not widely available, is not reimbursed and is unlikely to change management. HCV genotyping should be repeated, as a genotype switch indicates reinfection. However, the absence of a genotype switch does not exclude HCV reinfection.

In the setting of a confident diagnosis of HCV reinfection, we recommend treatment as for people who are treatment-naïve. Otherwise, we recommend treatment for virological failure as described below.

#### 5.10.1.1 Sofosbuvir plus velpatasvir plus voxilaprevir

Sofosbuvir plus velpatasvir plus voxilaprevir was specifically developed as a pan-genotypic salvage regimen for people who did not respond to previous treatment with a first-line DAA regimen. This is the preferred salvage regimen. It is not approved for people who are treatment-naïve. The regimen includes three classes of antiviral agent: an NS5B nucleotide inhibitor (sofosbuvir), NS5A inhibitor (velpatasvir) and NS3 protease inhibitor (voxilaprevir). All three drugs are coformulated into a once-daily, single-pill regimen. The recommended treatment duration is 12 weeks for all patients (**Tables 2 and 3**). In clinical trials, SVR rates > 95% were observed.<sup>44</sup> SVR rates were high regardless of prior treatment experience (prior NS5A inhibitor, prior regimen that did not involve an NS5A inhibitor), the presence of cirrhosis or HCV genotype. The presence of RASs at baseline (NS3/NS5A/NS5B, frequency > 15%) was not associated with lower SVR rates.<sup>44</sup>

The most common adverse events in clinical trials were headache, fatigue and diarrhoea. Diarrhoea was more common (18%–20%) than with sofosbuvir plus velpatasvir or placebo. Most occurrences of diarrhoea were mild in severity; the incidence of grade

2 diarrhoea was low (1% to 3%). Sofosbuvir and its main metabolite GS-331007 are renally excreted. In view of emerging data supporting the safety of sofosbuvir in patients with severe renal impairment, the US FDA has recommended that no dosage adjustment of sofosbuvir-based regimens is required in patients with mild, moderate or severe CKD, including those on dialysis.<sup>42</sup> An update to the Australian product information is anticipated (see Section 12.2). Voxilaprevir is a protease inhibitor, and exposure is increased in the setting of hepatic impairment. No dose adjustment is required for patients with mild hepatic impairment (Child–Pugh class A), but treatment with voxilaprevir is not recommended for patients with moderate or severe hepatic impairment (Child–Pugh class B or C).

#### 5.10.1.2 Glecaprevir plus pibrentasvir

This regimen is approved for people who are treatment-naive (Section 5.4.2), as well as for those who did not respond to prior IFN-free DAA therapy. Glecaprevir plus pibrentasvir is PBS-listed for (i) people previously treated with an NS5A inhibitor without prior treatment with a protease inhibitor; or (ii) people previously treated with a protease inhibitor without prior treatment with an NS5A inhibitor, as well as people treated with sofosbuvir plus ribavirin (**Table 3**). Glecaprevir plus pibrentasvir should not be used for people in whom treatment that included both a protease inhibitor and an NS5A inhibitor has previously failed. The recommended treatment duration varies from 8 to 16 weeks according to prior treatment history, HCV genotype and the presence of cirrhosis (**Table 3**).

Although this regimen is a first-line pan-genotypic treatment option for people who are treatment-naive, the data supporting efficacy in people in whom DAA therapy has failed are limited.<sup>59,60</sup> MAGELLAN-1 was a randomised, multipart, open-label study of 141 patients with Gt 1 or 4 HCV who failed prior treatment with a regimen containing NS5A and/or protease inhibitors: Part 1 ( $n = 50$ ) was a randomised dose-finding study,<sup>59</sup> and Part 2 ( $n = 91$ ) was a randomised study of patients with or without cirrhosis that compared 12 weeks versus 16 weeks of treatment.<sup>60</sup> The SVR in protease inhibitor-experienced

(NS5A inhibitor-naive) patients with or without cirrhosis who received 12 weeks of treatment was 100% (14/14). The SVR in patients who had treatment experience with NS5A inhibitors (alone or with a protease inhibitor) was 94% (17/18) in those exposed to an NS5A inhibitor only, and 81% (13/16) in those who had previously failed treatment that included both a protease inhibitor and an NS5A inhibitor.<sup>60</sup> Glecaprevir plus pibrentasvir has not been evaluated as salvage therapy for people with Gt 2 or 3 HCV infection in whom treatment with sofosbuvir plus ribavirin has failed, but it is approved on the basis that these people have not been exposed to an NS5A inhibitor or protease inhibitor.

#### 5.10.1.3 Decompensated liver disease

Salvage therapy for people with decompensated liver disease is complicated. The DAA regimens that are PBS-listed for the treatment of people in whom prior DAA therapy has failed both include protease inhibitors, which are not recommended for people with Child–Pugh B or C cirrhosis. These people should therefore be considered for expedited liver transplantation (Section 8). For those who are not transplant candidates, treatment options are limited. PBS restrictions do not prohibit patients receiving retreatment with the same regimen, and treatment with sofosbuvir plus velpatasvir plus ribavirin for 24 weeks or longer should be considered. These patients should be referred to a specialist experienced in the management of HCV and cirrhosis.

#### 5.10.2 People with Gt 1 HCV who did not respond to treatment with peginterferon-alfa plus ribavirin, with or without a protease inhibitor

There are few people in whom previous treatment with pegIFN plus ribavirin, with or without a protease inhibitor, has failed and who have not yet been retreated with a DAA regimen. Several DAA regimens are approved for use in this situation (**Table 3**). Response rates are similar to those observed in treatment-naive individuals. The combination of sofosbuvir plus velpatasvir plus voxilaprevir is not approved for people who have not yet received treatment with an IFN-free DAA regimen.

<b>Consensus recommendations</b>	<b>Grade</b>
All individuals with chronic HCV infection should be considered for antiviral therapy.	A1
Choice of treatment regimen should be based on: <ul style="list-style-type: none"> <li>• HCV genotype and subtype</li> <li>• the presence or absence of cirrhosis</li> <li>• the presence or absence of liver decompensation</li> <li>• prior treatment history</li> <li>• the potential for drug–drug interactions</li> <li>• comorbidities</li> </ul>	A1
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
Breastfeeding women should not be treated with DAAs.	B1
<b>People who are treatment-naïve (see Table 2)</b>	
First-line treatment regimens that are pan-genotypic include: <ul style="list-style-type: none"> <li>• sofosbuvir + velpatasvir for 12 weeks</li> <li>• glecaprevir + pibrentasvir for 8 or 12 weeks</li> </ul>	A1
Recommended treatment regimens for chronic Gt 1 HCV infection and compensated liver disease are: <ul style="list-style-type: none"> <li>• sofosbuvir + velpatasvir for 12 weeks</li> <li>• glecaprevir + pibrentasvir for 8 or 12 weeks</li> <li>• elbasvir + grazoprevir for 12 weeks</li> <li>• sofosbuvir + ledipasvir for 8 or 12 weeks</li> </ul>	A1
Recommended treatment regimens for chronic Gt 2 HCV infection and compensated liver disease are: <ul style="list-style-type: none"> <li>• sofosbuvir + velpatasvir for 12 weeks</li> <li>• glecaprevir + pibrentasvir for 8 or 12 weeks</li> </ul>	A1
Recommended treatment regimens for chronic Gt 3 HCV infection and compensated liver disease are: <ul style="list-style-type: none"> <li>• sofosbuvir + velpatasvir ± ribavirin for 12 weeks</li> <li>• glecaprevir + pibrentasvir for 8 or 12 weeks</li> </ul>	A1
Recommended treatment regimens for chronic Gt 4 HCV infection and compensated liver disease are: <ul style="list-style-type: none"> <li>• sofosbuvir + velpatasvir for 12 weeks</li> <li>• glecaprevir + pibrentasvir for 8 or 12 weeks</li> <li>• elbasvir + grazoprevir for 12 weeks</li> </ul>	A1
Recommended treatment regimens for chronic Gt 5/6 HCV infection and compensated liver disease are: <ul style="list-style-type: none"> <li>• sofosbuvir + velpatasvir for 12 weeks</li> <li>• glecaprevir + pibrentasvir for 8 or 12 weeks</li> </ul>	A1

Consensus recommendations (continued)	Grade
<b>People in whom DAA therapy has failed (see Table 3)</b>	
People in whom first-line DAA therapy fails should be referred to a specialist centre for consideration of salvage therapy	B1
<p>The recommended treatment regimen for people with compensated liver disease in whom first-line DAA therapy has failed is:</p> <ul style="list-style-type: none"> <li>• sofosbuvir + velpatasvir + voxilaprevir for 12 weeks</li> </ul>	A1
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

## 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 4). All patients should be provided with contact details for a clinician to contact if problems arise in between appointments. For many people, no assessment will be required during treatment, and review at 12 weeks after completion of therapy can be organised to document SVR.

More intensive monitoring may be required in certain populations. On-treatment and end-of-treatment virological assessments may be considered if there are concerns about adherence to therapy, particularly if there are risk factors for reinfection. Low levels of plasma HCV RNA can be detected in up to 20% of people using sensitive PCR assays at Week 4 of treatment, but this does not predict treatment failure, nor does it require treatment extension. The product information for the regimen of elbasvir plus grazoprevir recommends that liver function tests be performed at Week 8 for people treated for 12 weeks' duration, and at Week 8 and Week 12 for those receiving 16 weeks of treatment.<sup>49</sup>

Patients treated with ribavirin require monitoring of haemoglobin levels. People with advanced liver disease (portal hypertension or hepatic decompensation) require more intensive monitoring. In this setting, more frequent liver function tests 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.

Screening for HCC is recommended at baseline for all people living with cirrhosis. We recommend ongoing surveillance with liver ultrasound every 6 months. The impact of DAA treatment on HCC risk is not yet clear (see Section 14). HCV treatment should not suspend HCC screening programs. We recommend a liver ultrasound be performed before starting DAA treatment (within 1 month before starting treatment) for all patients with cirrhosis to ensure that HCC screening remains up to date during the treatment and follow-up period.

People with HCV–HBV coinfection are at risk of HBV reactivation during DAA therapy for HCV (see Section 11). Specific monitoring for HBV reactivation is required. It is recommended that these people be treated by a specialist with experience in treating HCV and HBV infection.

Consensus recommendations	Grade
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 4. 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 an 8–12-week treatment regimen:

Week 0	<ul style="list-style-type: none"> <li>Pre-treatment blood tests, including LFTs, HCV PCR (Table 1)</li> </ul>
Week 12 post-treatment (SVR)	<ul style="list-style-type: none"> <li>LFTs, HCV PCR (qualitative)</li> </ul>

- More intensive monitoring may be required in certain populations (see text).
- People treated with elbasvir plus grazoprevir should have LFTs at Week 8 to screen for hepatotoxicity.

#### B. Monitoring after SVR

SVR, no cirrhosis and normal LFT results (males, ALT  $\leq$  30 U/L; females, ALT  $\leq$  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  $\alpha$ -1-antitrypsin level

SVR and cirrhosis:

- Patients with cirrhosis require long-term monitoring and should be enrolled in screening programs for:
  - HCC — liver ultrasound  $\pm$  serum  $\alpha$ -fetoprotein level
  - oesophageal varices — gastroscopy
  - osteoporosis — dual emission x-ray absorptiometry

SVR and risk of reinfection:

- Patients with with ongoing risk of HCV infection should have at least annual HCV RNA testing
- Anti-HCV antibodies will remain positive in all people with prior exposure and this does not require repeated testing

ALT = alanine aminotransferase; AMA = anti-mitochondrial antibody; ANA = anti-nuclear antibodies; ASMA = anti-smooth muscle antibodies; HCC = hepatocellular carcinoma; LFT = liver function test; LKM = liver–kidney microsome; PCR = polymerase chain reaction; SVR = sustained virological response at least 12 weeks after treatment (cure).

## 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 SVR at 24 weeks.<sup>61</sup> 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 SVR that persistence of anti-HCV antibodies is expected and that this does not represent active infection, nor does it confer immunity to reinfection. The medical records of patients for whom SVR is confirmed should be amended to reflect that they are no longer living with HCV.

Those who fail to achieve 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.

People with ongoing risk factors for the transmission of HCV infection should have at least annual HCV RNA testing performed. As noted, anti-HCV antibodies will remain positive in all people with prior exposure and this does not require repeated testing.

### 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 4**). All people with cirrhosis need to enter appropriate surveillance programs for HCC and oesophageal varices, as recommended by existing guidelines.<sup>62-64</sup>

As liver stiffness decreases after cure of HCV, due to a reduction in inflammation, people with cirrhosis continue to require long-term monitoring for complications of cirrhosis even if they have a liver stiffness measurement < 12.5 kPa after treatment. 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
People with ongoing risk factors for the transmission of HCV infection should have at least annual HCV RNA testing performed.	B1

## 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  $\geq$  B7 or MELD score  $\geq$  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.<sup>65</sup>

In people with decompensated liver disease, the goal of therapy is SVR, with the aim of improving liver function. The first regimen to be specifically

listed on the PBS for treatment of decompensated liver disease was sofosbuvir plus velpatasvir plus ribavirin. The eligibility criteria for other DAA regimens that are PBS-listed for the treatment of HCV do not distinguish between people with compensated versus decompensated liver disease, with the exception of regimens that include a protease inhibitor (glecaprevir plus pibrentasvir, sofosbuvir plus velpatasvir plus voxilaprevir, or elbasvir plus grazoprevir), which are contraindicated in the setting of hepatic decompensation (Child–Pugh score B or C) (**Table 5**).

The efficacy of several DAA regimens in people with decompensated liver disease has been formally evaluated in clinical trials.<sup>66–72</sup>

Data from the ASTRAL-4 study support the combination of sofosbuvir plus velpatasvir plus ribavirin for 12 weeks as a first-line treatment for patients with HCV and decompensated liver disease.<sup>73</sup> In this study, 267 patients with Gt 1, 2, 3, 4 or 6 HCV and decompensated cirrhosis (90% Child–Pugh class B or C) were randomly assigned to treatment with sofosbuvir plus velpatasvir for 12 weeks, or sofosbuvir plus velpatasvir plus ribavirin (daily, according to body weight: < 75 kg, 1000 mg;  $\geq$  75 kg, 1200 mg) for 12 weeks, or sofosbuvir plus velpatasvir for 24 weeks.<sup>73</sup> SVR was 94% in people treated with sofosbuvir plus velpatasvir plus ribavirin for 12 weeks, versus 83% with sofosbuvir plus velpatasvir for 12 weeks, versus 86% with sofosbuvir plus velpatasvir for 24 weeks. Post-treatment virological relapse was observed in 2% of the 12-week group receiving sofosbuvir plus velpatasvir plus ribavirin, compared with 12% and 9%, respectively, in the groups that did not receive ribavirin. Although the ASTRAL-4 study was not powered to generate statistical significance, the data suggest that sofosbuvir plus velpatasvir plus ribavirin for 12 weeks is the optimal regimen for patients who will tolerate ribavirin. For patients in whom there is a concern about ribavirin intolerance, we recommend a starting dose of 600 mg

**Table 5. Recommended treatment protocols for hepatitis C virus (HCV) infection in people with decompensated liver disease**

Regimen	HCV genotype	Duration
Sofosbuvir 400 mg, orally, daily + Velpatasvir 100 mg, orally, daily + Ribavirin 600 mg, orally, daily*	1–6	12 weeks
Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily ± Ribavirin 600 mg, orally, daily*†	1	12 weeks (24 weeks if ribavirin-intolerant)

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

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

† Ribavirin is not PBS-listed for use in combination with sofosbuvir + ledipasvir.

**Notes:** The combination of sofosbuvir + velpatasvir + ribavirin is the only DAA regimen to 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). Regimens containing the protease inhibitors glecaprevir, voxilaprevir or grazoprevir (glecaprevir + pibrentasvir, sofosbuvir + velpatasvir + voxilaprevir, and elbasvir + grazoprevir) are contraindicated in people with decompensated liver disease.

daily, or treatment for 24 weeks without ribavirin. Important exclusion criteria for the ASTRAL-4 study included Child–Pugh score > C9, haemoglobin level < 100 g/L, platelet count  $\leq 30\,000/\text{mm}^3$ , bilirubin level > 85.5  $\mu\text{mol/L}$  and creatinine clearance < 50 mL/min.

The combination of sofosbuvir plus ledipasvir plus ribavirin for 12 weeks is another first-line regimen for Gt 1 HCV.<sup>66,67</sup> 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 available under the PBS and can be recommended as a reasonable alternative (Table 5).

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. The rates of SVR observed using these regimens for

Gt 1 HCV in the setting of Child–Pugh B cirrhosis were 85%–95%.<sup>67,70,74,75</sup> 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%<sup>67,70,74,75</sup>) than in those with Child–Pugh B scores. Important exclusion criteria for the Phase II SOLAR-1/2 studies that evaluated ribavirin-containing regimens included a haemoglobin level < 100 g/L, platelet count <  $20 \times 10^9/\text{L}$ , bilirubin level > 170  $\mu\text{mol/L}$  (with the exception of those with fibrosing cholestatic hepatitis [FCH]; see Section 9.4) and serum creatinine level >  $2.5 \times \text{ULN}$ . Prescriptions for sofosbuvir plus daclatasvir decreased dramatically after the introduction of sofosbuvir plus velpatasvir, which is a single-tablet regimen. Note that daclatasvir-containing regimens will be removed from the PBS later in 2020.

Patients with Gt 3 HCV and decompensated liver disease are harder to cure.<sup>71</sup> The combination of sofosbuvir plus velpatasvir plus ribavirin for 12 weeks is the only regimen to be prospectively evaluated in a Phase III study of patients with decompensated liver

disease and should be first-line treatment. Again, we recommend that ribavirin dosing in this population be started at 600 mg daily and incremented as tolerated.

There are very limited clinical data available to support treatment recommendations for patients with Gt 2, 4, 5 or 6 HCV infection and decompensated liver disease, which are based on expert opinion. As for patients with Gt 1 or 3 HCV, we recommend treatment with sofosbuvir plus velpatasvir plus ribavirin for 12 weeks.

People with decompensated liver disease should not be treated with glecaprevir, voxilaprevir or elbasvir plus grazoprevir. 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 HCV cure 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.<sup>71,75</sup> 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.

Note that ribavirin can cause adverse events, including anaemia, rash, cough, dyspnoea, insomnia and anxiety. Anaemia is more common in patients with decompensated liver disease, and it is recommended that ribavirin be started at a low dose of 600 mg daily for these patients. Ribavirin is renally excreted, and dose adjustment is required according to eGFR (see Section 12). Patients with renal impairment have increased risk of anaemia during ribavirin therapy. Monitoring of haemoglobin levels is recommended every 2–4 weeks during ribavirin therapy in people with decompensated liver disease.

As ribavirin is teratogenic, both women and men should be counselled about the risks of pregnancy and advised that two forms of contraception are recommended while taking ribavirin and for 6 months after treatment.

Consensus recommendations	Grade
Indications for assessment by a liver transplant centre include a Child–Pugh score $\geq$ B7, MELD score $\geq$ 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 $\geq$ B7.	A1
The first-line treatment regimens for chronic Gt 1 HCV infection and decompensated liver disease are (see Table 5):	
<ul style="list-style-type: none"> <li>sofosbuvir + velpatasvir + ribavirin for 12 weeks</li> </ul>	A1
<ul style="list-style-type: none"> <li>sofosbuvir + ledipasvir <math>\pm</math> ribavirin for 12 or 24 weeks</li> </ul>	A1
The first-line treatment regimen for chronic Gt 3 HCV infection and decompensated liver disease is (see Table 5):	
<ul style="list-style-type: none"> <li>sofosbuvir + velpatasvir + ribavirin for 12 weeks</li> </ul>	A1
The first-line treatment regimen for chronic Gt 2, 4–6 HCV infection and decompensated liver disease is (see Table 5):	
<ul style="list-style-type: none"> <li>sofosbuvir + velpatasvir + ribavirin for 12 weeks</li> </ul>	A1
The following treatments should NOT BE USED in people with decompensated liver disease:	A1
<ul style="list-style-type: none"> <li>sofosbuvir + velpatasvir + voxilaprevir (protease inhibitor)</li> <li>glecaprevir (protease inhibitor) + pibrentasvir</li> <li>elbasvir + grazoprevir (protease inhibitor)</li> </ul>	

## 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.<sup>76</sup> 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.<sup>77</sup> Furthermore, in the setting of immunosuppression, 2%–5% of patients develop FCH within 6 months of transplantation.<sup>78</sup> 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.

Since the introduction of DAA treatments, most Australian patients with established HCV recurrence after liver transplantation have been treated. Issues regarding HCV and liver transplantation have shifted significantly. Patients requiring transplantation for decompensated cirrhosis associated with HCV may have been successfully treated and come to transplantation without viraemia (Section 8). Despite viral clearance, liver function may have failed to improve in these patients, usually associated with adverse baseline factors, including ascites or encephalopathy, serum albumin level < 35 g/L, ALT

level < 60 U/L, and body mass index > 25 kg/m<sup>2</sup>, which are associated with an increased risk of not achieving a reduction in Child–Pugh score to class A,<sup>79</sup> or significant comorbidities (eg, alcohol use, obesity, diabetes). In other patients, antiviral treatment may have failed in association with the development of RASs. Salvage therapy with a protease inhibitor is contraindicated in this setting and must therefore be deferred until after transplantation. Antiviral treatment of HCC patients on the waiting list is controversial, with some clinicians electing to treat before transplantation and others choosing to wait until after transplantation (Section 14).

### 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 patient 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.<sup>68</sup> 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. Potential drug–drug interactions in the post-transplant setting should be considered.

**Table 6. Recommended treatment protocols after liver transplantation for hepatitis C virus (HCV) infection in people with compensated liver disease**

Regimen	HCV genotype	Duration
Sofosbuvir 400 mg, orally, daily + Velpatasvir 100 mg, orally, daily	1–6	12 weeks
Glecaprevir 300 mg, orally, daily + Pibrentasvir 120 mg, orally, daily	1–6	12 weeks
Sofosbuvir 400 mg, orally, daily + Velpatasvir 100 mg, orally, daily + Voxilaprevir 100 mg, orally, daily	1–6	12 weeks
Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily	1	12 weeks

## 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 6). None of the currently available DAAs in Australia include a specific indication for treating HCV after liver transplantation.

Clinical trial data are limited. The safety and efficacy of sofosbuvir plus velpatasvir has not been formally evaluated in the post-transplant setting but should be safe and effective. The role of ribavirin combined with sofosbuvir plus velpatasvir in the post-transplant setting is not clear, but it should be considered. 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).<sup>66</sup> SVR was observed in 96%–98% (157/162) and there was no significant difference between 12 and 24 weeks of treatment. Treatment was well tolerated in these studies and there were no clinically significant drug–drug interactions between sofosbuvir plus ledipasvir and calcineurin inhibitors or mTOR inhibitors.

The combination of glecaprevir plus pibrentasvir has been evaluated in the post-transplant setting. In the MAGELLAN-2 study, 80 liver transplant recipients and 20 kidney transplant recipients without cirrhosis were treated with glecaprevir plus pibrentasvir for 12 weeks.<sup>80</sup> Patients with Gt 1, 2, 3, 4 and 6 HCV were included. SVR was observed in 98%, with one post-treatment relapse and one loss to follow-up. Treatment was well tolerated. One episode of mild rejection occurred that was assessed to be unrelated to drug–drug interactions.

Sofosbuvir plus velpatasvir plus voxilaprevir has not specifically been studied in post-transplant

patients but should be used for people who did not respond to a prior DAA regimen, particularly one containing an NS5A inhibitor. As with all other DAA regimens in post-transplant patients, drug–drug interactions should be taken into consideration.

### 9.3 Treatment of HCV and decompensated liver disease 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).<sup>66</sup> 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 the regimens used for people with decompensated liver disease before liver transplantation (**Table 5**).

### 9.4 Treatment of fibrosing cholestatic hepatitis C

As it is now recommended to treat patients either before or shortly after liver transplantation, FCH should rarely be observed after liver transplantation. If it does occur, diagnosis of FCH should be made according to established criteria.<sup>81</sup> Treatment

with DAAs results in rapid clinical improvement and high rates of SVR. Clinical trial data evaluating the efficacy of DAAs are limited, but available data are encouraging.<sup>66,82</sup> In the absence of prospective clinical trials, we recommend people with FCH be treated with regimens recommended for people after liver transplantation, according to whether liver disease is compensated or decompensated (**Tables 5 and 6**).

### 9.5 Transplantation of HCV RNA-positive donor organs into HCV RNA-negative recipients

Another issue that has emerged is the use of donor organs, including livers, kidneys, hearts and lungs, from HCV-positive donors, which were previously used only in HCV viraemic recipients. Now, and with appropriate consent, HCV viraemic donor livers have been used in HCV-negative recipients in Australia. This strategy has the potential to increase donor organ availability and reduce waiting list times. International experience has shown that HCV-positive donor kidneys, hearts and lungs can also be successfully transplanted into HCV-negative recipients.

When an anti-HCV-positive/HCV RNA-positive donor is used, HCV infection will be transmitted and should be treated with DAAs in the early post-transplant period. Deferring antiviral therapy increases the risk of symptomatic acute hepatitis C infection; cases of FCH have been reported. This is an evolving and complicated area.

Transmission from anti-HCV-positive/HCV RNA-negative donors is extremely rare and, where reported, probably reflects acute infection in high-risk donors.

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 about 6 weeks after transplantation is recommended.	B1
Preferred treatment options for chronic HCV infection and compensated liver disease after transplantation are (see Table 6): Gt 1 HCV:	
• sofosbuvir + velpatasvir for 12 weeks	B1
• glecaprevir + pibrentasvir for 12 weeks	A1
• sofosbuvir + ledipasvir for 12 weeks	A1
• sofosbuvir + velpatasvir + voxilaprevir for 12 weeks (if prior DAA failure)	B1
Gt 2, 3, 4, 6 HCV:	
• sofosbuvir + velpatasvir for 12 weeks	B2
• glecaprevir + pibrentasvir for 12 weeks	B1
• sofosbuvir + velpatasvir + voxilaprevir for 12 weeks (if prior DAA failure)	B1
Preferred treatment options for chronic HCV infection and decompensated liver disease after transplantation are (see Table 5): Gt 1 HCV:	
• sofosbuvir + velpatasvir + ribavirin for 12 weeks	B1
• sofosbuvir + ledipasvir ± ribavirin for 12 or 24 weeks	A1
Gt 2, 3, 4, 6 HCV:	
• sofosbuvir + velpatasvir + ribavirin for 12 weeks	B2
Treatment with sofosbuvir + velpatasvir, sofosbuvir + ledipasvir, or ribavirin does not require dose adjustment of calcineurin inhibitors or mTOR inhibitors.	A2
<b>Notes:</b> 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 6).	

## 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,<sup>83</sup> even in those achieving full HIV virological suppression with antiretroviral treatment (ART) for HIV.<sup>84,85</sup> 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 mono-infection.<sup>86–91</sup> 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 thrombocytopenia 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 (per mucosal) 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.<sup>92</sup> 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,<sup>93</sup> 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.<sup>94</sup> 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.<sup>95</sup> HIV ART-naïve 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<sup>3</sup>). 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<sup>3</sup> 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.<sup>96</sup>

### 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.<sup>86-91,97</sup>

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](http://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. Caution should also be exercised in selecting the 8-week regimen of sofosbuvir plus ledipasvir for individuals with Gt 1 HCV and HIV coinfection and an HCV viral load less than 6 000 000 IU/mL due to the lack of high-quality efficacy data in this population; cirrhosis and advanced fibrosis should be definitively ruled out using transient elastography before selecting this regimen.

#### 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.<sup>98</sup> Sofosbuvir is not recommended for use with tipranavir because of the potential of tipranavir to induce P-glycoprotein.

#### 10.3.2 Ledipasvir

Tenofovir disoproxil fumarate (TDF) 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 TDF and ledipasvir, with frequent monitoring for tenofovir-associated kidney injury, and if the ART regimen also includes ritonavir or cobicistat boosting, an alternative to ledipasvir should be considered.

Tenofovir alafenamide (TAF) has been PBS-listed for the treatment of HIV in Australia (TAF is not yet listed for the treatment of HBV). As tenofovir pharmacokinetics are lower with TAF relative to TDF based on data in healthy volunteers, TAF may be an alternative to TDF during sofosbuvir plus ledipasvir treatment for patients who take elvitegravir–cobicistat or ritonavir-boosted HIV protease inhibitors as part of their ART. The combination of ledipasvir with TAF is not expected to cause kidney injury.

#### 10.3.3 Velpatasvir

Drug interaction studies with velpatasvir plus sofosbuvir have been performed in HIV and HCV seronegative volunteers. As with ledipasvir plus sofosbuvir, tenofovir exposures are increased when velpatasvir is coadministered with TDF, which may be problematic for individuals with eGFR values of less than 60 mL/min or in those receiving ritonavir- or cobicistat-containing ART with tenofovir. The use of TAF in place of TDF should be considered in those requiring ritonavir- or cobicistat-containing ART — the combination of velpatasvir with TAF is not expected to cause kidney injury. If the combination of TDF with a ritonavir- or cobicistat-containing ART is required, renal parameters should be checked at baseline and regularly thereafter while taking sofosbuvir plus velpatasvir.

Velpatasvir exposures are significantly reduced with efavirenz, and this combination is not recommended. Etravirine has not been studied with sofosbuvir plus velpatasvir but is also not recommended. Indirect bilirubin level increases have been reported when sofosbuvir plus velpatasvir is used in patients taking atazanavir–ritonavir, but these changes are not considered clinically significant.

#### 10.3.4 Glecaprevir plus pibrentasvir

Coadministration of glecaprevir plus pibrentasvir and OATP1B inhibitors, including all HIV protease inhibitors, is contraindicated because of markedly increased exposure to both glecaprevir and pibrentasvir and an increased risk of elevation in ALT level. Coadministration with cobicistat-boosted HIV protease inhibitors has not been studied but is not recommended. Coadministration with elvitegravir–cobicistat–emtricitabine–TAF moderately increased glecaprevir exposure, but within acceptable limits. Although it has not been studied, coadministration of glecaprevir plus pibrentasvir with HIV non-nucleoside reverse-transcriptase inhibitors, including efavirenz, etravirine and nevirapine, is not recommended due to drug–drug interactions leading to decreased exposure to glecaprevir and pibrentasvir.

#### 10.3.5 Sofosbuvir plus velpatasvir plus voxilaprevir

Coadministration of voxilaprevir with HIV antiretrovirals has only been studied in a combination regimen including sofosbuvir and velpatasvir. Coadministration of sofosbuvir plus velpatasvir plus voxilaprevir and HIV protease inhibitors, excluding daily darunavir, is not recommended because of HIV protease inhibition of OATP1B and P-glycoprotein leading to markedly increased exposure to voxilaprevir and moderately increased exposure to sofosbuvir and velpatasvir. Clinically significant drug–drug interactions are not considered likely with concurrent administration of sofosbuvir plus velpatasvir plus voxilaprevir and daily-dosed darunavir, including when it is boosted with either cobicistat or ritonavir. Concomitant twice-daily darunavir should be used with additional caution and avoided in patients with cirrhosis.

Coadministration of sofosbuvir plus velpatasvir plus voxilaprevir with cobicistat in combination with elvitegravir–emtricitabine–TAF did not lead to any significant changes in exposure to either

regimen, but coadministration with cobicistat and atazanavir is not recommended. Coadministration of HIV non-nucleoside reverse-transcriptase inhibitors and voxilaprevir has not been studied but is not recommended because of CYP3A4 inhibition leading to decreased exposure to sofosbuvir plus velpatasvir plus voxilaprevir. Patients receiving concurrent sofosbuvir plus velpatasvir plus voxilaprevir and TDF should be closely monitored for tenofovir-related adverse effects, such as acute kidney injury and bone mineral density loss.

#### 10.3.6 Elbasvir plus grazoprevir

Significant drug–drug interactions preclude the concurrent use of elbasvir plus grazoprevir with many antiretroviral agents. This regimen is not suitable for use with HIV protease inhibitors. All HIV protease inhibitors inhibit OATP1B, leading to substantial increases in the plasma concentration of grazoprevir and increasing the risk of late elevations in ALT level. Coadministration with the quadruple-combination HIV agent elvitegravir–cobicistat–emtricitabine–TAF has not been studied but should be avoided because the same antiretroviral combination using TDF resulted in substantially increased grazoprevir exposure. Elbasvir plus grazoprevir should not be coadministered with non-nucleoside reverse-transcriptase inhibitors, which will decrease elbasvir plus grazoprevir exposure (proven in the case of efavirenz; a potential concern in the case of nevirapine and etravirine). Rilpivirine is the exception — no significant effect on elbasvir plus grazoprevir exposure was seen with concomitant rilpivirine administration.<sup>49</sup>

#### 10.3.7 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. However, cirrhosis and advanced fibrosis should be excluded by transient elastography or other imaging modality before use of an 8-week regimen of sofosbuvir plus ledipasvir in people with Gt 1 HCV infection.	B1
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

All individuals with chronic HCV infection should be tested for HBV infection. Testing should include HBsAg, anti-HBc and anti-HBs serology (all three tests for HBV may be requested if the clinical notes indicate acute or chronic hepatitis). Current hepatitis B infection is defined by HBsAg positivity, with chronic hepatitis B infection defined as presence of infection for more than 6 months (Table 7). All individuals with current HBV infection should be referred for specialist management. Past HBV infection is defined by HBsAg negativity, positive anti-HBc  $\pm$  positive anti-HBs serology (note that anti-HBs titre may wane over time and become undetectable; Table 7). Occult hepatitis B infection is very rare, but is defined by positive HBV DNA in the absence of HBsAg — in most cases, the HBV DNA level is very low; anti-HBc is normally positive.<sup>99</sup>

In October 2016, the US FDA issued a boxed warning regarding the risk of HBV reactivation in patients undergoing treatment with DAA therapy. The warning was issued on the basis of 24 case reports notified to the FDA and/or published in the literature between November 2013 and July 2016.<sup>100</sup> Full details of all 24 cases are not publicly available, although the FDA released a summary of key findings. The cases occurred in patients with differing HBV serological profiles before commencing DAA therapy, including those who were HBsAg-positive, with both detectable HBV DNA ( $n = 7$ ) and undetectable HBV DNA ( $n = 4$ ), and in those with serological profiles consistent with past HBV infection (anti-HBc positive, HBsAg-negative and undetectable HBV DNA;  $n = 3$ ). The two clinically significant cases of HBV reactivation among anti-HBc-positive, HBsAg-negative people were associated with a history of immunosuppression (previous Burkitt lymphoma, HIV coinfection). In 10 cases, baseline HBV status was not available. No patients were receiving HBV antiviral therapy. No pattern was observed with regard to HCV genotype or DAA regimen used. In almost all cases, elevation of HBV DNA level was observed within the initial 4–12 weeks of

DAA therapy, as HCV RNA levels fell rapidly to undetectable. In some patients, elevation of HBV DNA level was asymptomatic and settled without further intervention, but hepatic decompensation occurred in three patients, resulting in the death of two patients and liver transplantation in one patient. Twelve patients commenced HBV antiviral therapy (entecavir or tenofovir), with resultant HBV DNA suppression and normalisation of ALT levels. HCV RNA remained undetectable in all cases.

There is biological plausibility for the development of HBV reactivation during HCV therapy, although the exact mechanism is unknown. When HCV and HBV coexist in the same host, HCV exerts a dominant immunosuppressive effect, resulting in lower HBV DNA and HBV antigen levels and reflecting a state of immune control. Reactivation of HBV DNA during HCV treatment with IFN-containing regimens has been well described and shown to occur in up to 31% of coinfecting patients,<sup>101</sup> although the anti-HBV effect of IFN meant that this was rarely clinically significant. In the context of DAA therapy, rapid suppression of HCV RNA may trigger complex immunological change, allowing uncontrolled HBV reactivation and replication. This theory is consistent with the timing observed in reported cases. It remains unclear how common significant clinical reactivation is in the context of HCV–HBV coinfecting patients undergoing DAA therapy. It is also unclear whether all patients should commence HBV antiviral therapy or whether a period of watchful waiting is appropriate.

In the absence of further data at this time, the following conclusions have been drawn about risk of HBV reactivation. There is a risk gradient for the occurrence of HBV reactivation, wherein HBsAg-positive individuals have a moderate risk of HBV reactivation. HBsAg-positive people should have HBV DNA levels measured at baseline and should be considered for antiviral therapy according to current guidelines (see below). If antiviral therapy for HBV is not indicated, active monitoring of ALT

**Table 7. Definitions of hepatitis B virus (HBV) infection, by HBV test results**

Test	Current HBV infection	Past HBV infection	Occult HBV infection	Vaccine-induced immunity
HBsAg	+	–	–	–
Anti-HBc	+	+	+	–
Anti-HBs	–	+/-	+/-	+
HBV DNA	+/-	–	+ (typically very low level)	–

and HBV DNA levels should be performed during HCV treatment (see below).

Anti-HBc-positive and HBsAg-negative individuals have a negligible risk of reactivation. Anti-HBc-positive and HBsAg-negative serostatus is common in people who were exposed to HCV through injecting drug use. Anti-HBc-positive, HBsAg-negative people were not excluded from clinical trials, and no cases of acute HBV reactivation have been reported in any clinical trials evaluating DAA combination regimens in patients infected with HCV.<sup>102</sup> Emerging data specifically addressing the risk of HBV reactivation in anti-HBc-positive individuals are reassuring.<sup>102,103</sup>

Of 173 HBsAg-negative people treated for Gt 1 HCV with open-label sofosbuvir plus ledipasvir as part of a Phase IIIb study in Korea, 60% were observed to be anti-HBc-positive.<sup>102</sup> At 24 weeks after treatment, all 173 remained HBsAg-negative, with HBV DNA levels < 20 IU/mL. In two patient samples, HBV DNA level was < 20 IU/mL but was detectable. No ALT flares were observed through Week 4 after treatment, the last time point at which ALT level was evaluated. There was no difference in laboratory abnormalities, including ALT levels, between patients who were anti-HBc-positive and anti-HBc-negative.

A second single-centre study of 327 Chinese patients receiving DAA treatment for HCV included 124 patients with occult HBV infection, defined as HBV DNA-positive, HBsAg-negative.<sup>103</sup> Patients were followed every 2 weeks during treatment and every 4 weeks after treatment until SVR. HBsAg and HBV DNA levels were measured at all time points in the subset with occult HBV infection. No case of acute HBV reactivation was observed in this population.

Given the negligible risk of reactivation, we recommend routine monitoring only for anti-HBc-positive and HBsAg-negative people who are treated with HCV DAAs, as recommended for people who are seronegative for all markers of HBV infection (see Section 6). We do not recommend routine HBV DNA testing in anti-HBc-positive, HBsAg-negative people at baseline. HBV reactivation should be considered in any patient who experiences an ALT flare during or after DAA treatment. A final caution: the risk of HBV reactivation may be higher in people with isolated anti-HBc and a history of immunosuppression, including HIV coinfection. It is reasonable to monitor such patients more closely during and after treatment.

Consensus recommendations	Grade
All patients with HCV infection undergoing DAA therapy should be screened for HBV infection with anti-HBc, HBsAg and anti-HBs testing.	A1
Non-immune (HBsAg, anti-HBc and anti-HBs-negative) patients should be offered HBV vaccination.	A1
<b>HBsAg-positive patients</b>	
Patients with HCV infection who are HBsAg-positive should be managed by, or in conjunction with, a specialist experienced in the treatment of both conditions.	A1
Patients should be counselled regarding the risk of HBV reactivation and advised to immediately report any signs or symptoms indicative of serious liver disease.	A1
All patients who are HBsAg-positive should undergo HBV DNA testing before commencing DAA therapy.	A1
Anti-HBV therapy with tenofovir or entecavir should be commenced before DAA therapy in all non-cirrhotic patients with an HBV DNA level > 2000 IU/mL and in <b>all</b> patients with underlying cirrhosis, regardless of HBV DNA level.	A1
Non-cirrhotic patients with an HBV DNA level < 2000 IU/mL should be monitored for evidence of HBV reactivation. We recommend the following minimum requirements for monitoring: <ul style="list-style-type: none"> <li>• ALT — every 4 weeks until the end of treatment and at SVR</li> <li>• HBV DNA — every 12 weeks until SVR, plus if ALT level rises</li> <li>• If HBV DNA level remains &lt; 2000 IU/mL at SVR, routine monitoring as per HBV guidelines can be reinstated</li> </ul>	A1
A rise in HBV DNA level > 2000 IU/mL at any time during therapy and/or elevation in ALT level accompanied by any rise in HBV DNA level should prompt consideration of antiviral therapy and intensive monitoring.	A1
Coinfected patients who are already receiving anti-HBV therapy and have suppressed HBV DNA levels do not appear to be at increased risk and can continue with routine clinical monitoring.	A1
<b>Anti-HBc-positive, HBsAg-negative patients</b>	
Patients who are anti-HBc-positive and HBsAg-negative have a low risk of HBV reactivation.	A2
Routine monitoring guidelines for patients treated with HCV DAAs should be followed, as recommended for people who are seronegative for HBV infection.	B1
HBV reactivation should be considered in any patient who experiences an ALT flare during or after DAA treatment.	A1

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

Hepatitis C is associated with intrinsic renal disease, including cryoglobulinaemia and glomerulonephritis.<sup>104</sup> 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 (note that any patient with HCV who is treated with B cell-depleting therapy must be screened for HBV infection, and patients who have been exposed to HBV will require antiviral therapy to prevent HBV reactivation). 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.<sup>105,106</sup> People with moderate–severe renal impairment (eGFR < 50 mL/min/1.73 m<sup>2</sup>) 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<sup>2</sup>)

For people with mild to moderate renal impairment (eGFR, 30–80 mL/min/1.73 m<sup>2</sup>), no dose adjustment is required for sofosbuvir, velpatasvir, ledipasvir, voxilaprevir, glecaprevir, pibrentasvir, elbasvir or grazoprevir. 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.<sup>107</sup> The product information recommends that ribavirin should not be used in individuals with an eGFR < 50 mL/min/1.73 m<sup>2</sup>. In specialist centres, ribavirin-containing regimens may be considered for those with an eGFR < 50 mL/min/1.73 m<sup>2</sup>. 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<sup>2</sup>, no dose adjustment; 30–50 mL/min/1.73 m<sup>2</sup>, alternating doses of 200 mg and 400 mg every other day; < 30 mL/min/1.73 m<sup>2</sup>, 200 mg daily; haemodialysis, 200 mg pre-dialysis.

### 12.2 People with severe renal impairment (eGFR < 30 mL/min/1.73 m<sup>2</sup> 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. As sofosbuvir is renally excreted, it is not currently recommended for use in people with an eGFR < 30 mL/min/1.73 m<sup>2</sup>. This advice was based on pharmacokinetic studies of a single 400 mg dose of sofosbuvir that 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, in people with an eGFR < 30 mL/min/1.73 m<sup>2</sup>. However, data showing the clinical safety of sofosbuvir-based regimens in patients with severe CKD are emerging. The US FDA has recently approved updated labelling for sofosbuvir-containing regimens, stating that no dosage adjustment is recommended for patients with any degree of renal impairment, including patients requiring dialysis. An update to the Australian product information is anticipated.

Glecaprevir and pibrentasvir are cleared by hepatic metabolism, and this is now a preferred treatment regimen for people with severe renal impairment. The efficacy of this pan-genotypic regimen was evaluated in 104 patients with Gt 1–6 HCV infection enrolled in a Phase III study.<sup>108</sup> All patients had severe renal impairment (eGFR < 30 mL/min/1.73 m<sup>2</sup>) or were dependent on dialysis. The SVR rate was 98% (102/104). No virological failures were observed. Adverse events were common, and 24% of patients experienced at least one serious adverse event. High

rates of adverse events, including serious adverse events, are common in people with severe renal impairment.

Elbasvir and grazoprevir are also cleared by hepatic metabolism and can be used in people with severe renal impairment. This was the first regimen to be evaluated in a large Phase III study enrolling people with severe renal impairment. Its efficacy in people with chronic kidney disease (eGFR < 30 mL/min/1.73 m<sup>2</sup>, with or without haemodialysis requirements) was evaluated in a large Phase III randomised study in which 224 people with chronic Gt 1 HCV infection were randomly assigned to immediate or deferred therapy with elbasvir and grazoprevir.<sup>48</sup> The deferred treatment arm provided a placebo comparator to the immediate treatment arm. Ribavirin was not used, despite 52% of the cohort being infected with Gt 1a HCV. In the immediate treatment arm,

the SVR rate was 94.3% in the full analysis set. The SVR rate was 99.1% in a modified analysis set that excluded patients who discontinued treatment for reasons that were not related to virological failure. Adverse events were frequent in this population with significant comorbidities but were comparable between the immediate and deferred treatment groups (76% v 84%). People with Gt 1a or Gt 1b HCV, as well as those with Gt 4 HCV infection, who have severe renal impairment (eGFR < 30 mL/min/1.73 m<sup>2</sup>) or end-stage renal disease, including patients receiving dialysis, should be treated with elbasvir plus grazoprevir without ribavirin.<sup>48</sup>

As noted above, severe renal impairment necessitates a significant dose reduction for ribavirin. Ribavirin should only be used in this setting under the supervision of a specialist with experience in treating HCV infection in people with severe renal impairment.

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 <sup>2</sup> ) 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 <sup>2</sup> ), no dose adjustment is required for: <ul style="list-style-type: none"> <li>• sofosbuvir + velpatasvir</li> <li>• sofosbuvir + ledipasvir</li> <li>• glecaprevir + pibrentasvir</li> <li>• elbasvir + grazoprevir</li> </ul>	A1
If indicated, ribavirin should be used with caution in people with an eGFR < 50 mL/min/1.73 m <sup>2</sup> ; 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 <sup>2</sup> or haemodialysis): <ul style="list-style-type: none"> <li>• sofosbuvir cannot currently be recommended, pending an update to the product information*</li> <li>• glecaprevir + pibrentasvir can be used to treat Gt 1–6 HCV</li> <li>• elbasvir + grazoprevir can be used to treat Gt 1a, 1b and 4 HCV</li> <li>• if indicated, low-dose ribavirin should be used (eg, ribavirin 200 mg daily for patients not on haemodialysis; ribavirin 200 mg pre-dialysis for patients on haemodialysis), with close monitoring of haemoglobin levels</li> </ul>	B1 A1 A1/B1 B1
* It is anticipated that the product information for sofosbuvir + velpatasvir and sofosbuvir + velpatasvir + voxilaprevir will be updated later in 2020 to recommend that no dosage adjustment is required for patients with any degree of renal impairment, including patients requiring dialysis.	

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

Acute HCV infection refers to the 6-month period after infection acquisition, although definitions vary<sup>109</sup> and the distinction between acute and early chronic infection is somewhat arbitrary. In Australia, it is estimated that about 8500–9000 new infections occur each year.<sup>1,3</sup> While in some cases acute HCV infection may develop after discrete exposure (eg, a needle-stick 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.<sup>92,110,111</sup>

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.<sup>112</sup>

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  $>10 \times$  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  $>10 \times$  ULN; or ii) an acute rise in ALT level  $>5 \times$  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<sup>113</sup> 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.<sup>114</sup> 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.<sup>115</sup> Predictors of spontaneous clearance include jaundice, elevated ALT level, female sex, younger age and host genetic polymorphisms (including *IFNL3*), 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.<sup>116</sup> Fluctuating viraemia is common in the first few months after infection, with variable patterns.<sup>117</sup> 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.<sup>118</sup>

### 13.3 Treatment of acute HCV infection

The optimal timing and regimen for acute hepatitis C treatment is 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.<sup>119</sup> This paradigm is unproven in the setting of IFN-free DAA therapies and is 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 in 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 PWID and 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 (note that the PBS criteria for treatment specify chronicity as a criterion for eligibility). 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 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 (note that the PBS criteria for treatment specify chronicity as a criterion for eligibility).	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
Individuals with ongoing risk factors for HCV reinfection should be screened annually for HCV infection with HCV RNA (PCR).	A1

## 14. Direct-acting antiviral therapy and risk of hepatocellular carcinoma in people with cirrhosis

Recent reports from Europe questioned whether IFN-free DAA therapy is associated with an increase in recurrent HCC in people with cirrhosis, and whether recurrent tumours have an altered, more aggressive clinical course. A Spanish study identified 58 patients with a complete radiological response to prior HCC therapy who were subsequently treated with DAAs (SVR in 97%).<sup>120</sup> The median time between HCC response and start of DAA therapy was 11 months. Among the 58 patients, 16 (28%) experienced recurrence within a median of 3.5 months from the start of DAA treatment. Although there was no control group in this study, the recurrence rate is higher than that reported by a previous meta-analysis of IFN-based therapy, which showed a significant decrease in the risk of HCC recurrence following SVR (odds ratio, 0.22).<sup>121</sup> The Spanish investigators were suitably cautious in their data interpretation and reported these patients so that others could compare with their experience. Subsequently, an Italian study of 344 patients with HCV and cirrhosis treated with DAAs (SVR in 91%) observed HCC recurrence in 17 of 59 patients (29%) with a history of HCC, and de novo HCC in nine of 285 patients (3%) with no history of HCC, in the 24 weeks after antiviral treatment.<sup>122</sup> The authors also hypothesised that DAAs may accelerate HCC recurrence. In contrast, a French collaborative group reported outcomes from three prospectively studied cohorts, including 346 HCV patients with treated HCC and 314 patients who underwent liver transplantation for HCC.<sup>123</sup> Over a median follow-up of 20 months, there was no difference in HCC recurrence rates according to DAA treatment. In the transplant group, all of whom were DAA-treated, HCC recurred in 2.2%, compared with a historical recurrence rate of 8%–20% in the first 2 years after transplantation. Therefore, whether or not DAA therapy influences HCC recurrence in people with cirrhosis is unclear based on published data.

Incident HCC is a separate issue, but emerging data are reassuring. A large prospective registry is following 1067 people with cirrhosis who have been treated with sofosbuvir-containing regimens. A preliminary analysis of people followed for a median of 85 weeks from the end of treatment observed a rate of incident HCC of 0.50 per 100 patient-years in 663 people with compensated cirrhosis.<sup>124</sup> Similarly, in a prospective Italian cohort, among 2007 patients with cirrhosis followed for a median of 301 days, the rate of incident HCC was 1.63 per 100 patient-years.<sup>125</sup> The data compare favourably to rates of incident HCC reported among people with compensated cirrhosis who achieved SVR after treatment with IFN-based therapy (1.39–1.82 per 100 patient-years).<sup>126</sup> In a prospective study of 406 patients with cirrhosis, most with Child–Pugh B+ liver disease, who were treated with DAAs through the English Expanded Access Programme, the SVR rate was 81%.<sup>127</sup> Compared with a control group of 261 untreated patients with cirrhosis followed for 6 months, there was no difference in HCC incidence between the DAA-treated and untreated groups, or between those who achieved SVR and those who did not.

Therefore, we strongly recommend DAA therapy for all individuals with advanced liver disease who do not have a history of HCC. We recommend continuing to offer DAA therapy to patients with advanced liver disease and previous HCC, after informed discussion of potential risks. These people should all be enrolled in HCC screening programs. HCV treatment should not suspend HCC screening. We recommend a liver ultrasound within 1 month before DAA therapy for all individuals with cirrhosis to ensure that HCC screening remains up to date during the treatment and follow-up period. Importantly, there are no data to suggest that HCC risk may be increased in people with no cirrhosis. We do not recommend HCC screening for people with no cirrhosis who are treated for HCV.

<b>Consensus recommendations</b>	<b>Grade</b>
All individuals with cirrhosis should be enrolled in HCC screening programs.	A1
All individuals with cirrhosis should be offered DAA treatment for HCV infection.	A1
People with cirrhosis and prior HCC should be closely monitored for HCC recurrence during and after DAA therapy for HCV infection.	B2
HCC screening for all individuals with no cirrhosis is not cost-effective.	A1

## 15. 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.<sup>128</sup>

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
CKD	chronic kidney disease
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
RAS	resistance-associated substitution
HSD	Highly Specialised Drugs
SVR	sustained virological response at least 12 weeks after treatment (cure)
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
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	$\text{APRI} = (\text{AST [IU/L]} \div \text{AST ULN [IU/L]} \times 100) \div \text{platelet count } (\times 10^9/\text{L})$ Online calculator: <a href="http://www.hepatitisc.uw.edu/page/clinical-calculators/apri">http://www.hepatitisc.uw.edu/page/clinical-calculators/apri</a>	APRI < 1.0
Hepascore	Patented formula combining bilirubin, GGT, hyaluronate, $\alpha$ -2-macroglobulin, age and sex	Hepascore < 0.80
FibroGENE	Patented formula based on age, platelet count, AST, GGT and <i>IFNL3</i> (rs12979860) genotype Online calculator: <a href="http://www.fibrogene.com/viral_hepatitis.html">http://www.fibrogene.com/viral_hepatitis.html</a>	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; ELF = Enhanced Liver Fibrosis; GGT = gamma-glutamyl transferase; HIV = human immunodeficiency virus; MMP-3 = matrix metalloproteinase-3; TIMP-1 = tissue inhibitor of metalloproteinase-1; ULN = upper limit of normal.

\* 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 thrombocytopenia 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**

<b>A. Child–Pugh score</b>			
	<b>Points</b>		
<b>Clinical measure</b>	<b>1</b>	<b>2</b>	<b>3</b>
Albumin (g/L)	> 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
<b>Interpretation</b>			
<b>Classification</b>	<b>1-year mortality</b>	<b>Consider transplant centre referral</b>	
Class A (5–6 points)	0	No	
Class B (7–9 points)	20%	Yes*	
Class C (10+ points)	55%		
<b>B. MELD score</b>			
MELD = $10 \times ((0.957 \times \text{Log}_e(\text{creatinine}/88.4)) + (0.378 \times \text{Log}_e(\text{bilirubin}/17.1)) + (1.12 \times \text{Log}_e(\text{INR}))) + 6.43$ Online calculators are available.			
<b>Classification</b>	<b>3-month mortality</b>	<b>Consider transplant centre referral</b>	
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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