

Curing hepatitis C in general practice

A 12-step guide

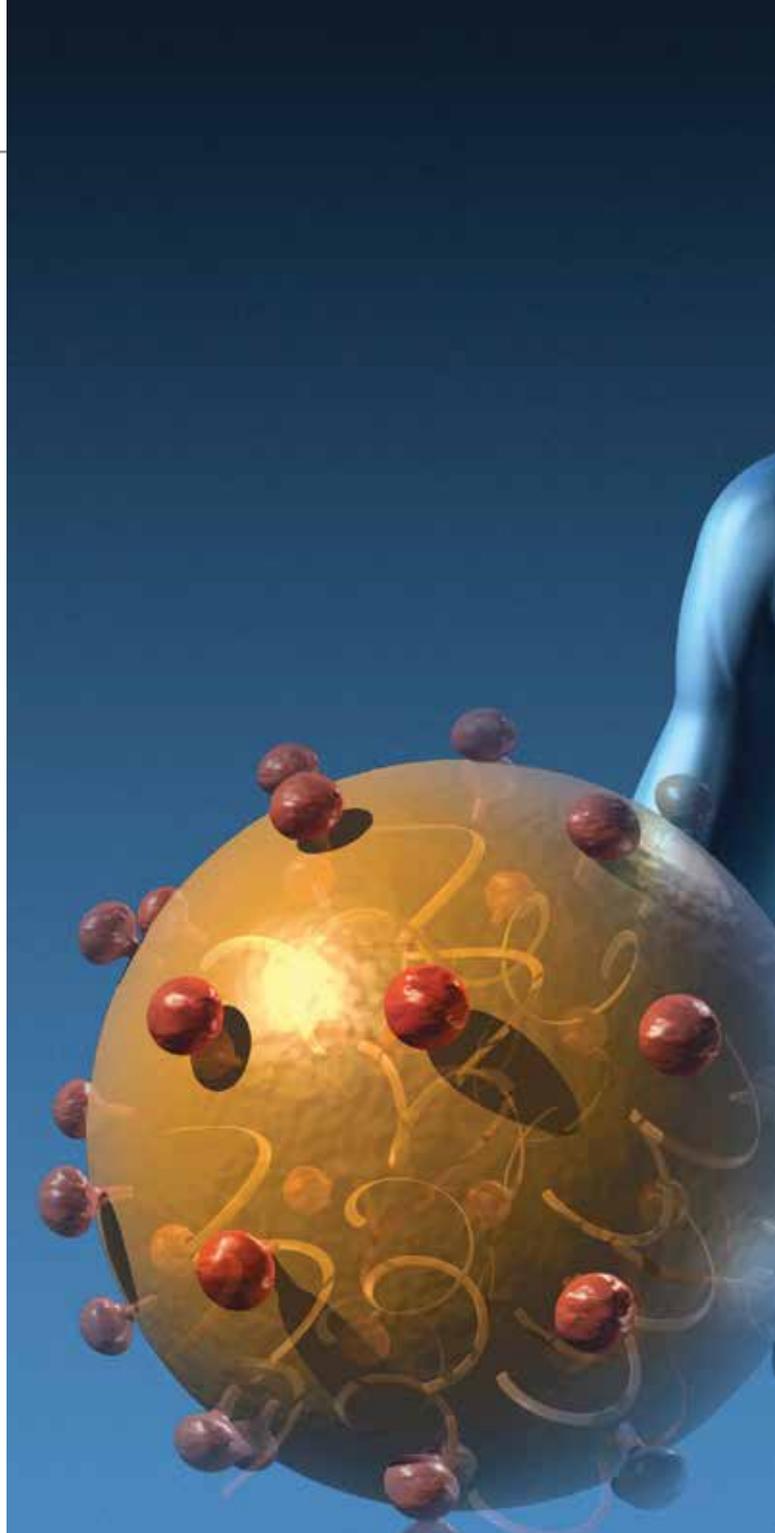
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The recent PBS listing of the direct-acting antivirals (DAAs) gives GPs the opportunity to cure most of their patients living with chronic hepatitis C. A 12-step approach can help GPs to assess their patients, to select the appropriate treatment regimen, to monitor through treatment and to refer for specialist care when necessary.

A miracle of modern medicine occurred on 1 March 2016, when all adults living with chronic hepatitis C infection in Australia were given access to new interferon-free treatment listed on the PBS. These new agents, the direct-acting antivirals (DAAs), offer hepatitis C cure rates of over 90%, with few side effects and only 12 weeks of treatment for most people. There has been very rapid uptake of these new treatments, with an estimated 22,470 individuals initiating DAA therapy between March and June 2016.¹

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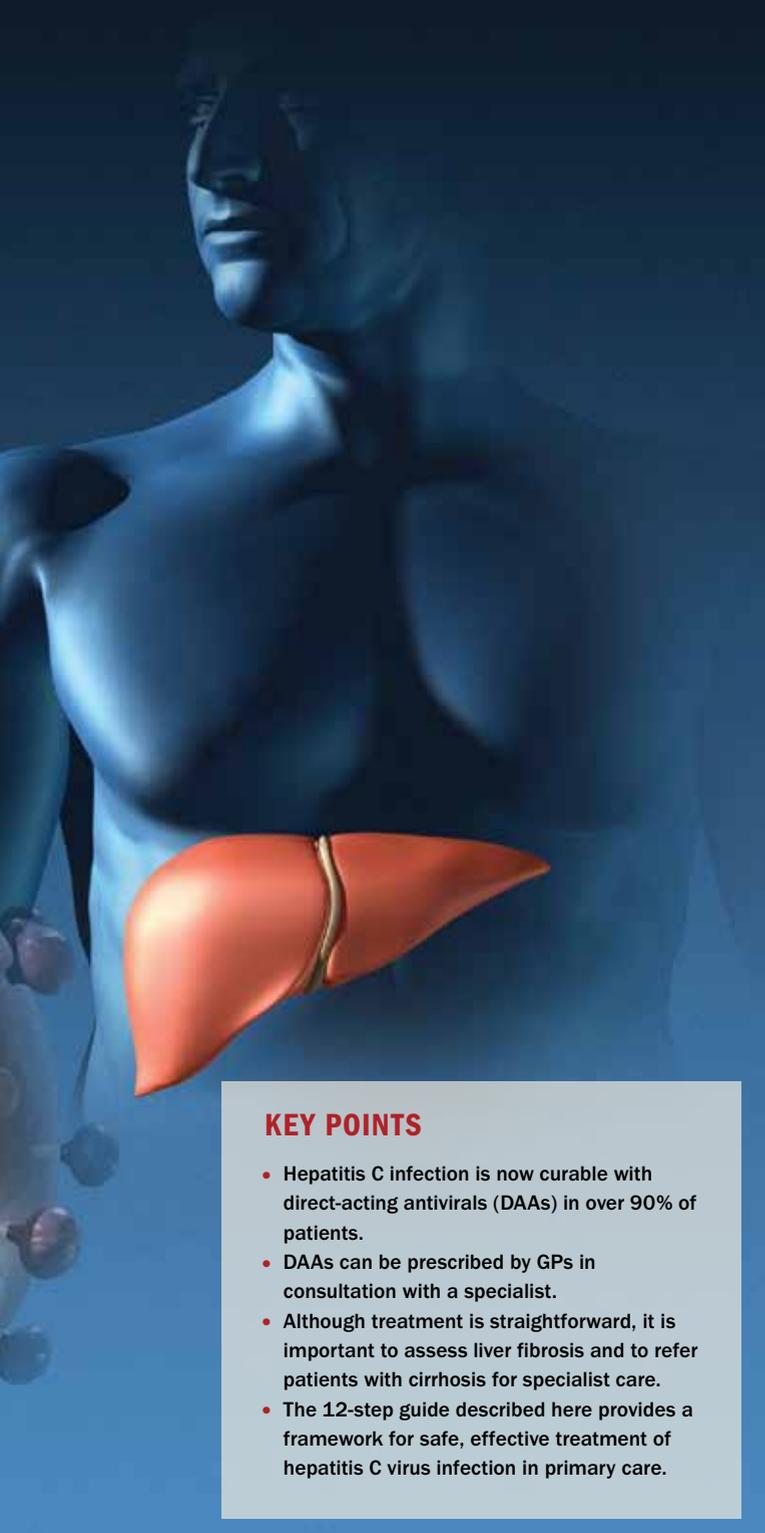


Cure of hepatitis C reduces progression to cirrhosis and the risk of complications such as hepatocellular carcinoma, and also prevents transmission of hepatitis C virus (HCV) to others.²

GPs are able to prescribe new hepatitis C medicines in consultation with a gastroenterologist, hepatologist or infectious diseases physician. Consultation can be by phone, fax, or email. This review details the steps in prescribing DAAs for patients with chronic hepatitis C.

Hepatitis C in Australia

An estimated 230,470 people are living with chronic HCV infection in Australia.³ Following infection, about 25% of people



KEY POINTS

- Hepatitis C infection is now curable with direct-acting antivirals (DAAs) in over 90% of patients.
- DAAs can be prescribed by GPs in consultation with a specialist.
- Although treatment is straightforward, it is important to assess liver fibrosis and to refer patients with cirrhosis for specialist care.
- The 12-step guide described here provides a framework for safe, effective treatment of hepatitis C virus infection in primary care.

clear the virus. The remaining 75% have chronic infection. Liver damage (fibrosis) is usually quite slow through the stages of fibrosis (F0 to F4), with about 7% of patients having cirrhosis (F4) after 20 years of infection.

Estimates of the distribution of liver disease suggest that around 10% of patients have cirrhosis (F4), which always requires specialist review, 13% have advanced fibrosis (F3), and the remaining 77% have earlier stage disease (F0 to F2).⁴ This means that most people living with chronic HCV infection have earlier stage disease and can be treated in a primary care setting. Patients with earlier disease can generally be treated with 12 weeks of combination DAA therapy, with a high likelihood of cure.

Complex patients with comorbidities such as renal disease or co-infections (hepatitis B or HIV) should also be referred for specialist review.

Identifying people eligible for treatment

An estimated 75% of people living with hepatitis C in Australia have already been diagnosed (Figure 1).³ However, it is important to continue to screen at-risk patients, particularly people born in a high prevalence country and those with a history of injecting drug use or imprisonment, or abnormal liver function test (LFT) results.⁵ Many patients have failed previous interferon-based treatment and are eligible for retreatment. Reinfection can occur despite previous successful treatment, so patients at ongoing risk need to be screened with HCV RNA tests. A positive result indicates reinfection.

12 steps to curing hepatitis C

The following 12-step approach to curing hepatitis C is based on the *Australian Recommendations for the Management of Hepatitis C Virus Infection: a Consensus Statement 2016*.⁶ This guideline is updated regularly to reflect the release of new treatments. Note that many of these steps will be performed together during patient assessment. The steps are summarised in Table 1.⁶ A case study that illustrates their application in general practice is shown in Box 1.

Step 1. Confirm chronic HCV infection

A positive HCV antibody (anti-HCV) test result indicates exposure to HCV virus. Current infection needs to be confirmed with a positive HCV RNA (PCR) test. About 25% of people exposed to HCV will spontaneously clear the virus and thus will be positive for anti-HCV but negative for HCV RNA.

Step 2. Check genotype and viral load

HCV genotype determines treatment choice, and HCV genotyping is a PBS requirement for DAA use.⁷ Most patients in Australia are infected with HCV genotypes 1 (50 to 55%), 3 (35 to 40%) or 2 (5 to 10%), which can be treated with interferon-free regimens on the PBS. Infections with HCV genotypes 4, 5 and 6 are uncommon but currently require treatment with interferon-containing regimens; patients infected with these genotypes should therefore be referred for specialist care.

A quantitative HCV RNA (viral load) assay should also be performed. If the viral load is low (less than 6×10^6 U/mL) then a shorter duration of therapy may be possible for patients who are treatment naïve (no prior HCV treatment) with genotype 1 infection and early disease.

Suggested baseline tests before HCV treatment with DAAs are shown in Box 2. GPs can order HCV genotype and HCV viral load tests reimbursed by Medicare as part of patient pretreatment assessment.

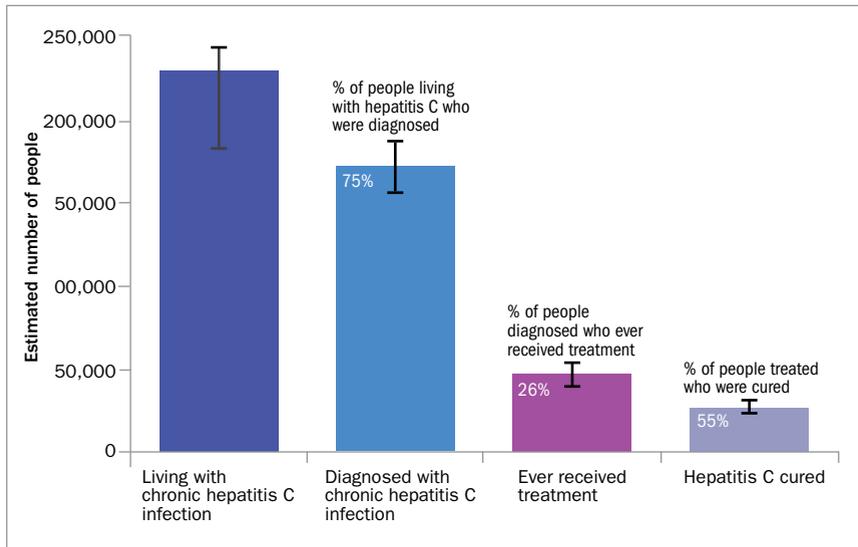


Figure 1. The Australian hepatitis C cascade of care, showing the estimated number of people in Australia who were living with hepatitis C infection, had been diagnosed, had ever been treated or had been cured in 2014.³

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TABLE 1. 12 STEPS TO CURING HEPATITIS C

Step	Role of primary care provider	When to refer for specialist review
1	Confirm chronic HCV infection	
2	Check HCV genotype and viral load	HCV genotype 4, 5 or 6
3	Assess liver fibrosis to exclude cirrhosis	Cirrhosis present
4	Detect comorbid liver disease	Co-infected with HIV or HBV
5	Detect other major comorbidities	Renal impairment (eGFR <50 mL/min/1.73 m ²)
6	Review previous HCV treatment	DAA treatment failure
7	Discuss contraception, pregnancy	
8	Assess adherence needs	
9	Select treatment regimen and review potential drug interactions	Complex drug interactions
10	Consult with a specialist	
11	Treat and monitor	Major adverse events
12	Post-treatment follow up	DAA treatment failure, persistently abnormal LFT results

Abbreviations: DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; LFT = liver function test.

Step 3. Assess liver fibrosis to exclude cirrhosis

Documentation of the presence or absence of cirrhosis is required in determining PBS eligibility for DAAs. All patients with cirrhosis need specialist referral. They will need additional investigations and regular screening for complications such as hepatocellular carcinoma. They often need longer and sometimes more complex therapy.

Risk factors for the development of cirrhosis include longer duration of infection, male sex and the presence of comorbidities such as alcohol abuse and viral co-infection (hepatitis B virus, HIV). Signs of cirrhosis include a stiff liver edge, spider naevi, palmar erythema, jaundice, ascites and peripheral oedema. Results of common investigations that suggest cirrhosis include a low albumin level or a low platelet count. Abdominal ultrasound examination may also suggest cirrhosis.

All patients should be investigated by a noninvasive measure of liver fibrosis. Methods include transient liver elastography (e.g. FibroScan) and evaluation of serum biomarkers through calculation of a score such as the aspartate transaminase (AST) to platelet ratio index (APRI), Fibrosis-4 (FIB-4) score or HepaScore.

Transient liver elastography can be performed in most liver clinics around Australia and increasingly in community settings. Liver stiffness above 12.5 kPa suggests cirrhosis. If transient liver elastography is not available then the APRI score can be easily calculated by hand or using an online calculator (Figure 2):

$$APRI = \frac{AST \text{ level (U/L)}}{AST \text{ upper limit of normal (U/L)}} \times \frac{10^9/L}{\text{platelet count (10}^9/L)} \times 100.$$

An APRI score greater than 1.0 has a sensitivity of 76% and specificity of 72% for predicting cirrhosis and should prompt specialist referral.⁸ A low APRI score with no other signs or symptoms of advanced liver disease suggests early liver disease.

1. CASE STUDY: TREATING A PATIENT WITH CHRONIC HEPATITIS C IN GENERAL PRACTICE

Presentation

Chris, aged 46 years, was diagnosed with hepatitis C at age 33 years. He used heroin regularly from the age of 18 years until his early 30s when he started methadone treatment. He is now stable with methadone dispensed at his local pharmacy. He was diagnosed with schizophrenia during a period of imprisonment in his late 20s. His symptoms are well controlled with daily olanzapine. Chris lives in a Department of Housing unit and receives a disability support pension as he can manage only occasional work. He has gained weight and now weighs 108 kg, with a body mass index of 31.6 kg/m².

Recent testing showed that Chris has chronic hepatitis C virus (HCV) infection, genotype 1a, with a viral load of 6.2 x 10⁶ U/mL. He attended a local liver outreach clinic where he underwent transient elastography (FibroScan) of the liver, but no reading could be obtained because of his obesity. He is keen to start hepatitis C treatment.

Management

You calculate Chris's APRI score, based on an AST level of 31 U/L (normal range <40 U/L) and platelet count of 188 x 10⁹ cells/L: APRI = 31/40/188 x 100 = 0.412. This score suggests that Chris has a low risk of cirrhosis. Other baseline investigations showed normal renal function and no viral co-infections. He is immune to hepatitis B following vaccination.

You check for drug–drug interactions between direct-acting antivirals (DAAs) and Chris's current medications, finding that these are unlikely. After checking the Australian consensus statement, you select sofosbuvir 400 mg daily plus ledipasvir 90 mg daily, coformulated as a single tablet to be taken once daily for 12 weeks.⁶

During Chris's assessment you complete a GP Management Plan including a Team Care Arrangement. You include his community pharmacist in the plan, who agrees to provide Chris with his medication in a dosette box. You also complete a *Remote Consultation Request for Initiation of Hepatitis C Treatment* form, which you email to your local gastroenterologist who replies that your plan is reasonable. You telephone the PBS prescription authority line, provide the required information and print out a sofosbuvir–ledipasvir prescription that Chris takes to his community pharmacist.

Chris understands the importance of good adherence to the regimen and agrees to contact you if he experiences significant side effects.

Follow up

Chris returns for follow up after 4 weeks. He reports mild nausea with the medication but is finding it manageable. He reports missing two doses. You order a full blood count, liver function tests (LFTs) and HCV quantitative RNA testing. At his next consultation, Chris is delighted that his LFT results are now normal and that the HCV RNA level is 'undetectable'. You explain that these results are excellent and that HCV cure is likely but that the final assessment has to wait until 12 weeks after the end of treatment.

Outcome

You continue to see Chris for periodic review of his opioid substitution therapy and mental health. Given his good adherence to DAA treatment and favourable results at 4-week follow up, you do not order any further monitoring pathology tests until 3 months following completion of DAA treatment. Chris is relieved to find that the HCV qualitative RNA test at this time is negative and his LFT results are normal, indicating HCV cure. Although he does not report any ongoing injecting drug use, you will repeat HCV RNA testing once a year as part of his regular health care.

Step 4. Detect comorbid liver disease

Many patients with hepatitis C have other causes of liver damage, such as alcohol-related liver disease, fatty liver or other viral infections (hepatitis B and HIV infection).

It is important to review alcohol use, check patients' weight and body mass index and offer appropriate counselling and treatment for other contributors to liver disease. All patients should have full hepatitis A and B serological testing (including hepatitis B

2. RECOMMENDED BASELINE TESTS BEFORE PRESCRIBING DAAs FOR PATIENTS WITH HEPATITIS C²

- Liver function tests
- Full blood examination
- Electrolytes, urea and creatinine levels
- Fasting blood sugar and lipid levels
- Hepatitis C genotyping
- Quantitative assay of HCV RNA by PCR (viral load)
- Hepatitis A serology (hepatitis A IgG)
- Hepatitis B serology (anti-HBs, anti-HBc, HBsAg)
- HIV antibody testing

Abbreviations: Anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; DAAs = direct-acting antiviral drugs; HBsAg = hepatitis B surface antigen; IgG = immunoglobulin G; PCR = polymerase chain reaction.

surface antigen, antibody to hepatitis B core antigen and antibody to hepatitis B surface antigen) and hepatitis A and B vaccination if susceptible.

Patients should be further investigated if LFT results remain elevated after treatment of hepatitis C.

Step 5. Detect other major comorbidities

It is important to note that psychiatric comorbidity or ongoing injecting drug use is not a contraindication to treatment with DAAs. However, people living with hepatitis C have higher rates of comorbidity compared with the general population.⁹ Historically, this group has had a significant risk of mortality from drug overdose.¹⁰ For some patients it may be necessary to stabilise drug and alcohol use before HCV treatment.

Patients with renal impairment (estimated glomerular filtration rate less than 50 mL/min/1.73 m²) should be referred for specialist review as dose adjustment or alternative regimens may be needed.

Ribavirin will not often be used in primary care but is associated with side effects including anaemia. It should be used with caution in patients with heart disease.

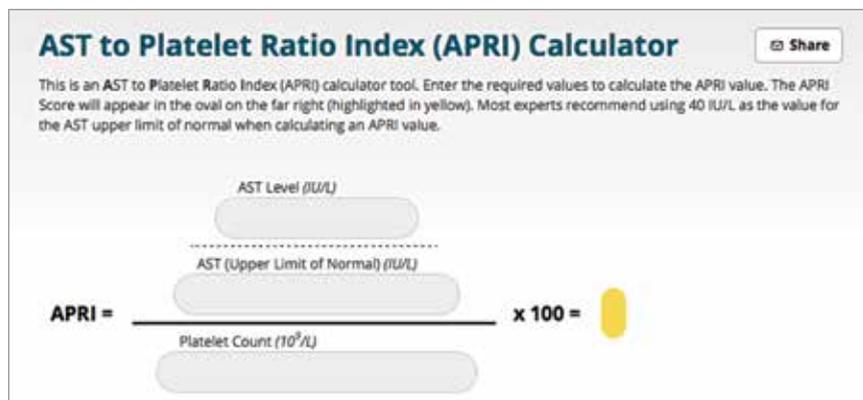


Figure 2. A simple calculator for the aspartate transaminase to platelet ratio index (APRI), available online (www.hepatitisc.uw.edu/page/clinical-calculators/apri).

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Step 6. Review previous HCV treatment

Many patients with hepatitis C have had previous treatment with interferon and ribavirin. In general, this group can be treated with the new DAAs without modifying treatment. However, patients who have failed treatment with new DAA-based therapy should be referred for specialist review.

Step 7. Review contraception and pregnancy

DAAs should not be used in pregnant or breastfeeding women. A pregnancy test should be ordered before treatment and contraception reviewed.

Ribavirin is classed as category X in pregnancy. If ribavirin is prescribed to women of childbearing age then dual forms of contraception are required during treatment and for six months after treatment. Because of its association with significant risks, ribavirin should be prescribed only by clinicians experienced in its use.

Step 8. Assess adherence needs

Patients need to be able to take the proposed treatment for the recommended duration. For people with early liver disease, treatment is not urgent, allowing their readiness to be fully assessed, and adherence supports to be developed if needed. This can involve

the formation of a support team, including practice or community nurses, psychologists and pharmacists. Other adherence supports can range from simple aids such as pillboxes through to supervised daily dosing.

Step 9. Select treatment regimen and review potential drug interactions

At Step 9, GPs will have patients who are infected with HCV genotype 1, 2 or 3 and have earlier stage disease. Cirrhosis and major relevant comorbidities will have been excluded. GPs must select the appropriate treatment based on genotype. Table 2 shows the commonly used medications based on genotype for patients without cirrhosis.

Existing medication should be checked for drug–drug interactions with the proposed DAA regimen using online tools such as the University of Liverpool drug interaction website (www.hep-druginteractions.org). If there are potential drug interactions then DAA selection and dosage or current medication may need to be modified before treatment. For example, dosages of statins, proton pump inhibitors and calcium channel blockers may need to be reduced before DAA therapy. Patients may need to consult the appropriate specialist for review if the potential interactions are complex (e.g. amiodarone is contraindicated with most DAAs).

TABLE 2. MAIN PBS-LISTED MEDICATIONS FOR PATIENTS WITH HEPATITIS C GENOTYPE 1, 2 OR 3 INFECTION WITHOUT CIRRHOSIS

Genotype	Regimen*	Total tablets per day
1a or b	Ledipasvir-sofosbuvir 90 mg/400 mg daily (Harvoni) [†] OR	1 tablet
	Sofosbuvir (Sovaldi) 400 mg daily + daclatasvir (Daklinza) 60 mg daily OR	2 tablets
1a	Paritaprevir–ritonavir–ombitasvir (150 mg/100 mg/25 mg) daily + dasabuvir 250 mg twice daily + ribavirin 1000 or 1200 mg (weight-based) daily (Viekira Pak-RBV)	4 tablets plus twice daily ribavirin
1b	Paritaprevir–ritonavir–ombitasvir (150 mg/100 mg/25 mg) daily + dasabuvir 250 mg twice daily (Viekira Pak)	4 tablets
2	Sofosbuvir (Sovaldi) 400 mg daily + ribavirin (Ibavyr) 1000 or 1200 mg daily (weight-based)	1 tablet plus twice daily ribavirin
3	Sofosbuvir (Sovaldi) 400 mg daily + daclatasvir (Daklinza) 60 mg daily	2 tablets

* Treatment duration 12 weeks; all medications are taken orally.
[†] Treatment duration may be shortened to 8 weeks if HCV RNA count <6 x 10⁶ U/mL.

Step 10. Consult with a specialist

PBS listing allows the new hepatitis C medicines to be prescribed by gastroenterologists, hepatologists or infectious diseases physicians who are experienced in the treatment of chronic HCV infection, and also by GPs in consultation with one of these specialists. Consultation can be by phone, fax, or email.

A pro forma consultation request (*Remote Consultation Request for Initiation of Hepatitis C Treatment*) is available from the Gastroenterological Society of Australia website (www.gesa.org.au/professional.asp?cid=77&id=454).¹¹ The completed form can be sent to a local specialist for review.

Step 11. Treat and monitor

Patients do not require intensive monitoring during treatment with DAAs unless they have significant comorbidities or difficulties that may affect adherence. The Australian consensus statement has suggested an appropriate schedule of visits

(Box 3).⁶ At each visit it is important to discuss side effects, adherence and the use of any new medication. Patients taking ribavirin or those with cirrhosis need more regular monitoring depending on their level of anaemia.

Unlike interferon-based hepatitis C treatment, DAA treatment does not generally require regular monitoring of HCV RNA level during treatment. Quantitative HCV RNA tests can be performed at week 4, particularly when there are adherence concerns, with qualitative HCV RNA testing at the end of treatment.

Common side effects of treatment with DAAs include headache, fatigue and nausea; however, few patients have to cease treatment because of adverse events. Therapy with ribavirin has more side effects, including anaemia, rash, cough, shortness of breath, insomnia and anxiety.

Step 12. Post-treatment follow up

The aim of treatment is virological cure. This is a sustained virological response,

defined as undetectable plasma HCV RNA at least 12 weeks after treatment has ceased (SVR12). Patients with an SVR12 and normal LFT results require no further clinical follow up (Box 3). It is important to note that patients who are cured will remain positive for anti-HCV antibodies, generally for life. Therefore, if there is concern about HCV reinfection (particularly among people with ongoing injecting drug use, or HIV-infected gay and bisexual men), repeat qualitative HCV RNA testing is recommended annually.

Patients who fail DAA therapy or have ongoing signs of liver disease or persistently abnormal LFT results after treatment need referral to a gastroenterologist, hepatologist or infectious diseases physician (Box 3).⁶

Prescriber training

All GPs can prescribe DAAs in consultation with a specialist hepatologist, gastroenterologist or infectious diseases specialist. Ideally, GPs will have some experience and

3. SUGGESTED MONITORING OF PATIENTS WITHOUT CIRRHOSIS RECEIVING A 12-WEEK DAA REGIMEN*

Week 0 (before treatment)

- FBE, urea and electrolyte levels, LFTs, INR, HCV RNA level (quantitative)

Week 4 of treatment†

- FBE, LFTs†
- Medication adherence
- Treatment adverse effects
- Drug–drug interactions

Week 12 (end of treatment)

- FBE, LFTs, HCV RNA (qualitative)

Week 24 (12 weeks after end of treatment)

- FBE, LFTs, HCV RNA (qualitative)

Monitoring after SVR12

- SVR12 and normal LFT results: no clinical follow up required
- SVR12 and abnormal LFT results: refer for gastroenterology review (evaluation for other liver diseases)

Abbreviations: DAA = direct-acting antiviral; FBE = full blood examination; HCV = hepatitis C virus; LFT = liver function test; and SVR12 = sustained virological response at least 12 weeks after treatment (cure).

* Adapted from Hepatitis C Virus Infection Consensus Statement Working Group (2016). Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016.⁶

† The need for more frequent review should be individualised. Patients taking ribavirin may require FBE at Week 2 and Week 4 and then every 4 weeks.

‡ Routine HCV RNA testing during treatment is not mandated but may be considered where there is a clinical concern about nonadherence to treatment, especially in people with cirrhosis.

training before prescribing DAAs. Training is available online through the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM), which runs regular prescriber updates (www.ashm.org.au/hcv/training).

Conclusion

GPs have an ongoing vital role in diagnosing bloodborne viral infections including hepatitis C. With the listing of new DAAs on the PBS, GPs now also have the opportunity to cure HCV infection in most patients. Some useful resources for GPs prescribing DAAs for patients with

4. USEFUL RESOURCES FOR GPs PRESCRIBING DAAs FOR PATIENTS WITH HEPATITIS C

- *Australian Recommendations for the Management of Hepatitis C Virus Infection: a Consensus Statement 2016*⁶ (www.hepcguidelines.org.au)
- AST to Platelet Ratio Index (APRI) calculator (www.hepatitisc.uw.edu/page/clinical-calculators/apri)
- *Remote Consultation Request for Initiation of Hepatitis C Treatment pro forma* (www.gesa.org.au/professional.asp?cid=77&id=454)
- ASHM online prescriber training (www.ashm.org.au/hcv/training)

hepatitis C are listed in Box 4. Cure of hepatitis C will reduce liver-related complications for patients as well as being a great public health achievement. As with all new therapies, doctors will need some training to gain confidence in patient assessment and treatment. Ultimately, curing a patient living with a serious illness is life changing for the patient and wonderfully rewarding for the doctor. MT

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COMPETING INTERESTS: Dr Baker has received trial funding and conference sponsorship and has participated in advisory board meetings for Gilead, Bristol-Myers Squibb, MSD and AbbVie.

ONLINE CPD JOURNAL PROGRAM

What baseline tests are needed before treatment of hepatitis C with direct-acting antivirals?



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