Australian recommendations for the management of hepatitis C virus infection: a consensus statement (2022)

GESA Gastroenterological Society of Australia

ASID Australasian Society for Infectious Diseases

Australasian Hepatology Association

ashm Supporting the HIV, Viral Hepatitis and Sexual Health Workforce

hepatitis australia

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Australian recommendations for the management of hepatitis C virus infection: a consensus statement (2022)

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

Chronic hepatitis C virus (HCV) infection is a major public health challenge for Australia, affecting about 120 000 people who are at risk of progressive liver fibrosis leading to cirrhosis, liver failure and hepatocellular carcinoma (HCC). Before the introduction of direct-acting antiviral (DAA) therapy, HCV infection was a common cause of liver disease (and liver cancer) requiring liver transplantation in Australia. It remains an important cause of liver-related morbidity and mortality in people who progress to cirrhosis. 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 DAAs 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* (2022). 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?

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

Update to the recommended definition of chronic hepatitis C

The recommended definition for chronic hepatitis C has been expanded to include people who have detectable HCV RNA in plasma or whole blood and the absence of clinical features of acute hepatitis (Section 3).

Update to the recommendations for screening and diagnosis of hepatitis C

When screening for hepatitis C, we recommend that clinicians request reflex testing for HCV RNA if HCV serology is positive (Section 3).

We recommend ongoing evaluation of the role of point-of-care tests for plasma or whole-blood HCV RNA in high-prevalence clinical settings, to increase rates of screening and reduce the rate of loss to follow-up between testing and diagnosis. There are practical issues that remain to be resolved for the long-term implementation of these tests, including establishment of relationships between high-prevalence clinical settings and National Association of Testing Authorities (NATA)-accredited medical testing laboratories, development and participation in quality assurance programs, and reimbursement for HCV RNA testing in the absence of documented HCV serology (Section 3).

Update to the recommended indications for treatment for hepatitis C infection

We continue to recommend that, except for those with limited (<12 months) life expectancy due to non-liver or non-HCV-related comorbidities, all people living with hepatitis C should be considered for treatment. The recommendation for treatment has been extended to include all people with a risk factor for hepatitis C transmission who are found to have detectable HCV RNA in plasma or whole blood, regardless of the duration of infection. This includes treatment for acute hepatitis C, which is recommended for people with risk factors for hepatitis C transmission, to prevent transmission events (Section 5 and Section 13.3).

Label updates: glecaprevir plus pibrentasvir

The recommended treatment duration using glecaprevir plus pibrentasvir is now 8 weeks for treatment-naive people with or without cirrhosis (Section 5.4.2).

The Australian product information for glecaprevir plus pibrentasvir now includes treatment for children 3 years or older (no dose adjustment is required for children aged 12 years or older or those weighing > 45 kg) (Section 5.7).

Label updates: sofosbuvir plus velpatasvir

The Australian product information for sofosbuvir plus velpatasvir has been updated to include efficacy and safety data for adult patients with severe renal impairment or end-stage renal disease (ESRD). No dose adjustment is required for patients with renal impairment, including those with ESRD requiring dialysis (Section 5.4.1 and Section 12).

The Australian product information for sofosbuvir plus velpatasvir now includes treatment for children aged 12 years or older and weighing > 30 kg (no dose adjustment is required) (Section 5.7).

Simplified testing pathway to confirm cure

Recent data suggest there is a very high correlation between SVR4 (undetectable plasma or whole-blood HCV RNA using a highly sensitive polymerase chain reaction (PCR) assay 4 weeks after completion of DAA therapy) and SVR12 (undetectable plasma or whole-blood HCV RNA using a highly sensitive PCR assay 12 weeks after completion of DAA therapy; the current definition for cure). Therefore, opportunistic testing of HCV RNA at any time beyond 4 weeks after treatment completion is adequate, especially when

there is concern about subsequent loss to follow-up (e.g. in prisoners for whom release to the community may be imminent) (Section 7.1).

Use of non-invasive tools to screen for complications of portal hypertension in people living with cirrhosis

All individuals with cirrhosis should be assessed for their risk of clinically significant portal hypertension (CSPH). Guidelines now recommend that non-invasive tools (liver stiffness measurement and platelet count) be used to triage risk of CSPH (Section 4.2.1).

Updates on treatment of hepatitis C in people with HCC

Treatment of hepatitis C in people with cirrhosis reduces their risk of HCC. There is a small reduction in the rate of sustained virological response (SVR) in people with HCC. There are no conclusive data that DAA therapy is associated with risk of recurrent HCC or rapid progression of HCC. All people with HCC should be considered for DAA therapy, but treatment decisions should be individualised, taking into account life expectancy, and made in consultation with a multidisciplinary team. All people with HCV cirrhosis remain at risk of HCC, even after achieving SVR, and surveillance should continue long term (Section 14).

Recommendations for managing dose interruptions in people receiving DAA therapy

Adherence to DAA therapy is important and should be actively supported. Dose interruption is not recommended. However, as dose interruption does occur, specific recommendations regarding management of dose interruptions are now included (Section 6).

1. The epidemiology of HCV in Australia

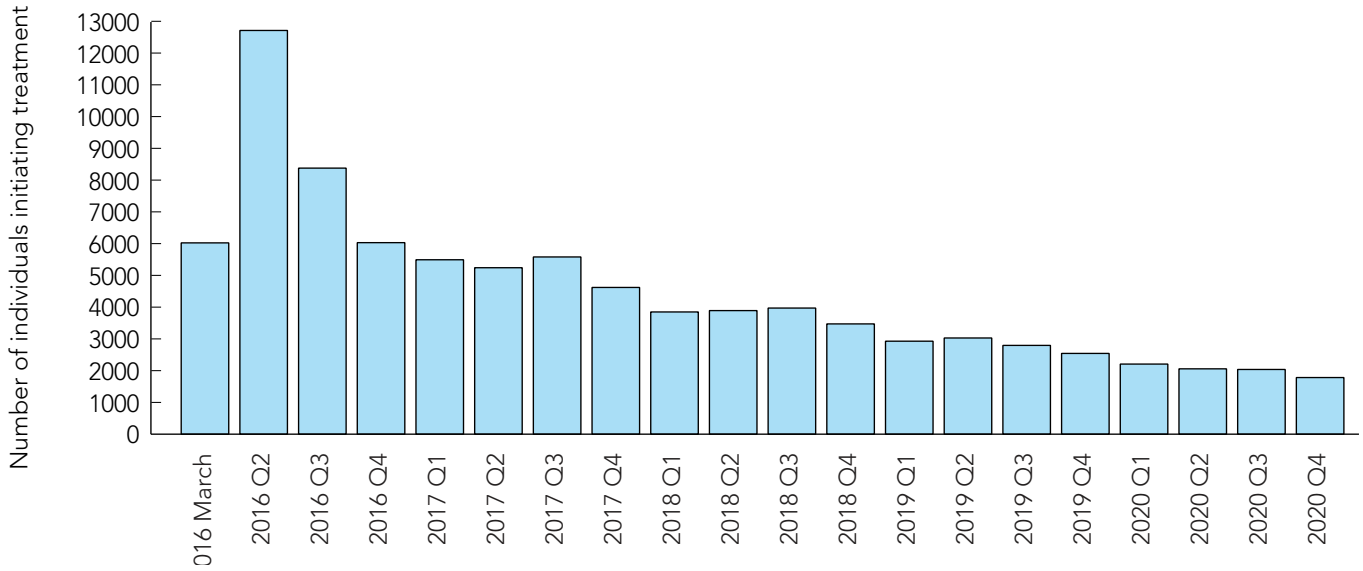
Hepatitis C virus (HCV) infection is a major public health challenge for Australia. Acute infection progresses to chronic disease in about 75% of cases, and these people are at risk of progressive liver fibrosis leading to cirrhosis, liver failure and hepatocellular carcinoma (HCC). About 20%–30% of 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.[1-3] At the end of 2020, it was estimated that there were 117 814 people in Australia living with chronic hepatitis C.[4]

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 declined to 8500–9000 new infections in 2013.[1,3] There is evidence of further declines in the incidence of HCV infection since the unrestricted availability of direct-acting antiviral (DAA) therapy in 2016.[4]

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, between March 2016, when interferon (IFN)-free DAA regimens were listed on the Pharmaceutical Benefits Scheme (PBS), and the end of 2020, a total of 88 790 people received HCV treatment (**Figure 1**).[5]

Figure 1. Estimated number of people initiating direct-acting antiviral treatment each quarter in Australia, 2016–2020



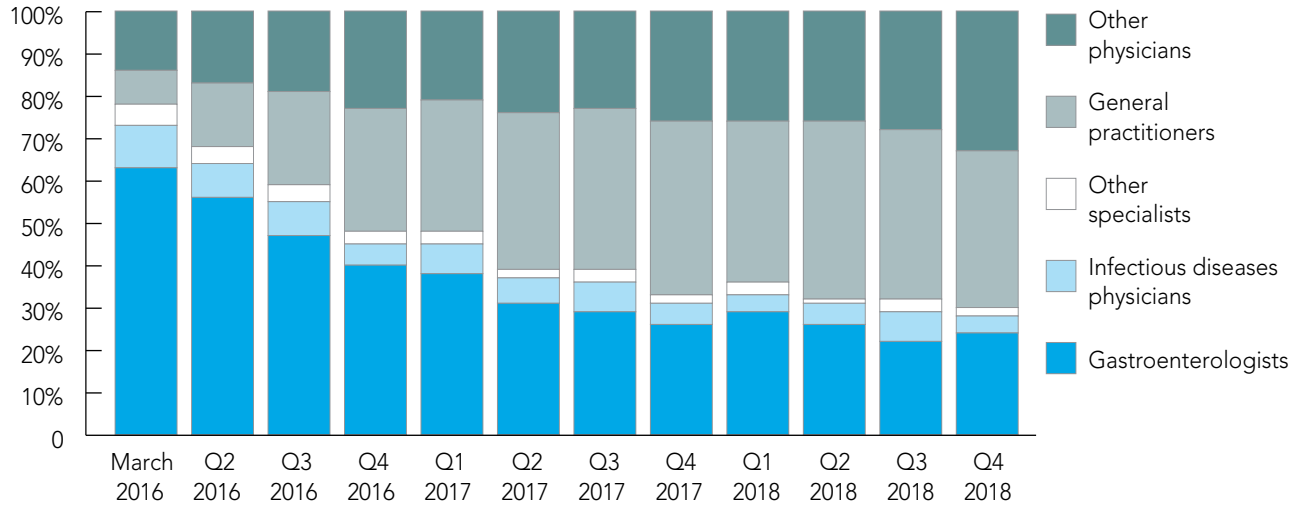
Source: The Kirby Institute.[5]

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**).[6]

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"). Recent evidence from the Surveillance and Treatment of Prisoners with Hepatitis C (SToP-C) study in New South Wales prisons shows a halving of incidence after rapid upscaling of DAA therapy.[7] Encouragingly, among PWID in Australia, the estimated HCV antibody prevalence declined from 51% in 2016 to 39% in 2020, and the estimated prevalence of current HCV infection declined from 33% in 2016 to 16% in 2020.[8] Data also indicate that HCV treatment uptake in the DAA era has been higher among people with current drug dependency or injecting drug use than among those in the broader population of people with hepatitis C.[9]

Ongoing efforts will be required to sustain DAA treatment uptake, particularly among highly marginalised populations. Elimination programs in Australia should focus on increasing testing rates and linkage with care to maintain adequate levels of treatment.[10] 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.

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.[6]

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

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.[11] 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.[12] 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/education/clinical-information).

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.[13]

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.[14,15] 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 NSW and Victoria.[16,17] 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

- www.ashm.org.au/HCV/training
- www.racgp.org.au/education/professional-development/online-learning/webinars/hiv-and-hepatitis/hepatitis-c-cure-chronic-disease
- www.hepatologyassociation.com.au
- https://learn.nps.org.au/mod/page/view.php?id=14268

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.[13] 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.[18,19] 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.[19,20]

Nurse practitioners can prescribe DAAs independently. The PBAC has 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%,[21] 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,[14,22-25] 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.[26] As noted, the SToP-C study showed a halving of incidence after rapid upscaling of DAA therapy in NSW prisons.[7]

Prison hepatitis programs are increasingly important to the national goal of eliminating hepatitis C as a public health threat. Prisons are now estimated to be responsible for more than a third of all hepatitis C treatment prescriptions in Australia.[27] Detailed discussion can be found in the recent *Consensus statement on the management of hepatitis C in Australia's prisons*.[28]

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.[29] 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.[30] 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.[31-33] 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.

The Therapeutic Goods Administration (TGA) approved the Xpert® HCV viral load point-of-care assay (Cepheid) in May 2020. It 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.[16,17] 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.[14,34] 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[14,34] 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.[35] 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.[36,37]

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 standard-of-care 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. We recommend that, when ordering HCV serology, clinicians request reflex testing for HCV RNA if HCV serology is positive. This request must be documented on the initial pathology form. 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 or whole blood. Current criteria for PBS eligibility require evidence of chronic infection documented by repeated HCV antibody positivity and HCV RNA positivity. The traditional clinical definition of chronic HCV infection is duration longer than 6 months. Documentation of seropositivity for longer than 6 months should not be required; a clinical assessment of chronicity is sufficient. The recommended definition for chronic HCV infection has therefore been expanded to include people who have detectable HCV RNA in plasma or whole blood and the absence of clinical features of acute hepatitis (Section 13). A history of injecting drug use or another risk factor for transmission of HCV infection is supportive but not required to make the diagnosis.

The testing protocols described above require venepuncture for collection of whole blood samples. This can present a barrier to care for PWID who have difficult venous access. Finger-prick sample collection can be used to test for hepatitis C. In NSW, a pilot study of dry blood spot (DBS) testing for HCV RNA, using finger-prick sample collection, has been successfully conducted.[38] DBS testing can also be used for human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infection. DBS samples need to be sent to a central laboratory for testing, meaning that the result is not available on the day of sample collection. As DBS testing has not yet been approved by the TGA, confirmatory testing using standard diagnostics is required before prescribing DAAs.

There is no point-of-care test for anti-HCV antibodies that is approved for use in Australia. As noted, the Xpert® (Cepheid) point-of-care test for HCV RNA has been approved and uses a finger-prick blood sample (100 uL). The real-time PCR machine can sit onsite and provide a result in less than 60 minutes. This test has been successfully used for screening in high-prevalence clinics (e.g. needle and syringe programs, safe injecting facilities, prison reception centres[37] and mental health units). On the basis of these data, the use of point-of-care tests for HCV RNA is being actively evaluated for

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)

screening in high-prevalence clinical settings, to increase rates of screening and reduce the rate of loss to follow-up between testing and diagnosis. In 2021, the Commonwealth Government established a national program to scale up hepatitis C point-of-care testing using the Xpert® HCV viral load assay. The program will support access to point-of-care tests for high-prevalence clinics, including staff training, establishment of relationships with NATA-accredited medical testing laboratories and participation in quality assurance programs.

Beyond this national program, however, reimbursement needs to be considered. The current Medicare Benefits Schedule (MBS) reimbursement criteria for HCV RNA testing require documentary evidence of HCV seropositivity. This is a barrier to reimbursement for point-of-care HCV RNA testing in high-prevalence clinics, in the absence of an approved point-of-care test for anti-HCV antibodies and where previous serology results are not readily available. However, evidence suggests that i) the rates of HCV seropositivity among PWID in high-prevalence clinical settings in Australia are very high (> 50% among PWID in correctional settings or high-prevalence community settings, such as needle and syringe programs and safe injecting facilities); ii) many PWID have been previously tested, but the information technology systems do not exist to track results from other providers in a reliable, rapid manner; and iii) the prevalence of hepatitis C (HCV RNA positivity) in PWID remains > 20%,[39] which is a reasonable threshold for screening tests. We therefore recommend that, until point-of-care-testing for anti-HCV antibodies becomes available in the community, funding mechanisms should be created to support point-of-care HCV RNA testing without the need for documentation of HCV seropositivity in prescribed high-prevalence clinical settings.

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. Annual testing should be performed using either venepuncture or point-of-care finger-prick testing. 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.

Consensus recommendations	Grade
HCV seronegative people with risk factors for HCV transmission should be screened annually for HCV infection.	A1
The 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. Clinicians should request reflex testing for HCV RNA if HCV serology is positive.	A1
Point-of-care HCV RNA tests should be evaluated for hepatitis C screening in high-prevalence clinical settings, to increase rates of screening and reduce the rate of loss to follow-up between testing and diagnosis.	A1
Chronic HCV infection can be diagnosed in people who have detectable HCV RNA in plasma or whole blood and the absence of clinical features of acute hepatitis.	B2
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 hepatitis C 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
  - identify the genotype of HCV infection (may be considered)
  - document the HCV treatment history
- Evaluate for the presence of cirrhosis
  - If present, screen for complications of cirrhosis
- Evaluate for the presence of HBV or HIV coinfection
- Consider whether coexisting liver diseases are present
- Consider concomitant medications for risk of drug–drug interactions, including ethinyloestradiol-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. As noted, the first point-of-care test for HCV RNA was approved by the TGA in May 2020. The Xpert® 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

Documentation of HCV genotype was important in the era of genotype-specific DAAs. However, 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).

Documenting HCV genotype may be useful for people at high risk of reinfection, where genotype switch can differentiate reinfection from relapse. HCV genotyping continues to be MBS-reimbursed.

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

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

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

Investigations	• Full blood examination, liver function tests, eGFR, INR
	• Pregnancy test for women of childbearing potential
	• Liver fibrosis assessment,§ eg:
	  ▸ Elastography (FibroScan®, ARFI, SWE)
	  ▸ Serum biomarker (APRI, FIB-4, Hepascore, ELF test)
	• For people with cirrhosis:
	  ▸ Liver ultrasound to exclude hepatocellular carcinoma (should be performed within 3 months before starting DAAs)
	  ▸ Screening for clinically significant portal hypertension and osteoporosis

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; FIB-4 = Fibrosis-4; 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.

* 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). Testing HCV genotype may be considered (see text).

† All three tests for HBV may be requested if the clinical notes indicate acute or chronic hepatitis.

‡ If testing for HBV and HIV cannot be performed before starting DAA therapy, especially in high-prevalence clinics where people are being screened for HCV using point-of-care tests, HBV and HIV testing should be performed within 4 weeks of starting DAAs.

§ If fibrosis assessment cannot be organised in a timely fashion, people should immediately start hepatitis C treatment, especially when there is concern about loss to follow-up.

Note: People living with hepatitis C can receive information, support and referral from community services, including:

- Hepatitis Australia: www.hepatitisaustralia.com
- Hepatitis Information Line: 1800 437 222
- Australian Injecting & Illicit Drug Users League: www.aivl.org.au

absence of cirrhosis. Although all people with chronic HCV infection are eligible for treatment, regardless of liver fibrosis stage, the presence of cirrhosis can influence 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 thrombocytopaenia. Low albumin levels, raised bilirubin levels and a raised international normalised ratio (INR) are markers of reduced liver functional reserve and decompensated liver disease.

Formal evaluation for cirrhosis with a non-invasive test is recommended for all individuals with chronic HCV infection. Evaluation of liver fibrosis stage should be performed before commencing treatment. None of the non-invasive tests have been validated for diagnosing cirrhosis after SVR, and there is a risk of false negative results when performed after treatment. However, the inability to organise liver fibrosis assessment beforehand should not preclude starting DAA therapy, especially in marginalised individuals who may become lost to follow-up. People should be given the opportunity to have a cirrhosis assessment performed, but curing hepatitis C should be prioritised to reduce the risk of liver-related morbidity and mortality.

Transient elastography (e.g. using 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[40] and outperforms serum biomarkers for detecting cirrhosis.[41] FibroScan® is available in most metropolitan centres. A liver stiffness measurement (LSM) of >12.5 kPa using FibroScan® is a reasonable threshold for identifying people with cirrhosis for treatment decision making.[42,43] 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), Fibrosis-4 (FIB-4), Hepascore, Enhanced Liver Fibrosis (ELF) test and FibroTest. The APRI is a simple biochemical marker that can be calculated from routine blood test results. The FIB-4 is similar to the APRI but also incorporates age into the algorithm. Hepascore and the ELF test are alternative serum fibrosis markers that are available in Australia but not currently MBS-reimbursed. FibroTest is not yet available in Australia. Serum biomarkers may be used to exclude the presence of cirrhosis in settings where other tools, such as transient elastography, are not accessible in a timely fashion. **Supplementary Table 1** presents further information and key clinical thresholds for excluding the presence of cirrhosis in people using the serum biomarkers for liver fibrosis that are available in Australia.

It is important to remember that none of the methods for non-invasive assessment of liver fibrosis are perfectly accurate, and the results must be interpreted in the context of the pre-test probability based on other clinical information. For example, a 50-year-old obese man with a 30-year duration of HCV infection, a past history of heavy alcohol consumption, spider naevi evident on examination and a platelet count of 90×10^9/L is very likely to have cirrhosis, even if the LSM is 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.

4.2.1 Screen for complications of cirrhosis

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. People with cirrhosis should be assessed for their risk of clinically significant portal hypertension (CSPH). Guidelines now recommend that non-invasive tools be used to triage risk of CSPH. CSPH can be assumed if LSM is > 25 kPa. CSPH can also be diagnosed if LSM is 20–25 kPa and platelet count is $< 150 \times 10^9$/L or if LSM is 15–20 kPa and platelet count is $< 110 \times 10^9$/L.[44] People with CSPH should be considered for non-selective beta-blocker (NSBB) therapy as primary prophylaxis to reduce the risk of liver decompensation. People with CSPH who start NSBB therapy do not need a screening gastroscopy. Among people with cirrhosis who do not start NSBB therapy, gastroscopy should be performed to screen for oesophageal varices that need treatment if LSM is ≥ 20 kPa or platelet count is $< 150 \times 10^9$/L.[44] People living with cirrhosis and who do not require NSBB therapy or screening gastroscopy can be monitored by yearly assessment of LSM and platelet count. If LSM increases (≥ 20 kPa) or platelet count declines ($< 150 \times 10^9$/L), screening gastroscopy should be performed to look for varices needing 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 ≥ B7, Model for End-Stage Liver Disease (MELD) score ≥ 13 or one of the following clinical events: refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, recurrent or chronic hepatic encephalopathy, small HCC or severe malnutrition (**Supplementary Table 2**[45]).

Bone densitometry is also recommended to screen for osteoporosis.

Performance of these screening tests should not delay treatment for HCV infection among people who have been diagnosed with cirrhosis, but they may be scheduled simultaneously or after treatment. 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. Testing for HBV and HIV should be performed before starting treatment. However, waiting for the results of HBV and HIV testing should not preclude starting DAA therapy, especially in marginalised individuals who may become lost to follow-up. If testing for HBV and HIV cannot be performed before starting DAA therapy, especially in high-prevalence clinics where people are being screened for HCV using point-of-care tests, HBV and HIV testing should be performed within 4 weeks of starting DAAs. 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).

It is also important to consider whether another liver disease is present, as this increases the risk of cirrhosis 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. 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) 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 10 standard drinks a week and no more than four standard drinks on any one day; the less a person drinks, the lower the risk of harm from alcohol[46]). 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*.[47] 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) for further information.[48]

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
Documentation of HCV genotype may be considered 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: • HCC (liver ultrasound) • CSPH (see text) • osteoporosis (bone densitometry).	A1
All people with cirrhosis should be referred to, and managed in consultation with, a specialist familiar with the management of this condition.	A1
Vaccination against 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 to cure hepatitis C (known as SVR). 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

Except people with limited (<12 months) life expectancy due to non-liver or non-HCV-related comorbidities, all those living with hepatitis C should be considered for treatment. This includes people with chronic hepatitis C, as well as all individuals with a risk factor for hepatitis C transmission who are found to have detectable HCV RNA in plasma or whole blood, regardless of the duration of infection. 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.

Pan-genotypic regimens are recommended as first-line treatment for people with chronic hepatitis C infection (see Section 5.4). Several genotype-specific regimens for the treatment of HCV infection have previously been available for the treatment of hepatitis C but are no longer marketed in Australia and have been removed from this consensus statement. These include elbasvir plus grazoprevir; sofosbuvir plus ledipasvir; sofosbuvir plus daclatasvir, with or without ribavirin; sofosbuvir plus ribavirin; and paritaprevir (ritonavir-boosted) plus ombitasvir plus dasabuvir, with or without ribavirin.

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

There are now three pan-genotypic DAA regimens listed on the PBS: sofosbuvir plus velpatasvir, glecaprevir plus pibrentasvir, and sofosbuvir plus velpatasvir plus voxilaprevir. The first-line regimens for treatment-naive people living with hepatitis C are sofosbuvir plus velpatasvir or glecaprevir plus pibrentasvir. The recommended treatment regimen for people who do not respond to sofosbuvir plus velpatasvir or glecaprevir plus pibrentasvir is the triple-combination regimen of sofosbuvir plus velpatasvir plus voxilaprevir (**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.[49,50] 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 (**Tables 2 and 3**). Rates of SVR ≥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%–96%).[50,51] Patients with decompensated liver disease should be treated with sofosbuvir plus velpatasvir plus ribavirin; the addition of ribavirin has been associated with higher rates of SVR in people with decompensated liver disease (see Section 8).

The most common adverse events in clinical trials were headache, fatigue, nausea and nasopharyngitis; rates were not significantly different compared

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 number	No cirrhosis	Cirrhosis
First-line regimens for people who are treatment-naive				
Sofosbuvir 400 mg, orally, daily + Velpatasvir 100 mg, orally, daily	1–6	1 pill daily	12 weeks	12 weeks
Glecaprevir 300 mg, orally, daily + Pibrentasvir 120 mg, orally, daily	1–6	Once daily (3 pills)	8 weeks	8 weeks*
Regimen for people who do not respond to first-line therapy due to virological failure				
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.
* A treatment duration of 12 weeks may be considered for patients with compensated cirrhosis, at the discretion of the prescriber.

with placebo.[49,50] Sofosbuvir and its main metabolite GS-331007 are renally excreted; however, no dose adjustment for sofosbuvir-containing regimens is required for patients with renal impairment, including those with end-stage renal disease (ESRD) requiring dialysis (see Section 12). 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 can vary according to the presence of cirrhosis and IFN-based treatment history (**Tables 2 and 3**). In treatment-naive individuals, the duration of therapy is 8 weeks for both those with and without cirrhosis.[52,53] SVR rates >95% have been observed for all genotypes of HCV.[54]

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 5.9.

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 contraindicated for patients with moderate or severe hepatic impairment (Child–Pugh class B or 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 5.9.1.1). 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-naive. 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.[55] 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 5.9.1.1.

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

5.6 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; glecaprevir, B1; pibrentasvir, 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

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

	Prior treatment history				
Salvage regimen (all doses are orally, daily)	Sofusbuvir + NS5A inhibitor	NS3 PI + NS5A inhibitor ± NS5B inhibitor	Sofusbuvir + RBV ***or*** PegIFN + RBV + sofusbuvir	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

Gt = genotype; HIV = human immunodeficiency virus; 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).

importance of not becoming pregnant during treatment or for 6 months after treatment.

Coadministration of ethinyloestradiol-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.

5.7 Children

Clinical trials have recently shown that treatment of HCV infection in children under the age of 18 years is safe and effective. Regimens that are available for the treatment of children aged under 18 years in Australia include sofosbuvir plus velpatasvir and glecaprevir plus pibrentasvir.[56-58] The Australian product information for glecaprevir plus pibrentasvir now includes treatment for children aged 3 years or older (no dose adjustment is required for children aged 12 years or older or those weighing > 45 kg). The Australian product information for sofosbuvir plus velpatasvir includes treatment for children who are

both aged 12 years or older and weigh > 30 kg, with no dose adjustment required. 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 now available on the websites of GESA and the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine.[59]

5.8 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-naive 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),[60,61] 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-naive 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.

5.9 Salvage therapy

5.9.1 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.

For people who do not respond to IFN-free DAA therapy, 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. People with cirrhosis should be referred to a specialist centre with experience in treating HCV infection (including salvage therapy) and advanced liver disease. 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-naive. Otherwise, we recommend treatment for virological failure as described below.

5.9.1.1 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-naive. 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.[55] 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.[55]

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%). As noted, sofosbuvir and its main metabolite GS-331007 are renally excreted, but no dose adjustment for sofosbuvir-containing regimens is required for patients with renal impairment, including those with ESRD requiring dialysis (see Section 12). 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).

People who do not respond to treatment with sofosbuvir plus velpatasvir plus voxilaprevir should be referred to a specialist centre with experience in treating HCV infection (including salvage therapy).

5.9.1.2 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.[62,63] 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,[62] and Part 2 ($n = 91$) was a randomised study of patients with or without cirrhosis that compared 12 weeks versus 16 weeks of treatment.[63] 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.[63] 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.

5.9.1.3 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 or are contraindicated 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 (Section 8). These patients should be referred to a specialist experienced in the management of HCV and cirrhosis.

5.9.2 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.

Consensus recommendations	Grade
All individuals with chronic HCV infection should be considered for antiviral therapy.	A1
Choice of treatment regimen should be based on: • patient preference, taking into consideration duration of treatment and number of pills • the potential for drug–drug interactions • the presence or absence of cirrhosis • the presence or absence of decompensated liver disease • prior treatment history	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

Consensus recommendations (continued)	Grade
People who are treatment-naive (see Table 2)	
First-line treatment regimens for people with no cirrhosis: • sofosbuvir + velpatasvir for 12 weeks • glecaprevir + pibrentasvir for 8 weeks	A1
First-line treatment regimens for people with cirrhosis and compensated liver disease: • sofosbuvir + velpatasvir for 12 weeks • glecaprevir + pibrentasvir for 8 (or 12) weeks	A1
People in whom DAA therapy has failed (see Table 3)	
People in whom first-line DAA therapy fails should be referred to a specialist centre for consideration of salvage therapy	B1
The recommended treatment regimen for people with compensated liver disease in whom first-line DAA therapy has failed is: • sofosbuvir + velpatasvir + voxilaprevir for 12 weeks	A1
Dose reduction or dose interruption of DAA therapies is not recommended.	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 HCV RNA in plasma or whole blood 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.

Management of dose interruptions should be individualised according to duration of the interruption and the DAA therapy completed. There is limited evidence to guide treatment decisions. A practical approach is outlined in **Table 4**. For people with dose interruptions of < 7 days, we recommend resuming DAA therapy and completing the prescribed course. For people with dose interruption of > 7 days, we make the recommendations shown in **Table 4** based on the duration of DAA therapy completed. People in whom dose interruption has been identified will require more intensive monitoring and support during the remainder of their treatment course.

Patients treated with ribavirin (see Section 8) require monitoring of haemoglobin levels. People with hepatic decompensation should commence at a reduced dose of ribavirin (600 mg daily) and 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, with or without estimation of α-fetoprotein level. 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.

Table 4. Monitoring of patients receiving antiviral therapy for hepatitis C virus (HCV) infection

A. On-treatment and post-treatment monitoring for virological response

Routine monitoring for an 8–12-week treatment regimen:*

Week 0	• Pre-treatment blood tests, including LFTs, HCV PCR (**Table 1**)
Week 12† post-treatment (SVR12)	• LFTs, HCV PCR (qualitative)

* More intensive monitoring may be required in certain populations (see text).

† Opportunistic testing of HCV RNA to check for SVR at any time beyond 4 weeks after treatment completion (SVR4) is adequate, especially when there is concern about subsequent loss to follow-up.

B. Management of DAA treatment interruption

Dose interruptions < 7 days:

- Resume DAA therapy and complete the original prescribed course

Dose interruptions > 7 days:

- Within the first 4 weeks of treatment:
  - start again, prescribing a complete course of DAA therapy
- Beyond Week 4 of treatment, test plasma or whole-blood HCV RNA, and:
  - if negative, repeat testing of plasma or whole-blood HCV RNA at Week 12‡ after treatment discontinuation to test for SVR
  - if positive, assume patient is a non-responder to first-line DAA therapy and retreat with sofosbuvir + velpatasvir + voxilaprevir for 12 weeks

‡ Testing of HCV RNA to check for SVR at any time beyond 4 weeks after treatment completion (SVR4) is adequate, especially when there is concern about subsequent loss to follow-up.

C. Monitoring after SVR

SVR, no cirrhosis and normal LFT results (male, ALT ≤ 30 U/L; female, ALT ≤ 19 U/L):

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

SVR and abnormal LFT results (male, ALT > 30 U/L; female, ALT > 19 U/L):

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

SVR and cirrhosis:

- Patients with cirrhosis require long-term monitoring and should be enrolled in screening programs for:
  - HCC — liver ultrasound ± serum α-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 those with prior exposure; this does not require repeated testing

ALT = alanine aminotransferase; AMA = anti-mitochondrial antibody; ANA = anti-nuclear antibodies; ASMA = anti-smooth muscle antibodies; DAA = direct-acting antiviral; HCC = hepatocellular carcinoma; LFT = liver function test; LKM = liver–kidney microsome; PCR = polymerase chain reaction; SVR = sustained virological response ; SVR12 = SVR at least 12 weeks after treatment (cure).

7. Post-treatment follow-up

7.1 Confirm SVR (cure)

Successful viral eradication (cure) is defined as undetectable plasma or whole-blood HCV RNA using a highly sensitive PCR assay at least 12 weeks after completion of DAA therapy (SVR12). Late relapse after SVR is very uncommon (< 0.5%), and the reappearance of HCV after this time point is most frequently due to reinfection. Recent data suggest there is a very high correlation between SVR4 (undetectable plasma or whole-blood HCV RNA using a highly sensitive PCR assay 4 weeks after completion of DAA therapy) and SVR12.[64,65] Therefore, opportunistic testing of HCV RNA at any time beyond 4 weeks after treatment completion is adequate, especially when there is concern about subsequent loss to follow-up (e.g. in prisoners for whom release to the community may be imminent).

People who do not have cirrhosis and who have normal liver function test results after SVR (male, ALT ≤ 30 U/L; female, 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 hepatitis C.

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 CSPH, as recommended by existing guidelines.[66-68] People with cirrhosis require long-term surveillance for HCC, even after SVR. HCC surveillance should continue long term even if LSM returns to the normal range. In contrast, in the absence of cofactors, patients with HCV-induced cirrhosis who achieve SVR and show consistent post-treatment improvements, with LSM values of < 12 kPa and platelet counts ≥ 150×10^9/L, can be discharged from surveillance for CSPH (LSM and platelet counts or endoscopy), as they do not have CSPH and are at negligible risk of hepatic decompensation.[44]

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 to confirm cure of hepatitis C (SVR12).	A1
Opportunistic HCV qualitative PCR can be performed at any time beyond 4 weeks after cessation of DAA therapy, especially when there is concern about subsequent loss to follow-up, to confirm cure of hepatitis C (SVR4).	A1
People with cirrhosis should continue in long-term surveillance programs: • for HCC • for varices needing treatment.*	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

* Exception: patients who achieve SVR, have normal liver function test results, have no cofactors for liver disease and show consistent post-treatment improvements, with LSM values of < 12 kPa and platelet counts ≥ 150 × 10^9/L, can be discharged from surveillance for CSPH (LSM and platelet counts or endoscopy), as they do not have CSPH and are at negligible risk of hepatic decompensation. These patients still require long-term surveillance for HCC.

8. Special populations: treatment of decompensated liver disease

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

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

Contraindications to liver transplantation may include advanced HCC, extrahepatic malignancy, uncontrolled extrahepatic infection, active alcohol or substance misuse, significant coronary or cerebrovascular disease or inadequate social support. For more information about liver transplantation, see the Transplantation Society of Australia and New Zealand guidelines.[69]

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 in the setting of hepatic decompensation (glecaprevir plus pibrentasvir is contraindicated and sofosbuvir plus velpatasvir plus voxilaprevir is not recommended for people with Child–Pugh B or C disease) (**Table 5**).

The efficacy of several DAA regimens in people with decompensated liver disease has been formally evaluated in clinical trials.[70-76]

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.[77] 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; ≥ 75 kg, 1200 mg) for 12 weeks, or sofosbuvir plus velpatasvir for 24 weeks.[77] 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 protocol 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 (24 weeks if ribavirin-intolerant)

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

Note: People with decompensated liver disease should not be treated with regimens that include the HCV protease inhibitors glecaprevir (contraindicated in Child–Pugh B or C disease) or voxilaprevir (not recommended in Child–Pugh B or C 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 ≤ 30 000/mm^3, bilirubin level > 85.5 µmol/L and creatinine clearance < 50 mL/min.

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 regimens that include the HCV protease inhibitors glecaprevir (contraindicated in Child–Pugh B or C disease) or voxilaprevir (not recommended in Child–Pugh B or C 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. The presence of ascites or encephalopathy, serum albumin level < 35 g/L, serum ALT level < 60 U/L and body mass index > 25 kg/m^2 are all associated with an increased risk of not achieving a reduction in Child–Pugh score to class A.[78] 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.[75,79] 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 ≥ B7, MELD score ≥ 13 or one of the following clinical events: refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, recurrent or chronic hepatic encephalopathy, small HCC or severe malnutrition.	A1
People with decompensated HCV cirrhosis, Child–Pugh score B and MELD score < 15 should be assessed by an expert hepatologist for consideration of treatment as soon as possible, as they are at risk of further decompensation and liver-related complications and death, which may be prevented by eradicating HCV.	B2
People with decompensated HCV cirrhosis, Child–Pugh score B or C and MELD score > 15 (who **are not** liver transplant candidates) should be assessed by an expert hepatologist for consideration of treatment where there is an anticipated benefit from such treatment.	B1
People with decompensated HCV cirrhosis, Child–Pugh score B or C and MELD score > 15 (who **are** liver transplant candidates) should be assessed by a liver transplant physician to consider the individual benefit and risks of treatment before transplantation.	B2
When making treatment decisions, decompensated liver disease should be defined by a Child–Pugh score ≥ B7.	A1
The first-line treatment regimen for chronic Gt 1–6 HCV infection and decompensated liver disease is (see Table 5):	
• sofosbuvir + velpatasvir + ribavirin for 12 weeks	A1
The following treatments should NOT BE USED in people with decompensated liver disease:	A1
• sofosbuvir + velpatasvir + voxilaprevir (protease inhibitor)	
• glecaprevir (protease inhibitor) + pibrentasvir	

9. Special populations: treatment of HCV after liver transplantation

Chronic hepatitis C was previously the leading indication for adult liver transplantation in Australia, accounting for about 40% of transplants.[80] Rates of liver transplantation for HCV-related cirrhosis and HCC have been declining since the introduction of DAA therapies.[81] Recurrence of hepatitis C after liver transplantation is universal and was a major clinical problem before the introduction of DAAs. 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.[82] Furthermore, in the setting of immunosuppression, 2%–5% of patients develop fibrosing cholestatic hepatitis (FCH) within 6 months of transplantation.[83] 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^2, which are associated with an increased risk of not achieving a reduction in Child–Pugh score to class A,[78] 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.[72] 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

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

* Data supporting the use of glecaprevir + pibrentasvir for 8 weeks in people with no cirrhosis in the post-transplantation setting are limited. Until additional real-world data are available, we continue to recommend a 12-week treatment duration. Treatment for 8 weeks may be considered on a case-by-case basis.

transplantation until a total treatment duration of 12 weeks has been achieved. Potential drug–drug interactions in the post-transplant setting should be considered.

9.2 Treatment of HCV and compensated liver disease after transplantation

Recommendations for the treatment of HCV after liver transplantation are based on clinical trial data where available. We have tried to avoid extrapolation from studies performed in non-liver transplant patients, given the complexity associated with post-transplant immunosuppression. Therefore, treatment recommendations may differ from those for the non-transplant population and may differ from the treatment regimens currently eligible for prescription under the PBS (**Table 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.

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.[84] 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. There are limited data available evaluating glecaprevir plus pibrentasvir for 8 weeks versus 12 weeks after liver transplantation. In one small multicentre study in Japan, 24 liver transplant recipients with recurrent HCV infection were treated with 8 weeks or 12 weeks of glecaprevir plus pibrentasvir; 96% achieved SVR12. All 13 patients treated for 8 weeks achieved SVR.[85] Until more data become available, we continue to recommend a 12-week treatment duration. However,

an 8-week treatment duration may be considered for some people without cirrhosis on a case-by-case basis.

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

There are no prospective clinical trial data that specifically evaluate the efficacy of treatment with sofosbuvir plus velpatasvir with or without ribavirin for post-transplant HCV in people with decompensated cirrhosis and HCV Gt 2, 3, 5 or 6. We recommend treatment with the regimens used for people with decompensated liver disease before liver transplantation (**Table 5**). The clinical benefit of achieving SVR in patients with decompensated liver disease due to recurrent HCV after liver transplantation was shown in a multicentre, prospective study of 52 patients with Gt 1 or 4 HCV who were treated with sofosbuvir plus ledipasvir plus ribavirin for 12 versus 24 weeks (SOLAR-1).[70] (Ledipasvir is an older genotype-specific NS5A inhibitor that is no longer marketed in Australia.) 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.

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.[86] 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.[70,87] 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. The optimal timing and duration of DAA therapy in this setting continue to be evaluated.

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 Gt 1–6 HCV infection and compensated liver disease after transplantation are (see Table 6):	
• sofosbuvir + velpatasvir for 12 weeks	B1* or B2†
• glecaprevir + pibrentasvir for 12 weeks‡	A1* or B1†
• sofosbuvir + velpatasvir + voxilaprevir for 12 weeks (if prior DAA failure)	B1
The preferred treatment option for chronic Gt 1–6 HCV infection and decompensated liver disease after transplantation is (see Table 5):	
• sofosbuvir + velpatasvir + ribavirin for 12 weeks	B1* or B2†
Treatment with sofosbuvir + velpatasvir or ribavirin does not require dose adjustment of calcineurin inhibitors or mTOR inhibitors.	A2

Notes: None of the currently available DAAs in Australia include a specific indication for the treatment of HCV infection after transplantation. Recommended or preferred treatment regimens may not be eligible for prescription on the PBS, reflecting the dynamic nature of this area (see Table 6).

* For Gt 1 HCV.

† For Gt 2, 3, 4 and 6 HCV.

‡ Data supporting the use of glecaprevir + pibrentasvir for 8 weeks in people with no cirrhosis in the post-transplantation setting are limited. Until additional real-world data are available, we continue to recommend a 12-week treatment duration. Treatment for 8 weeks may be considered on a case-by-case basis.

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,[88] even in those achieving full HIV virological suppression with antiretroviral treatment (ART) for HIV.[89,90] Eradication of HCV can prevent these complications, and people with HCV–HIV coinfection should be prioritised for treatment of HCV. In contrast to IFN-containing regimens, IFN-free DAA regimens for HCV are just as effective in the setting of HCV–HIV coinfection as they are in HCV monoinfection.[91-96] Drug–drug interactions, cumulative drug toxicities and increased pill burden are the main considerations when planning HCV treatment in people living with HIV. It is also important to note that thrombocytopaenia may occur secondary to HIV infection rather than portal hypertension; this may influence interpretation of APRI and FIB-4 serum markers for liver fibrosis staging. Serum bilirubin levels may be elevated by ARTs that inhibit biliary transporters. People with HIV–HCV coinfection should be cared for by a multidisciplinary team with experience in managing both viral infections.

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

HCV and HIV share common routes of acquisition. The risk of sexual (permucosal) transmission of HCV in people with HIV is increased, and the majority of sexual transmission of HCV occurs in HIV-positive people, particularly in men who have sex with men (MSM). High-risk practices include fisting, sharing sex toys, group sex and concurrent use of recreational drugs, particularly drugs absorbed through the mucosa.[97] 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,[98] 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.[99] 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.[100] HIV ART-naive people with HIV–HCV coinfection should have an ART regimen selected that will minimise drug–drug interactions with HCV medications and minimise potential liver toxicity. HIV should be controlled before HCV treatment, particularly in those with advanced HIV immunosuppression (CD4+ count, < 200 cells/mm^3). HIV-related opportunistic infections should be treated before initiation of HCV treatment. Treatment of people with a CD4+ cell count greater than 500 cells/mm^3 may be deferred until HCV treatment is completed, to avoid drug–drug interactions. ART should not be switched for people who are on a stable regimen unless an unavoidable and unmanageable drug–drug interaction is identified, because switching ART in HIV virologically suppressed patients has a risk of HIV virological failure.[101]

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.[91-96,102] Selection of DAA therapy for people with HIV–HCV coinfection should be as for HCV mono-infection, with the important caveat that ART increases the likelihood of clinically significant drug–drug interactions. A careful assessment of potential drug–drug interactions between DAAs and ART and drugs prescribed to manage HIV-related complications and comorbidities should be made before commencing HCV treatment, using the University of Liverpool's Hepatitis Drug Interactions website (www.hep-druginteractions.org). Caution is warranted even for combinations of HIV ART and HCV DAAs where a specific drug–drug interaction issue is not expected or reported, as further information on interactions is likely to emerge. Due to extensive drug–drug interactions, tipranavir should be avoided with concurrent HCV DAA therapy.

10.3.1 Sofosbuvir

Drug interaction studies of sofosbuvir with antiretroviral drugs (including efavirenz, tenofovir, emtricitabine, rilpivirine, ritonavir-boosted darunavir, and raltegravir) in uninfected individuals have not identified any clinically significant interactions.[103] Sofosbuvir is not recommended for use with tipranavir because of the potential of tipranavir to induce P-glycoprotein.

10.3.2 Velpatasvir

Drug interaction studies with velpatasvir plus sofosbuvir have been performed in HIV and HCV seronegative volunteers. Tenofovir exposures are increased when velpatasvir is coadministered with tenofovir disoproxil fumarate (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 tenofovir alafenamide (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.

10.3.3 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.

10.3.4 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.

10.3.5 Ribavirin

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

Consensus recommendations	Grade
People with HCV–HIV coinfection should be cared for by a clinician who is experienced in managing both viral infections.	B1
All people living with HCV should be tested for HIV.	A1
All HCV-negative people living with HIV should be tested for HCV annually if they have risk factors for HCV exposure.	A1
HIV should be controlled before HCV treatment.	B1
ART should not be switched for people who are on a stable regimen, unless an unavoidable and unmanageable drug–drug interaction is identified.	B1
The treatment regimens for chronic HCV infection in people living with HIV should be the same as those used for HCV mono-infection, because DAA regimens for the treatment of HCV are just as effective in the setting of HIV coinfection.	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 ± 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.[104]

In October 2016, the US Food and Drug Administration (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.[105] 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 coinfected patients,[106] 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 coinfected 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.[107] Emerging data specifically addressing the risk of HBV reactivation in anti-HBc-positive individuals are reassuring.[107,108] 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.[107] 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.[108] 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
HBsAg-positive patients	
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 **all** 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: • ALT — every 4 weeks until the end of treatment and at SVR • HBV DNA — every 12 weeks until SVR, plus if ALT level rises • If HBV DNA level remains < 2000 IU/mL at SVR, routine monitoring as per HBV guidelines can be reinstituted	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
Anti-HBc-positive, HBsAg-negative patients	
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

Management of hepatitis C in patients with renal impairment is possible. No dose adjustment is required for the current first-line DAA regimens of sofosbuvir plus velpatasvir, glecaprevir plus pibrentasvir, and sofosbuvir plus velpatasvir plus voxilaprevir. Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2 or haemodialysis) should be in specialist care, involving both a nephrologist and a clinician experienced in the treatment of hepatitis C.

Glecaprevir, pibrentasvir, velpatasvir and voxilaprevir are not renally excreted. Sofosbuvir is renally excreted; however, no dose adjustment for sofosbuvir-containing regimens is required for patients with renal impairment, including those with ESRD requiring dialysis.[109-113] Safety data remain limited for patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) and ESRD who are not receiving haemodialysis and are being treated with sofosbuvir.

Ribavirin is rarely used in the treatment of hepatitis C but 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.[114] The product information recommends that ribavirin should not be used in individuals with an eGFR <50 mL/min/1.73 m^2. In specialist centres, ribavirin-containing regimens may be considered for those with an eGFR <50 mL/min/1.73 m^2. In this setting, ribavirin therapy should be started at a low dose, with close monitoring of haemoglobin levels. Recommended ribavirin dose according to eGFR is: >50 mL/min/1.73 m^2, no dose adjustment; 30–50 mL/min/1.73 m^2, alternating doses of 200 mg and 400 mg every other day; <30 mL/min/1.73 m^2, 200 mg daily; haemodialysis, 200 mg pre-dialysis.

Treatment of people with hepatitis C and renal impairment is very effective. The efficacy of glecaprevir plus pibrentasvir in people with severe renal impairment was prospectively evaluated in 104 patients with Gt 1–6 HCV infection enrolled in a Phase III study.[115] All patients had an eGFR <30 mL/min/1.73 m^2 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. Glecaprevir plus pibrentasvir is a preferred regimen for treating hepatitis C in people with severe renal impairment.

Hepatitis C may rarely be associated with intrinsic renal disease, including cryoglobulinaemia and glomerulonephritis.[116] 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.

Consensus recommendations	Grade
In people with renal impairment, including those with ESRD requiring dialysis, no dose adjustment is required for: • sofosbuvir + velpatasvir • glecaprevir + pibrentasvir • sofosbuvir + velpatasvir + voxilaprevir	A1
As ribavirin is renally excreted and cannot be removed by dialysis, if indicated in people with renal disease, it should be used with caution, and treatment should be supervised by a specialist experienced in the treatment of HCV and renal failure.	A1
If ribavirin is indicated in people with an eGFR of 30–50 mL/min/1.73 m^2, a low dose (e.g. alternating doses of 200 mg and 400 mg every other day) should be used, with close monitoring of haemoglobin levels.	B1
If ribavirin is indicated in people with an eGFR < 30 mL/min/1.73 m^2 or haemodialysis, a very low dose (e.g. 200 mg daily for patients not on haemodialysis; 200 mg pre-dialysis for patients on haemodialysis) should be used, with close monitoring of haemoglobin levels.	B1

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[117] and the distinction between acute and early chronic infection is somewhat arbitrary. In Australia, modelling suggests that the incidence of HCV infection peaked at 14 000 new infections in 1999 and declined to 8500–9000 new infections in 2013.[1,3] There is evidence of further declines in the incidence of HCV infection since the unrestricted availability of DAA therapy in 2016.[4] In certain subpopulations, including HIV-positive MSM, incidence has declined dramatically.[118-124]

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.[97,125,126] 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.[127]

Acute HCV infection is characterised by the appearance of HCV RNA in blood within 2–14 days of exposure, elevation of liver-associated enzyme levels (particularly ALT), and development of HCV antibodies within 30–60 days of exposure. Up to 80% of acute HCV infections are asymptomatic, making detection and estimation of duration of infection difficult if seroconversion cannot be documented. Clinical features suggestive of acute infection include significant elevation of ALT level or an acute illness manifest by jaundice. However, only 15%–30% of those infected develop a symptomatic illness, and elevation of ALT level is non-specific. Acute infection should be suspected if the clinical signs and symptoms are compatible with acute hepatitis C — such as serum ALT level > 10 × ULN and jaundice in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent source of transmission is identifiable.

The preferred criteria for diagnosis of acute HCV infection are: i) positive anti-HCV IgG and a documented negative anti-HCV IgG in the previous 12 months; or ii) positive serum HCV RNA test and a documented negative serum HCV RNA test and negative anti-HCV IgG in the previous 12 months. Alternative, less stringent criteria are the presence of positive serum HCV RNA regardless of anti-HCV IgG and with: i) an acute rise in ALT level > 10 × ULN; *or* ii) an acute rise in ALT level > 5 × ULN, with documented normal ALT level within the past 12 months; *or* iii) in individuals with a previously high ALT level, an acute rise to 3.5 times the baseline ALT level; *and* in the absence of serological evidence of HAV or HBV infection or other causes of acute hepatitis. Documentation of seroconversion is difficult in the absence of routine serological testing, but monitoring of at-risk populations, including PWID[128] 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 be considered for antiviral therapy to reduce risk of transmission (see Section 13.3). If treatment is not indicated to reduce the risk of transmission, individuals 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.[129] 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.[130] Predictors of spontaneous clearance include jaundice, elevated ALT level, female sex, younger age and host genetic polymorphisms (including *IFNL4*), 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.[131] Fluctuating viraemia is common in the first few months after infection, with variable patterns.[132] 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.[133]

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. Among those who do not have ongoing risk factors for hepatitis C transmission, it is reasonable to observe people for spontaneous clearance. If spontaneous clearance has not occurred by 6 months after the transmission event, 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. Treatment is also actively recommended for people with risk factors for hepatitis C transmission, to prevent forward transmission events. Higher-risk populations for transmission include PWID and HIV-positive MSM. 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. Treatment in this phase has been shown to be safe and highly effective, with good adherence, even in high-risk populations.[120,122]

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
Early treatment for acute hepatitis C is recommended for people with risk factors for hepatitis C transmission, to prevent transmission events.	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 currently 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

14.1 Risk of de novo hepatocellular carcinoma and direct-acting antiviral therapy

People with hepatitis C and cirrhosis are at increased risk of HCC. Therefore, all people with hepatitis C and cirrhosis should be enrolled in surveillance for HCC, involving 6-monthly liver ultrasound with or without measurement of serum alpha-fetoprotein level.[134] The eradication of HCV is associated with a > 70% reduction in the risk of HCC. This was first shown in the setting of IFN-based treatment.[135-137] The risk of HCC in people with cirrhosis is also reduced after cure of hepatitis C with DAA therapy.[138-143] Therefore, we strongly recommend DAA therapy for all individuals with advanced liver disease who do not have a history of HCC. HCV treatment should not suspend HCC surveillance. We recommend a liver ultrasound within 1 month before starting DAA therapy for all individuals with cirrhosis to ensure that HCC surveillance remains up to date during the treatment and follow-up period. Importantly, although the risk of HCC is reduced after SVR, it is not abolished in people with cirrhosis, and HCC surveillance should continue long term for these people. There are no data to suggest that HCC risk is increased in people with no cirrhosis after SVR. We do not recommend HCC surveillance for people with no cirrhosis who are treated for HCV infection.

14.2 Treatment of HCV in patients with hepatocellular carcinoma

Important clinical questions to consider in deciding when to treat hepatitis C in a patient with HCC include: i) Will DAA therapy influence the natural history of HCC?; ii) Is the likelihood of SVR lower in patients with active HCC?; iii) Will DAA therapy improve liver synthetic function and increase tolerability of HCC treatment options?; iv) In patients who are candidates for liver transplantation, will DAA therapy influence waiting list time or waiting list dropout?; and v) Will DAA therapy influence the risk of recurrence of HCC after successful HCC treatment?

Reports from Europe soon after DAAs were introduced raised concerns about the possibility of DAA therapy being associated with early recurrence or rapid progression of HCC.[144,145] However, these concerns have not been borne out in subsequent studies. A 2017 systematic review, meta-analysis and meta-regression, which included 13 875 patients from 26 studies on HCC occurrence and 17 studies on HCC recurrence, concluded that there was no evidence for a difference in the incidence of de novo or recurrent HCC after achieving SVR.[146] A large retrospective cohort study of 797 North American patients with HCV-related HCC who achieved a complete response to local treatment (resection, ablation, transarterial chemo- or radio-embolisation or radiation therapy) reported a significant reduction in the overall risk of death associated with DAA therapy.[147] More recently, an expert review produced by the American Gastroenterological Association concluded that DAA therapy is associated with a reduction in the risk of de novo HCC and that there were no conclusive data that DAA therapy is associated with risk of recurrent HCC or rapid progression of HCC in patients with a complete response to HCC therapy.[148] Therefore, patients with early- or intermediate-stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage A/B) should be considered for DAA therapy.

People with hepatitis C who have a diagnosis of HCC should be treated with standard DAA regimens according to liver synthetic function (compensated versus decompensated) and whether they have had liver transplantation. Protease inhibitor therapy should not be prescribed for patients with decompensated (Child–Pugh class B/C) liver disease. There are reports that HCC is associated with a lower SVR rate. For example, in one meta-analysis of studies that compared SVR between patients with and without HCC, the SVR rate was 88% in patients with HCC compared with 92% in those without HCC.[149] Whether the lower rate of SVR can be attributed to

the unique biology of HCC or whether it reflects the presence of more advanced liver disease in patients with HCC is not clear.

The timing of DAA therapy should be individualised after discussion in a multidisciplinary meeting. In patients with early-stage HCC who have good synthetic function, DAA therapy may be deferred until complete response to HCC treatment is achieved. In patients who are being considered for liver transplantation, the timing of DAA therapy should be decided by considering the likelihood of SVR before versus after transplantation and the potential for DAA treatment to improve tolerance of locoregional therapy, to prevent tumour progression and reduce waiting list dropout, as well as the potential for improvement in liver synthetic function to extend waiting list time. In patients with advanced HCC (BCLC-C/D) who are receiving palliative management, treatment decisions should also be individualised, considering the potential for DAA therapy to improve liver synthetic function, the systemic treatment options for HCC and the patient's quality of life and life expectancy.

Consensus recommendations	Grade
All individuals with cirrhosis should be enrolled in HCC surveillance programs.	A1
HCC surveillance should involve liver ultrasound ± serum alpha-fetoprotein measurement performed every 6 months.	A1
All individuals with cirrhosis should be offered DAA treatment for HCV infection.	A1
HCC surveillance should continue long term after SVR in people with cirrhosis.	A1
Patients with HCC should be considered for DAA therapy.	A1
Decisions about the timing of DAA therapy for HCV in people with active HCC should be made with a multidisciplinary team.	B1
People with cirrhosis and prior HCC should be closely monitored for HCC recurrence during **and after** DAA therapy for HCV infection.	B2
HCC surveillance 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.[150] 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
CSPH	clinically significant portal hypertension
DAA	direct-acting antiviral
eGFR	estimated glomerular filtration rate
ELF	Enhanced Liver Fibrosis
ESRD	end-stage renal disease
FCH	fibrosing cholestatic hepatitis
FIB-4	Fibrosis-4
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
LSM	liver stiffness measurement
MSM	men who have sex with men
MELD	Model for End-Stage Liver Disease
mTOR	mammalian target of rapamycin
NSBB	non-selective beta-blocker
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCR	polymerase chain reaction
pegIFN	peginterferon-alfa
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	APRI = (AST [IU/L] ÷ AST ULN [IU/L] × 100) ÷ platelet count (× 10^9/L) Online calculator: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri	APRI < 1.0
FIB-4	FIB-4 = (age [years] × AST [U/L]) ÷ (platelet count [× 10^9/L] × √ALT [U/L]) Online calculator: https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4	FIB-4 < 1.45†
Hepascore	Patented formula combining bilirubin, GGT, hyaluronate, α-2-macroglobulin, age and sex	Hepascore < 0.80
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.

† FIB-4 score < 1.45 has a negative predictive value of 90% for advanced liver fibrosis.

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

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

A. Child–Pugh score

	Points		
Clinical measure	**1**	**2**	**3**
Albumin (g/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

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

B. MELD score

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

Online calculators are available.

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

INR = international normalised ratio.

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

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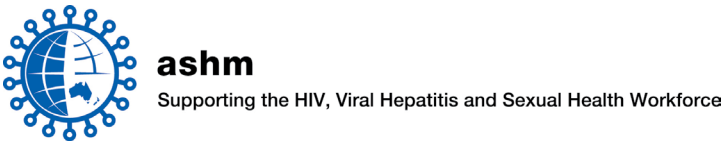
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