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

Summary

- Chronic hepatitis C virus (HCV) infection affects 230 000 Australians, who are at risk of progressive liver fibrosis leading to cirrhosis, liver failure and hepatocellular carcinoma.
- HCV infection is curable, and all Australians living with HCV should be considered for antiviral therapy.
- Interferon-free regimens involving combinations of sofosbuvir, ledipasvir, daclatasvir and/or ribavirin for 8, 12 or 24 weeks are now listed on the Pharmaceutical Benefits Scheme (PBS) for treating people with genotypes 1–3 HCV. Treatment for genotypes 4–6 HCV involves sofosbuvir plus peginterferon-alfa and ribavirin for 12 weeks.
- The PBS listing allows these therapies to be prescribed by specialists experienced in treating chronic HCV infection or by general practitioners in consultation with one of these specialists.
- People with cirrhosis and other special populations (eg, those with decompensated liver disease or renal impairment) should be referred for specialist care.
- Key issues during pre-treatment assessment include identifying HCV genotype, evaluating for cirrhosis and considering concomitant medications for risk of drug–drug interactions.

Chronic hepatitis C virus (HCV) infection is a major public health challenge for Australia, affecting about 230 000 people who are consequently at risk of progressive liver fibrosis leading to cirrhosis, liver failure and hepatocellular carcinoma (HCC). HCV infection is the most common cause of liver disease requiring liver transplantation in Australia. The burden of liver disease due to HCV is projected to triple by 2030. However, HCV infection is curable, and viral eradication is associated with multiple clinical benefits, including improvement in quality of life, loss of infectivity, regression of cirrhosis, lower risk of liver failure and HCC, and reduction in mortality. Until recently, the treatment of HCV involved interferon therapy, which had limited efficacy and was poorly tolerated. The introduction of direct-acting antiviral (DAA) therapies for HCV that are highly effective and well tolerated is a major medical advance. All Australians living with HCV should now be considered for antiviral therapy. Several of these new HCV medicines were listed on the Pharmaceutical Benefits Scheme (PBS) on 1 March 2016. DAAs may be prescribed by specialists experienced in treating HCV or by general practitioners in consultation with one of these specialists, meaning that treatment can occur in the community.

Here, we present a summary of the *Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016*. The consensus statement was prepared by an expert panel representing the Gastroenterological Society of Australia (Australian Liver Association), the Australasian Society for Infectious Diseases, the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, the Australasian Hepatology Association, Hepatitis Australia and the Royal Australian College of General Practitioners. The consensus statement is a living document that will be updated as new data emerge and is available at http://www.gesa.org.au.

Models of care for HCV

Despite one of the highest HCV diagnosis rates in the world, treatment uptake in Australia has been low (2000–4000 people/year). Upscaling treatment rates to the desired level to reduce population burdens of HCV and secondary liver disease (> 10 000 people/year)[1] will require the development of new models of care for HCV treatment. These should include traditional tertiary centre-led models of care, particularly for people with cirrhosis or special populations (eg, those with decompensated liver disease or renal impairment; see below), as well as community-based models of care involving GPs, specialist nurses and nurse practitioners. Specific models of care are needed for people who inject drugs, opioid substitution treatment centres, the prison system, rural and regional settings, Aboriginal and Torres Strait Islander people and migrants from high-prevalence regions (see full consensus statement).

The PBS listing allows the new HCV medicines to be prescribed by gastroenterologists, hepatologists or infectious diseases physicians who are experienced in treating chronic HCV infection, as well as by GPs in consultation with one of these specialists. The new HCV medicines will be available through the PBS General Schedule (Section 85), meaning approved pharmacists in the community can dispense the new HCV medications, as well as through the Section 100 Highly Specialised Drugs Program, which makes provision for treatment of prisoners.

Screening and diagnosis

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

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

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

polymerase chain reaction (PCR) assay for HCV RNA. 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. Harm reduction strategies (eg, needle and syringe programs, opioid substitution treatment) are important.

People with confirmed HCV infection should be tested for HCV genotype (Gt). The most common HCV genotypes in Australia are Gt 1 (50–55% of cases; Gt 1a : 1b = 2 : 1) and Gt 3 (35–40%).[2] HCV Gt 4–6 occur but are less common. As approved HCV treatment regimens are genotype-specific, HCV genotyping is necessary before treatment initiation.

Pre-treatment assessment

All people living with chronic HCV infection should be considered for antiviral treatment. Active psychosocial and substance use problems, including high-risk alcohol consumption, should be managed before starting therapy. People with stable psychiatric disease or stable injecting drug use are candidates for DAA treatment. People with no cirrhosis may continue to drink alcohol at low-risk levels during treatment (no more than two standard drinks on any day[3]). Complete abstinence from alcohol is recommended for people with cirrhosis or alcohol dependence.

It is important that all individuals undergo a comprehensive pre-treatment assessment (Box 2). Key elements include confirming the HCV diagnosis and genotype; documenting HCV treatment history; identifying comorbid liver disease or other bloodborne viral infections (hepatitis B virus [HBV], human immunodeficiency virus [HIV]); evaluating for the presence of cirrhosis; and considering concomitant medications, including over-the-counter and illicit drugs, for risk of drug–drug interactions.

All Australians with chronic HCV infection are eligible for DAA therapy, regardless of liver fibrosis stage. However, the presence of cirrhosis influences HCV treatment duration and regimen (see below) and requires long-term management. Documentation of the presence or absence of cirrhosis is required for PBS eligibility for DAA therapy. Formal evaluation for cirrhosis with a non-invasive test, such as elastography (eg, FibroScan [EchoSens], acoustic radiation force impulse technology, shear wave elastography) or a serum biomarker (eg, APRI [aspartate aminotransferase to platelet ratio index], Hepascore, Enhanced Liver Fibrosis [ELF] test, FibroGENE), is recommended for all individuals. FibroScan is available in most metropolitan centres. A liver stiffness of > 12.5 kPA measured using FibroScan can be used to define cirrhosis.[4-6] More details regarding non-invasive tests for liver fibrosis assessment are provided in the full consensus statement, including alternatives to FibroScan in regions where this is not accessible. Liver biopsy may still be required in a small proportion of patients. People with cirrhosis should be further evaluated for HCC and portal hypertension (Box 2); bone densitometry is recommended to screen for osteoporosis.

People with cirrhosis should be referred for specialist assessment due to the complexity of management. All individuals with decompensated liver disease should be considered for liver transplant assessment. Indications for assessment by a liver transplant centre include a 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 (see full consensus statement).[7]

Treatment for chronic HCV infection

The goal of treatment is cure, defined as undetectable plasma HCV RNA at least 12 weeks after treatment has ceased (sustained virological response [SVR]). Several genotype-specific interferon-free DAA treatment regimens have been PBS-listed for treating people with HCV Gt 1–3. Peginterferon-alfa (pegIFN) + ribavirin remains the backbone of PBS-listed treatments for HCV Gt 4–6. Treatment regimens described here are based on the most up-to-date international data, consistent with the wording of the PBS listing.

Genotype 1 HCV

The two interferon-free DAA regimens that are available for PBS prescription for treating Gt 1 HCV are the combinations of sofosbuvir + ledipasvir and sofosbuvir + daclatasvir ± ribavirin. The interferon-free DAA regimen of paritaprevir–ritonavir + ombitasvir + dasabuvir ± ribavirin has also been Therapeutic Goods Administration-approved and is expected to be PBS-listed in the near future, so has been included in the consensus statement. These regimens are all effective and can be considered first-line. In

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

History	• Estimated duration of HCV infection • Previous HCV treatment experience — date, regimen and response • Cofactors for liver disease progression: alcohol intake, marijuana use, virological cofactors (HIV, HBV), diabetes, obesity • For those planned to receive ribavirin, note history of ischaemic heart disease or cardiovascular risk factors • Vaccinations against HBV and HAV • Physical and psychiatric comorbidities • Ongoing risk factors for viral transmission and reinfection • Social issues — potential barriers to medication adherence
Medication	• Concomitant medications (prescription, over-the-counter, illicit)
Physical examination	• Features of cirrhosis: hard liver edge, spider naevi, leukonychia • Features of decompensation or portal hypertension: jaundice, ascites, oedema, bruising, muscle wasting, encephalopathy • Body weight and body mass index
Virology	• HCV genotype and subtype • HCV RNA level (quantitative) • HBV (HBsAg, anti-HBc, anti-HBs), HIV, HAV serology
Investigations	• Full blood examination, liver function tests, urea and electrolytes, eGFR, INR • Pregnancy test for women of childbearing potential • Liver fibrosis assessment, eg: ► Elastography (FibroScan, ARFI, SWE) ► Serum biomarker (APRI, Hepascore, ELF test, FibroGENE*) • Liver ultrasound should be performed in people with cirrhosis to exclude hepatocellular carcinoma • Electrocardiogram should be performed if ribavirin therapy is planned and patient is > 50 years of age or has cardiac risk factors

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

addition to the treatment considerations outlined below, the decision of which regimen to use will generally be based on the number of pills and avoiding ribavirin where possible. Treatment of Gt 1 HCV with pegIFN-containing regimens is now actively discouraged.

Sofosbuvir + ledipasvir for genotype 1 HCV. Sofosbuvir + ledipasvir is a coformulated, once-daily, single-pill regimen. The recommended treatment duration is 12 weeks, except for people with cirrhosis who have not responded to pegIFN-based therapy, who should receive treatment for 24 weeks (Appendix 1).[4,5] Rates of SVR ≥ 95% are achieved in all patient groups.[4,5] A shortened 8-week treatment duration may be considered in treatment-naive people with no cirrhosis who have baseline HCV RNA levels $< 6 \times 10^6$ IU/mL (see full consensus statement).[8] Adverse effects of fatigue, headache and nausea occur but are uncommon and typically mild.[4,5,8] Sofosbuvir is renally excreted. As safety data are lacking in people with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2, this regimen is not recommended in this setting.

Sofosbuvir + daclatasvir ± ribavirin for genotype 1 HCV. Sofosbuvir + daclatasvir ± ribavirin therapy is also approved as first-line treatment for Gt 1 HCV.[9,10] SVR rates are ≥ 95%. Sofosbuvir + daclatasvir (no ribavirin) for 12 weeks' duration is recommended for people with no cirrhosis who are treatment-naive or in whom treatment with pegIFN and ribavirin has previously failed (Appendix 1). People with cirrhosis are harder to cure and should be treated with either sofosbuvir + daclatasvir + ribavirin for 12 weeks or sofosbuvir + daclatasvir (no ribavirin) for 24 weeks. Sofosbuvir + daclatasvir (no ribavirin) for 24 weeks is recommended for people with or without cirrhosis who have not responded to prior treatment with a protease inhibitor + pegIFN + ribavirin (Appendix 1). Sofosbuvir + daclatasvir is well tolerated, with low (≤ 1%) discontinuation rates due to adverse events. The most common treatment-related adverse effects are fatigue, headache and nausea; again, these are typically infrequent and mild.

Paritaprevir–ritonavir, ombitasvir + dasabuvir ± ribavirin for genotype 1 HCV. The combination of paritaprevir (ritonavir-boosted), ombitasvir and dasabuvir (PrOD) is used with ribavirin for HCV Gt 1a, or without ribavirin for Gt 1b (Appendix 1).[11-15] Treatment is for 12 weeks, except for Gt 1a patients with cirrhosis and prior null response to pegIFN + ribavirin, who should receive treatment for 24 weeks. SVR rates ≥ 95% are observed in all groups. PrOD therapy is not recommended for prior non-responders to protease inhibitor therapy. The regimen should be used with caution in people with compensated cirrhosis and is contraindicated in patients with decompensated cirrhosis or history of liver decompensation. In people with renal impairment, dose adjustment is not required for PrOD but is required for ribavirin.

PrOD is well tolerated, with low (≤ 1%) discontinuation rates.[11] The most commonly reported adverse effects are nausea, pruritus and insomnia; these are uncommon and mild in most people. Rises in serum alanine aminotransferase (ALT) levels have been rarely observed, particularly among women taking ethinyl estradiol-containing contraceptives, which should be stopped before treatment. Alternative contraceptive agents (eg, progestin-only contraception) or methods are recommended. Transient isolated hyperbilirubinaemia may be seen early (Weeks 1–2) but typically resolves with ongoing therapy.

Elevation of ALT level above baseline or elevation of the bilirubin level to greater than twice the upper limit of normal during treatment should prompt close monitoring of liver function test results, and specialist opinion (see full consensus statement).

Ribavirin-related adverse events. Adverse events associated with ribavirin therapy include anaemia, rash, cough, dyspnoea, insomnia and anxiety. The mean reduction in haemoglobin level associated with PrOD + ribavirin is 24 g/L. Ribavirin is teratogenic, and both women and men should be counselled that two forms of contraception (but not ethinyl estradiol preparations in combination with PrOD) are required while taking ribavirin and for 6 months after treatment. Ribavirin is renally excreted and dose adjustment is required according to eGFR or if anaemia develops during treatment (see full consensus statement).

Genotype 2 HCV

The approved interferon-free treatment regimen for HCV Gt 2 is sofosbuvir + ribavirin for 12 weeks (Appendix 2). This regimen is highly effective in people with no cirrhosis, with cure rates of 90–95%.[16-19] Extending treatment duration to 24 weeks in people with cirrhosis may increase SVR rates but is not currently listed under the PBS.[16] Treatment is well tolerated, with the adverse event profile typical for ribavirin.

Genotype 3 HCV

The approved treatment regimens available under the PBS for Gt 3 HCV are sofosbuvir + daclatasvir for 12 or 24 weeks, sofosbuvir + ribavirin for 24 weeks, and the combination of sofosbuvir + pegIFN + ribavirin for 12 weeks (Appendix 2).[18,20,21]

Sofosbuvir + daclatasvir for genotype 3 HCV. Sofosbuvir + daclatasvir for 12 weeks is very effective for treating Gt 3 HCV in people with no cirrhosis, with SVR rates of 94–97%.[21] In people with cirrhosis, treatment should be extended to 24 weeks, which increases SVR rates from 58–69% to 85–90% (Appendix 2).[22,23]

Sofosbuvir + ribavirin for genotype 3 HCV. Treatment with sofosbuvir + ribavirin for 24 weeks is associated with SVR rates of 90–95% in treatment-naive people with no cirrhosis, and 58–76% in treatment-experienced people with cirrhosis.[16,18,19] Thus, this is an effective regimen for treatment-naive people with no cirrhosis but is not the preferred regimen for people with cirrhosis, particularly those who are treatment-experienced (Appendix 2).

Sofosbuvir + peginterferon-alfa + ribavirin for genotype 3 HCV. Triple therapy with sofosbuvir + pegIFN + ribavirin for 12 weeks is very effective for the treatment of Gt 3 HCV. This regimen is more effective than 16 or 24 weeks of sofosbuvir + ribavirin, including among treatment-experienced people with cirrhosis,[19] but is associated with pegIFN-related toxicity. This regimen may be useful as salvage therapy for people in whom first-line DAAs fail (Appendix 2).

Genotypes 4, 5 and 6 HCV

The first-line treatment regimen for Gt 4, 5 and 6 HCV that is currently listed on the PBS is the combination of sofosbuvir + pegIFN + ribavirin for 12 weeks (Appendix 3). In a Phase III study involving a small number of treatment-naive individuals with Gt 4–6 HCV, this regimen was associated with SVR rates of 96–100%.[17] There are no interferon-free treatment regimens for Gt 4–6 HCV currently available on the PBS. The combination of sofosbuvir + ledipasvir is effective for Gt 4 and 6 HCV.[24-27] Paritaprevir–ritonavir + ombitasvir + ribavirin is also effective for Gt 4 HCV.[28] It is likely that these regimens will be approved in Australia in the future.

Interferon-based therapy is associated with considerable morbidity, and intensive on-treatment monitoring is required (see full consensus statement). The most common adverse effects of pegIFN include influenza-like symptoms, fatigue, bone marrow suppression, mood disturbance and alopecia. PegIFN is contraindicated in people with untreated major depression or psychosis, immune-mediated disease (eg, inflammatory arthritis, lupus, ulcerative colitis) or decompensated liver disease. PegIFN-based treatment may precipitate hepatic decompensation in people with advanced liver disease; a platelet count $< 100 \times 10^9$/L and albumin level < 35 g/dL identify those at highest risk.[29] Despite the significant adverse event profile, the discontinuation rate among patients treated with 12 weeks of sofosbuvir + pegIFN + ribavirin was only 2% in clinical trials,[17] similar to that reported for interferon-free regimens.

Drug–drug interactions

Drug–drug interactions are a potential problem for all interferon-free treatment regimens. Important drugs to consider for potential interactions with DAAs include proton pump inhibitors, statins, St John's wort, antimicrobials, anti-epileptic agents, amiodarone, immunosuppressive agents and antiretroviral agents. All concomitant medications should be reviewed before starting treatment, using the University of Liverpool's Hepatitis Drug Interactions website (http://www.hep-druginteractions.org). We recommend working with an experienced pharmacist to confirm the safety of concomitant medications before starting DAA regimens. Patients should be advised to seek advice before starting any new medication during DAA therapy.

Pregnancy, breastfeeding and children

As there are no safety data for the use of any DAA regimen during pregnancy, treatment of pregnant women is not recommended. Ribavirin (classed as Category X) and pegIFN are contraindicated during pregnancy. Both women and men should be counselled about the risk of teratogenicity and the importance of avoiding pregnancy during and for 6 months after ribavirin treatment. As noted above, women treated with PrOD should avoid ethinyl estradiol-containing contraceptives. The safety of the listed DAA regimens during lactation has not

yet been established, so treatment of women who are breastfeeding is not recommended. Children under the age of 18 years are not currently eligible for treatment with the new PBS-listed HCV medicines. Studies in paediatric populations are ongoing. People under the age of 18 years should be referred to a paediatric gastroenterologist who is experienced in treating HCV for discussion about therapy.

Direct-acting antivirals and drug resistance

Resistance-associated variants (RAVs) have been identified for all of the approved DAAs. However, given the high SVR rates observed with combination therapy, there is currently no role for baseline HCV resistance testing in treatment-naive people or prior non-responders to pegIFN-based therapy. Resistance testing for NS3, NS5B and NS5A RAVs should be considered following DAA treatment failure, to guide salvage therapy. Resistance testing involves direct sequencing of the HCV genome and is available through specialised laboratories. HCV sequencing may also identify cases of reinfection.

Salvage therapy

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

People who are not cured by a first-line interferon-free treatment regimen should be referred to a specialist centre where there is greater access to evolving salvage treatment strategies and HCV resistance testing to help guide management.

On-treatment monitoring

In contrast to interferon-based treatment regimens, intense monitoring of most people undergoing DAA therapy is not necessary. For most people, one assessment at Week 4 of treatment will be sufficient during an 8-week or 12-week course (Appendix 4). More intensive monitoring is warranted for people in whom adherence is a concern, those with risk factors for ribavirin intolerance (eg, cardiac disease) or who develop ribavirin-induced anaemia, or people with advanced liver disease (portal hypertension or hepatic decompensation). Routine on-treatment assessment of HCV RNA levels is not required but may be considered if there are concerns regarding adherence to therapy.

Post-treatment follow-up

Confirm SVR

SVR is defined as undetectable plasma HCV RNA using a highly sensitive PCR assay 12 weeks after completion of DAA therapy (Appendix 4). Those who are not cured should be assessed for explanations for treatment failure, especially lack of adherence or reinfection. Referral to a specialist treatment centre is advisable for non-responders.

Long-term management of liver disease

People who do not have cirrhosis and who have normal liver function test results (males, ALT < 30 U/L; females, ALT < 19 U/L) after SVR do not need follow-up (Appendix 4). There is no reason to repeat anti-HCV serological tests. People who are cured should be told that persistence of anti-HCV antibodies is expected and does not represent active infection, nor does it confer immunity to reinfection. Individuals whose liver function test results remain abnormal after SVR should be assessed by a specialist for alternative causes of liver disease (Appendix 4). All individuals with cirrhosis need surveillance for HCC and oesophageal varices. Complications of chronic liver disease, including malnutrition and osteoporosis, should also be addressed.

Special populations

There are several patient groups in whom the treatment of HCV infection is complex. These special populations include people with decompensated liver disease, extrahepatic manifestations of HCV, HCV–HIV or HCV–HBV coinfection, renal impairment or acute HCV infection, as well as people who have had a liver transplant. All these people should be referred for management by a specialist who is experienced in the relevant areas (see full consensus statement). The optimal treatment regimen for patients with decompensated liver disease secondary to HCV, as well as whether face-to-face assessment by a transplant centre is warranted, should be discussed with a liver transplant physician before commencing antiviral therapy. Recommended treatment regimens for people with decompensated liver disease differ from those for people with compensated liver disease (see full consensus statement).

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