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November 2019

THE PEER REVIEWED JOURNAL OF CLINICAL PRACTICE

Supplement

Elimination of hepatitis C

The crucial role of GPs

Finding your patients with hepatitis C

Assessing your patient for antiviral treatment

Curing hepatitis C in general practice

Ongoing care after hepatitis C treatment

Practical steps in your practice

Online resources on hepatitis C for Australian GPs

Formerly **MODERN MEDICINE**

This supplement is provided as an educational service by **Gilead Sciences Pty Ltd**

SUPPLEMENT
ELIMINATION OF HEPATITIS C: THE CRUCIAL ROLE OF GPS
NOVEMBER 2019

ISSN 1443-430X

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Printed by Blue Star Web, Sydney.

The articles in this supplement were specially commissioned for this series and were originally published in *Medicine Today* and updated. Each has been subjected to *Medicine Today's* usual rigorous peer review process. This supplement has been sponsored by an unrestricted educational grant from Gilead Sciences Pty Ltd. The opinions expressed in the articles are those of the authors and not necessarily those of Gilead Sciences. Some products and/or indications mentioned may not be approved for use in Australia. Please review Product Information, available from the manufacturer, before prescribing any agent mentioned in these articles.

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THE PEER REVIEWED JOURNAL OF CLINICAL PRACTICE

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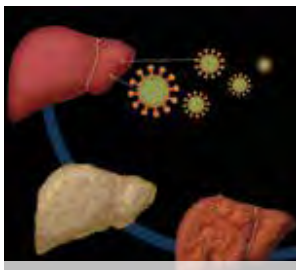
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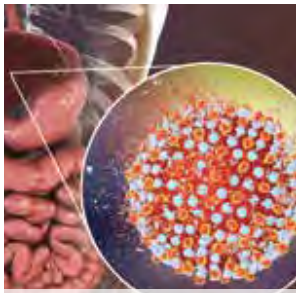
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* Equal first authors.

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Foreword
from the Supplement Editors

Elimination of hepatitis C
The crucial role of GPs

New curative treatments for hepatitis C, known as direct-acting antivirals (DAAs), have revolutionised the management of people living with hepatitis C. DAA therapy is highly effective, with more than 95% of patients being cured of their infection. DAAs are also tolerable and easy to take: just one to three tablets daily for eight or 12 weeks.

The advent of DAA therapy means it is possible to eliminate hepatitis C as a public health threat. Australia is aiming for the elimination of hepatitis C by 2030, in line with global targets, led by the WHO and Australia's National Hepatitis C Strategy 2018 to 2022.

GPs have a major role to play if Australia is to reach the 2030 elimination target, as the vast majority of Australians with hepatitis C will be managed in primary care. This supplement brings together a series of five articles, first published in *Medicine Today*, that guide GPs through hepatitis C testing, treatment, cure and follow up in primary care. A list of useful online resources for GPs managing patients with hepatitis C is also included.

The first article in the series – Finding your patients with hepatitis C – focuses on who and how to test for hepatitis C. The second article provides practical advice on assessing a patient diagnosed with hepatitis C before treatment. The third article gives GPs a practical guide to treatment with DAAs. The follow up of patients after hepatitis C treatment and cure, particularly those with significant liver disease, is the focus of the fourth article. The final article summarises practical steps GPs can follow in their practices to help eliminate hepatitis C from their local community.

We hope that this supplement will encourage GPs around Australia to participate in the miracle of hepatitis C cure and contribute to the elimination of this disease by 2030.

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Eliminating hepatitis C

Part 1. Finding your patients with hepatitis C

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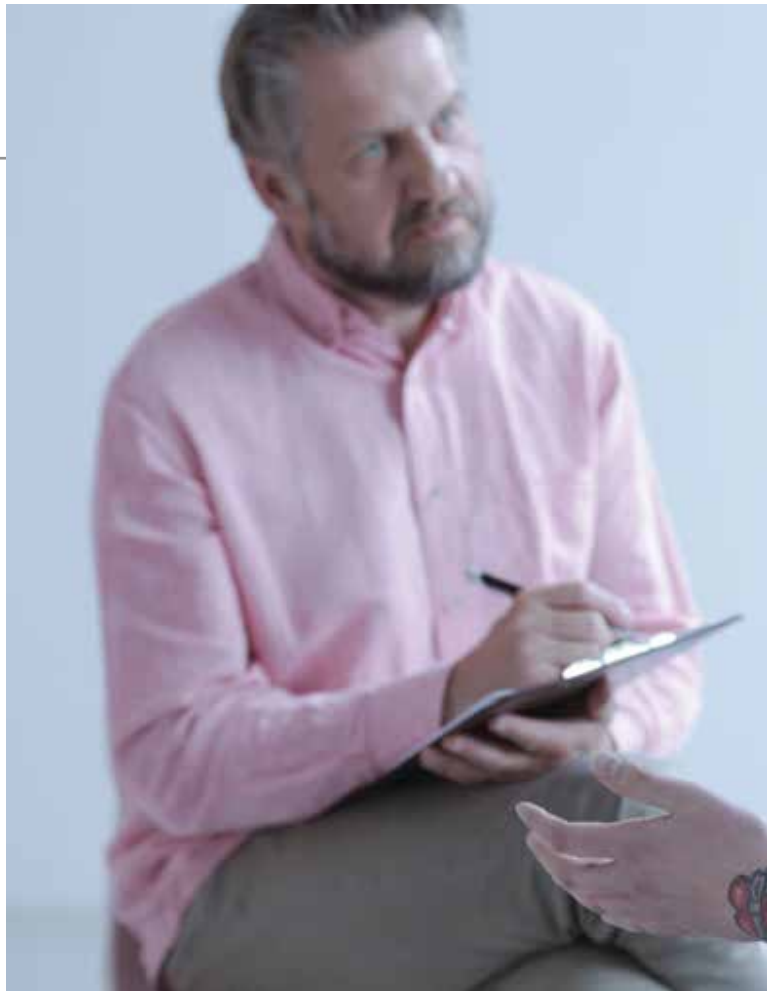

Direct-acting antivirals (DAAs) can now cure almost all patients with chronic hepatitis C. This gives us the opportunity to eliminate hepatitis C from Australia. However, the number of people receiving DAA therapy is declining despite an estimated 165,000 people living with chronic hepatitis C. GPs have a key role in identifying and treating their patients living with hepatitis C if we are to reduce disease burden and achieve hepatitis C elimination.

MedicineToday 2019; 20(11 Suppl): 4-9
First published: MEDICINE TODAY 2019; 20(6): 34-40
Updated November 2019

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New curative treatments for hepatitis C, known as direct-acting antivirals (DAAs), have revolutionised the management of people living with hepatitis C virus (HCV) infection. The simplicity and tolerability of DAAs means it is now easy to cure hepatitis C in most patients, making possible the elimination of hepatitis C in Australia. However, major challenges remain in finding people with hepatitis C who have not been diagnosed, linking people who have been previously diagnosed into care, and supporting patients to complete treatment. GPs have a crucial role in identifying and treating their patients with hepatitis C to help achieve the goal of eliminating hepatitis C in Australia by 2030.

This article is the first in a series about eliminating hepatitis C in Australia. The series will guide GPs through testing, treating and curing hepatitis C in primary care. This article focuses on who to test and how to test.

Hepatitis C virus infection

HCV is a bloodborne virus that can cause liver inflammation and liver scarring and puts people at risk of cirrhosis, liver failure and hepatocellular carcinoma (HCC). There are six main genotypes of HCV; the most common in Australia are genotype 1 and genotype 3.[1]

The natural history of HCV infection is summarised in Figure 1.[2] Following acute HCV infection, 15 to 25% of people will spontaneously clear the infection, with the other 75 to 85% progressing to chronic infection. About 20 to 30% of people with chronic HCV infection develop cirrhosis after 20 to 30 years of infection.[3] Hepatitis C is the most common cause of HCC in

KEY POINTS

- Direct-acting antivirals (DAAs) can cure over 95% of people with hepatitis C with only eight or 12 weeks of treatment.
- Curing patients of hepatitis C not only reduces disease burden for the individuals but can contribute to the elimination of hepatitis C in Australia.
- GPs, nurse practitioners and specialists can all prescribe DAA therapy.
- Of the estimated 165,000 people in Australia with chronic hepatitis C, about 20% are undiagnosed, and among those diagnosed more than half have not been treated.
- GPs have a crucial role in identifying their patients living with hepatitis C through sensitively raising the topic of HCV infection and offering testing and treatment.

Australia. HCC is the fifth most common cause of cancer death among males and the eighth most common cause of cancer death among females in Australia.[4] Incidence rates of HCC have increased more than those of any other cancer except thyroid cancer in Australia.[4]

What are the signs and symptoms of chronic hepatitis C?

Chronic HCV infection is usually asymptomatic. If symptoms are present, they are usually nonspecific, such as tiredness and lethargy. Serious symptoms occur when advanced liver disease develops, including confusion, jaundice, ascites, peripheral oedema, easy bruising and bleeding, haematemesis and muscle wasting.

Investigation results such as raised alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels can indicate liver inflammation and warrant further investigation, including testing for viral hepatitis.

What are the benefits of cure?

Curing hepatitis C reduces the risk of cirrhosis and HCC. During 2016-17, there was an estimated 20% decline in deaths from hepatitis C-related liver failure and HCC in Australia due to the rapid increase in number of people cured of HCV infection.[5]

Recent evidence suggests that people who achieve a sustained virological response or hepatitis C cure (defined as no detectable HCV RNA on a blood test 12 weeks after treatment completion) report improved quality of life. This includes physical health benefits, notably less fatigue, and an improved sense of psychological wellbeing related to less uncertainty about future health and no longer fearing infecting others.[6]

Australia's progress towards eliminating hepatitis C is shown in Box 1.[7-10]

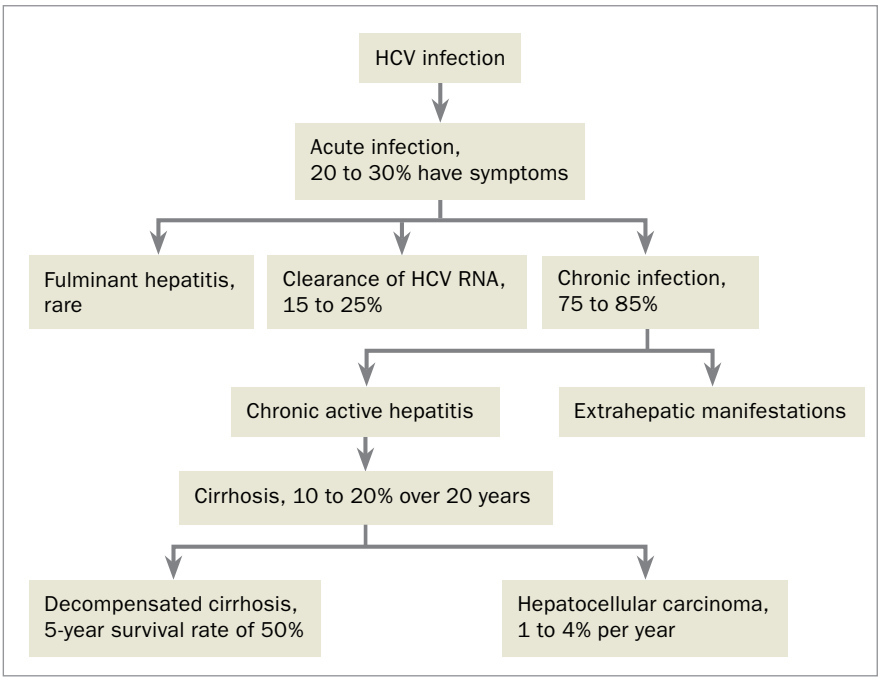


Figure 1. Natural history of hepatitis C virus (HCV) infection.
Adapted from Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006; 3: 47-52.[2]

1. AUSTRALIA'S PROGRESS TOWARDS ELIMINATING HEPATITIS C[7-10]

PBS listing of DAAs

In Australia, the new direct-acting antivirals (DAAs) were listed on the PBS on 1 March 2016, enabling universal access to highly effective treatments for everyone living with hepatitis C. This means that everyone with hepatitis C (including those in prison) can be treated. There are no PBS restrictions on stage of liver disease, alcohol or drug use or number of times a person can be treated. GPs, nurse practitioners and specialists can all prescribe DAAs.

WHO targets

The WHO has set targets for the elimination of hepatitis C as a public health threat by 2030, where we need to:

- treat more than 80% of people living with hepatitis C
- reduce hepatitis C-related deaths by 65%
- reduce new infections by 80%.[7]

Australia is one of 12 countries leading the world in reaching these targets because we have unrestricted access to DAAs, and hepatitis C treatments can be prescribed by a range of healthcare practitioners including specialists, GPs and nurse practitioners.[8]

Treatment uptake in Australia

However, more efforts are needed. Annual treatment numbers have been declining, from 35,659 in 2016 to 9598 in the first half of 2018. This decline in the number of people receiving treatment is jeopardising our chances to eliminate a chronic disease.[9]

Uptake of treatment is also not evenly distributed across Australia.[9] In more than half of the geographical areas across Australia, fewer than 8% of people living with hepatitis C have been treated; in particular, areas of socioeconomic disadvantage and areas where a higher proportion of the population were born overseas have low rates of treatment.[10] GPs have a major role to play in these areas as they are best placed to increase access to testing and treatment for all people living with hepatitis C.

How many people are living with hepatitis C?

Globally, an estimated 71.1 million people are living with chronic hepatitis C.[11] More than 70,000 people with hepatitis C in Australia have been treated and cured since DAAs became available in this country.[12] However, over 165,000 people in Australia are still living with hepatitis C (projections based on a published model and updates MBS and PBS data).[9]

The hepatitis C cascade of care describes the recommended pathway through clinical care for people at risk of hepatitis C. Numbers of people at each stage of the cascade of care in Australia in 2017 are shown in Figure 2.[13] An estimated 80% of people living with hepatitis C had a positive HCV antibody result (145,838), but only 47% of those people (68,544) had a positive HCV RNA PCR result confirming chronic HCV infection (not shown). Of these, 31% (21,530) received hepatitis C DAA treatment in 2017, with 95% achieving cure.[13]

It is worth noting that although an estimated 80% of people infected with hepatitis C in Australia have been diagnosed HCV antibody-positive, this refers to 'lifetime diagnosed'. Many people with chronic hepatitis C are not currently linked to health services for their hepatitis C and are missing out on treatment and cure. This is a key driver of the drop-off in the cascade from diagnosis to treatment. GPs can help reverse this drop-off through identifying patients who have been previously diagnosed with hepatitis C and supporting them into treatment.

Who should be tested for hepatitis C?

HCV is spread through blood to blood contact, where the blood of one person enters the bloodstream of another. Key risk factors and populations to consider for HCV testing in Australia are shown in Box 2.[3] Sometimes these risk factors may be difficult to identify during busy GP consultations, and they may have occurred in the distant past for many patients.

People who have ever injected drugs (recently or at some time in their life) are at risk of having hepatitis C because of the risk of acquiring HCV through sharing injecting equipment. With an estimated incidence of 5.4 per 100 person years among people who inject drugs, it is particularly important to test and treat people who currently inject drugs to reduce onward transmission of hepatitis C and prevent reinfections.[13]

In 2017, a total of 10,537 hepatitis C notifications were made in Australia.[13] Of the notified patients, 11% were Aboriginal or Torres Strait Islander people, 69% were male and more than half were aged 40 years and over. When classified by age, 11% of notified patients were under 25 years, 12% were between 25 and 29 years, 26% were between 30 and 39 years and 51% were 40 years and over.

The National HCV Testing Policy provides detailed information on who to test (http://testingportal.ashm.org.au/hcv). Apart from identifying risk factors for infection, an incidental finding suggestive of advanced liver disease or abnormal liver function test results warrant further investigation, including testing for viral hepatitis. GPs working in high-prevalence practices, such as in homeless health or opioid substitution therapy, might consider offering testing to all patients.

Tips on starting the conversation about testing

GPs may find it challenging to ask patients about current or past risk practices related to hepatitis C. Most doctors take a social history from new patients, and this is an opportunity to enquire sensitively about risk factors for hepatitis C, such as current or past drug use, along with recording demographic variables such as country of birth and sexual behaviour. This

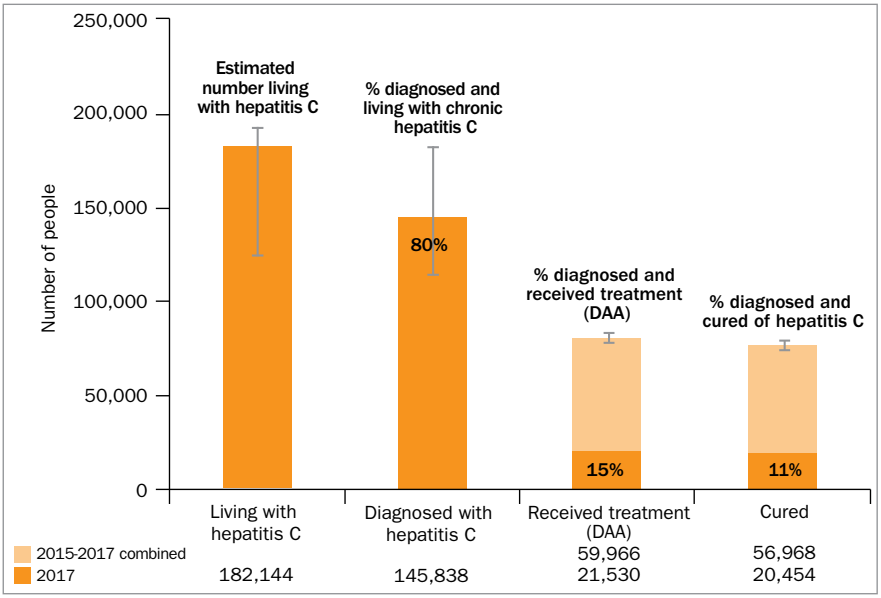


Figure 2. Estimated numbers of people at each stage of the hepatitis C care cascade in Australia, 2017.*

* For 'Received treatment (DAA)' and 'Cured', the top of the bar represents the cumulative number for the years 2015-2017 and the dark bar represents the cumulative number in the direct-acting antiviral (DAA) era (2016-2017).

Reproduced with permission from Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2018. Sydney: Kirby Institute, UNSW Sydney; 2018.[13]

information is also crucial for establishing whether there is a need to test for other bloodborne viruses, such as hepatitis B virus and HIV, which can all be undertaken as part of a 'new patient screen'.

Existing patients also need to be tested for hepatitis C. There are many opportunities for testing as part of general health checks, sexual health screens, pre-travel check-ups and antenatal screening and as part of health promotion campaigns.

Starting a conversation with a patient about hepatitis C is sometimes difficult, as discussing past or current drug use can be uncomfortable for both the patient and the GP. Patients may be unlikely to disclose a history of injecting drug use, even to GPs with whom they have a good relationship.

Having a focus on 'liver health' or 'new hepatitis C treatments' in the clinic as part of a targeted health promotion campaign can be a strategy to initiate a conversation about hepatitis C and to introduce testing to people who might be at risk. For example, a GP could explain 'Now that we have new effective treatments for hepatitis C that are available on the PBS, we want to make sure we offer this treatment to all our patients who are eligible. Would you be interested in knowing about the ways people get hepatitis C and seeing if you think you should get tested?'

Most people living with hepatitis C will have been previously diagnosed. This includes:

- individuals who are fully diagnosed or partly diagnosed (HCV antibody test but no HCV RNA PCR test)
- people who have previously been treated with older medications with treatment failure or who have been reinfected.

This group also includes people who have not previously been offered treatment, those who declined treatment and those who are not engaged with regular care. Many people living with hepatitis C have experienced stigma and discrimination related to their HCV infection or history of drug use. They may have had negative experiences when accessing health care in the past or have limited contact with the healthcare system. This is an important group to engage and to support into treatment.

Trying to engage this group into treatment can be difficult. Offering testing in the context of a discussion about the new treatments may be a good way to re-engage this group.

When discussing the new treatment options, GPs should cover the following:

- new treatments cure more than 95% of people with hepatitis C who complete the prescribed treatment course
- treatment lasts only eight or 12 weeks
- all treatments are oral (no injections)
- side effects, if any, are mild, such as fatigue, nausea and headaches; these generally subside after the first four weeks.

GPs can identify patients with hepatitis

2. POPULATIONS TO CONSIDER FOR HEPATITIS C VIRUS (HCV) TESTING[3]*

- 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
- 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 infected with HIV or hepatitis B virus
- 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)

* Testing is also recommended for all patients receiving opioid substitution therapy.

3. POINTS TO COVER WITH PATIENTS BEFORE A HEPATITIS C TEST

- Ask about any previous testing
- Provide information on testing, the meaning of different results, treatment and prevention, including the availability of curative treatments
- Allow the patient to be in control of their disclosure of risk
- Discuss what the patient thinks the result will be and whether they have someone to talk to if it is positive
- Explain the reason why a positive test result requires notification to state authorities (i.e. public health purposes)
- Ensure the patient gives informed consent to be tested and understands what the test will show and their options
- If the test result is positive, results should be provided in person along with an explanation of:
  - the natural history of modes of hepatitis C transmission
  - ongoing risk-reduction strategies
  - treatment availability and the process for starting treatment
  - support services such as Hepatitis Australia

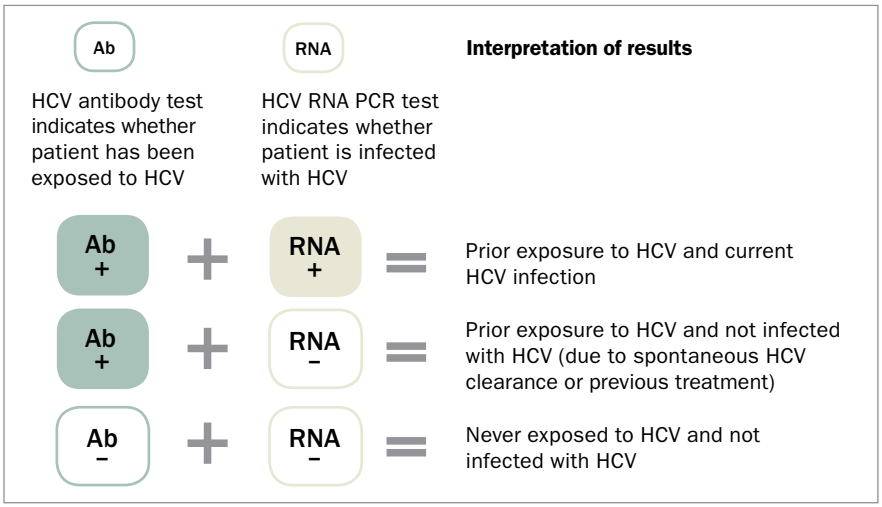


Figure 3. Interpretation of hepatitis C virus (HCV) test results.

C or requiring testing by searching their practice management system. Third-party tools such as POLAR or Pencat can help identify patients with potential risk factors and indicators (e.g. abnormal liver function test results) or known hepatitis C by conducting a practice audit. Training and support may be available through your local Primary Health Network.

Points to discuss with patients before testing are shown in Box 3. Informed consent to testing is required and it is important to ensure your patient understands the next steps. Positive results need to be conveyed in a sensitive manner.

What tests are needed?

Two tests are required to diagnose HCV infection:

- an antibody test to screen for HCV antibodies (indicating past exposure to HCV)
- a polymerase chain reaction (PCR) test for the presence of HCV RNA (indicating current HCV infection).

To reduce the number of appointments, blood draws and time to diagnosis, we recommend reflexive hepatitis C testing. Both the HCV antibody test and the PCR test for HCV RNA can be ordered on the same pathology order form by writing 'Please order hepatitis C PCR only if HCV antibody is detected' or 'HCV antibody +/- HCV RNA, if Ab positive'. The Medicare Benefits Schedule covers an HCV RNA PCR test only in the case of a positive HCV antibody result, and therefore it is recommended to add one of the above phrases in the clinical notes of the pathology request form to avoid an out-of-pocket cost for the patient.

A comprehensive bloodborne virus screen, including testing for hepatitis B and HIV infection, is also recommended for patients at risk of hepatitis C. This is because of the shared risk factors across all three infections and the availability of highly effective treatments for both hepatitis B and HIV infection.

Interpretation of HCV test results is shown in Figure 3. Documented chronic hepatitis C (duration of current HCV infection six months or longer) is a PBS eligibility criterion for accessing treatment. Test results in acute hepatitis C are discussed in Box 4.

If HCV RNA is not detected after a positive HCV antibody result then the patient

4. FEATURES OF ACUTE HEPATITIS C

- Acute hepatitis C, generally considered to represent the first six months after infection, is mostly asymptomatic. Some patients may have elevated alanine aminotransferase levels or acute illness with jaundice
- Hepatitis C virus (HCV) RNA is usually detectable by two to three weeks after infection, and almost always by four weeks, but HCV antibodies may not be detectable for up to four to 12 weeks
- Clinical monitoring is needed in the acute phase of hepatitis C, depending on the severity of symptoms or abnormal liver function results. Consider contacting a specialist if the patient is unwell
- About 15 to 25% of people with acute HCV infection (more if symptomatic) will go on to clear HCV without treatment
- Direct-acting antiviral treatment is not PBS funded in the acute phase of hepatitis C

has either spontaneously cleared HCV or been successfully treated in the past. HCV antibodies will most likely remain; however, HCV antibodies do not provide immunity to future infection, and there is currently no effective vaccine to prevent hepatitis C.

Hepatitis C is a notifiable condition (HCV antibody positive and/or RNA positive) by the laboratory or medical practitioner, depending on the jurisdiction. If results indicate current HCV infection, patients should consider recommending to their sexual or injecting partners to be tested also.

The diagnosis of hepatitis C can be distressing for patients. The support of a knowledgeable, caring GP is crucial. Patient support organisations such as Hepatitis Australia can be helpful in providing support by phone or in person. Useful resources on hepatitis C for GPs and patients are shown in the Box on the inside back cover.

Conclusion

An estimated 165,000 people are living with chronic HCV infection in Australia; however, the number of people being treated is declining. Renewed efforts are needed to reach everyone living with hepatitis C and ensure they are linked to testing and treatment. GPs are well placed to identify people at risk of hepatitis C and to offer testing and DAA therapy. Curing a patient with chronic hepatitis C is easier than ever before. It has the potential not only to benefit the individual by reducing their risk of liver disease and HCC and by preventing transmission but can also contribute to the elimination of hepatitis C in Australia. MT

Acknowledgement

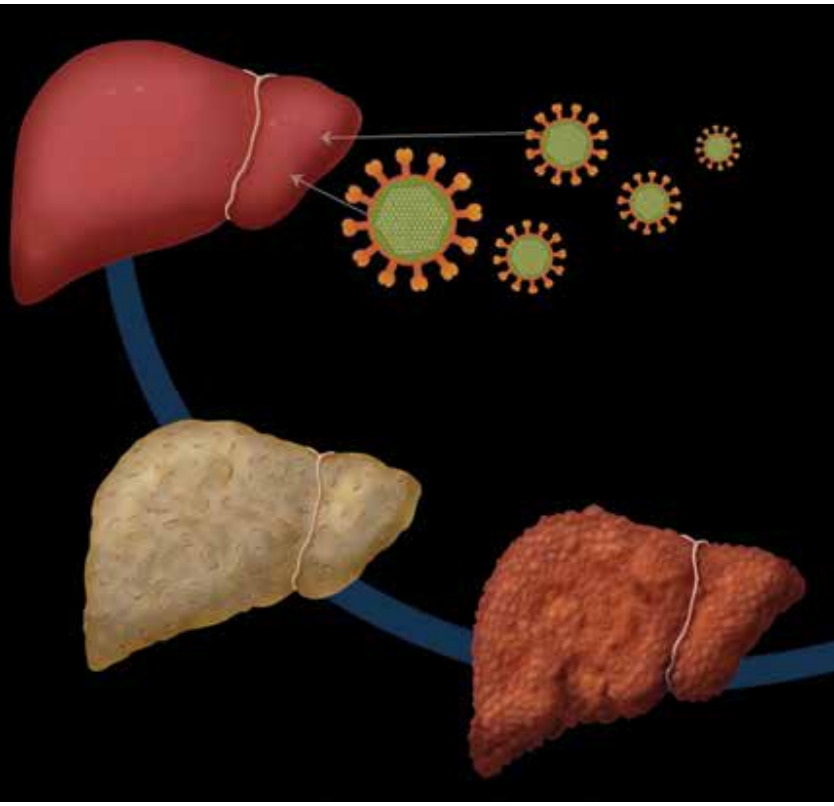
The authors gratefully acknowledge the contribution to this work of the Victorian Operational Infrastructure Support Program received by the Burnet Institute.

References

1. Bowden DS, Berzsenyi MD. Chronic hepatitis C virus infection: genotyping and its clinical role. Future Microbiol 2006; 1: 103-112.
2. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006; 3: 47-52.
3. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018). Melbourne: Gastroenterological Society of Australia; 2018. Available online at: www.gesa.org.au/resources/hepatitis-c-treatment (accessed June 2019).
4. Australian Institute of Health and Welfare (AIHW). Cancer in Australia: in brief 2019. Cancer series no. 122. Cat no. CAN 126. Canberra: AIHW; 2019. Available online at: www.aihw.gov.au/reports/cancer/cancer-in-australia-2019-in-brief/contents/table-of-contents (accessed June 2019).
5. Dore GJ. Population-level impact of DAA treatment programs [conference presentation]. Australasian Viral Hepatitis Elimination Conference 2018. Available online at: https://az659834.vo.msecnd.net/eventsairaueprod/production-ashm-public/6d397de113f142c48288ff37f0910484 (accessed June 2019).
6. Richmond JA, Ellard J, Wallace J, et al. Achieving a hepatitis C cure: a qualitative exploration of the experiences and meanings of achieving a hepatitis C cure using the direct acting antivirals in Australia. Hepatol Med Policy 2018; 3: 8.
7. WHO. Combating hepatitis B and C to reach elimination by 2030 (advocacy brief). Geneva: WHO; 2016. Available online at: www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en (accessed June 2019).
8. Murphy K. Just 12 countries worldwide on track to eliminate hepatitis C infection by 2030, with United Kingdom, Italy and Spain among those joining the list. 16 June 2018. Lafayette, CO: CDA Foundation; 2018. Available online at: https://cdafound.org/just-12-countries-worldwide-on-track-to-eliminate-hepatitis-c-infection-by-2030-with-united-kingdom-italy-and-spain-among-those-joining-the-list (accessed June 2019).
9. Scott N, Sacks-Davis R, Wade A, et al. Australia will need to increase testing to achieve hepatitis C elimination. Med J Aust 2019. In press.
10. Scott N, Hainsworth SW, Sacks-Davis R, et al. Heterogeneity in hepatitis C treatment prescribing and uptake in Australia: a geospatial analysis of a year of unrestricted treatment access. J Virus Erad 2018; 4: 108-114.
11. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017; 2: 161-176.
12. Kirby Institute. Monitoring hepatitis C treatment uptake in Australia. Issue 10. Sydney: Kirby Institute, UNSW Sydney; 2019. Available online at: https://kirby.unsw.edu.au/report/monitoring-hepatitis-c-treatment-uptake-australia-issue-10-june-2019 (accessed October 2019).
13. Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2018. Sydney: Kirby Institute, UNSW Sydney; 2018. Available online at: https://kirby.unsw.edu.au/report/hiv-viral-hepatitis-and-sexually-transmissible-infections-australia-annual-surveillance (accessed June 2019).

COMPETING INTERESTS: Ms Draper has an NHMRC Postgraduate Scholarship and receives investigator-initiated funding from AbbVie.
Dr Doyle receives funding for investigator-initiated research or consulting from AbbVie, Bristol-Myers Squibb, Gilead and MSD.
Dr Baker has received clinical trial funding and conference sponsorship and serves on the advisory board for AbbVie, Gilead and MSD.
Professor Stoové has an NHMRC Senior Research Fellowship and has received funding for investigator-initiated research from AbbVie, Bristol-Myers Squibb and Gilead.
Dr Pedrana receives funding for investigator-initiated research from AbbVie, Gilead and MSD.

PEER REVIEWED FEATURE 3 CPD POINTS



Eliminating hepatitis C

Part 2. Assessing your patient for antiviral treatment

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As soon as a patient is diagnosed with chronic hepatitis C, preparations can begin for treatment with direct-acting antivirals (DAAs). Most patients can receive DAA therapy in general practice. GPs are ideally placed to assess their patients in preparation for DAA therapy and to identify the minority who require specialist referral.

With the introduction of direct-acting antivirals (DAAs) in Australia in 2016, most people with chronic hepatitis C can be cured of this infection. GPs and suitably qualified nurse practitioners working in all areas of primary care have a key role in identifying, testing and treating their patients with hepatitis C.

The previous article in this series discussed how to identify your patients with hepatitis C. This article provides practical advice on assessing a patient after diagnosis in preparation for DAA therapy. This includes determining whether they can be safely treated in general practice or require specialist referral.

MedicineToday 2019; 20(11 Suppl): 10-15
First published: MEDICINE TODAY 2019; 20(7): 24-32
Updated November 2019

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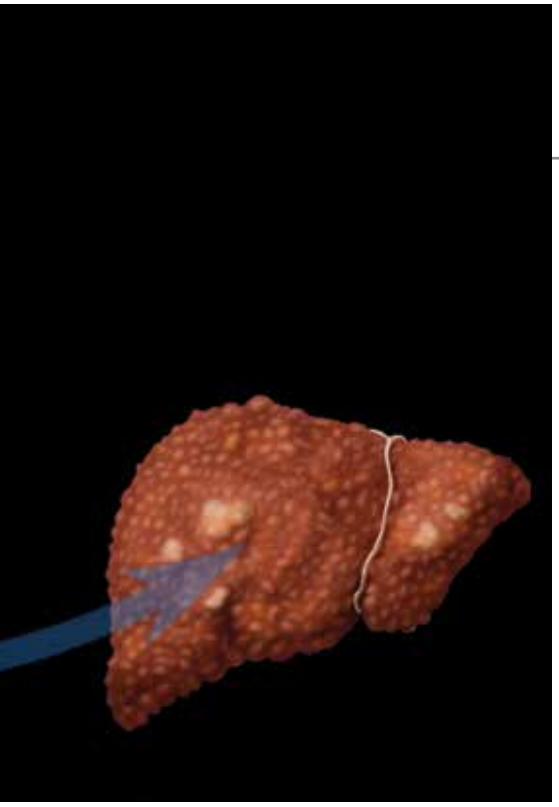
KEY POINTS

- **Most patients with hepatitis C can be treated with direct-acting antivirals (DAAs) in general practice.**
- **GPs are ideally placed to assess patients in preparation for DAA therapy.**
- **Pretreatment assessment includes a comprehensive medical and social history, medication review, physical examination and investigations.**
- **Key questions to determine the safety of DAA therapy in primary care concern the presence of cirrhosis, hepatitis C virus (HCV) genotype, hepatitis B or HIV coinfection, potential drug interactions, previous HCV treatment and renal function.**
- **Patients with cirrhosis, complex comorbidities or who have previously failed DAA therapy should be referred for specialist care.**



After diagnosis, what next?

All people diagnosed with hepatitis C should be considered for DAA therapy. DAAs have the potential to cure most people with hepatitis C and have few contraindications. As soon as a patient is diagnosed with hepatitis C, assessment for treatment can begin, in consultation with the patient.

Pretreatment assessment

Patient assessment in preparation for treatment includes:

- comprehensive medical and social histories
- medication review
- physical examination
- investigations, including a liver fibrosis assessment.

A full list of the required assessments and investigations appears in Box 1.[1]

Six key questions need to be answered to help determine whether the patient can be treated safely in primary care or needs to be referred to a specialist, and the most appropriate treatment option. These questions regard the individual, the hepatitis C virus (HCV) and the liver.

The key questions are:[2]

- Does the patient have cirrhosis?
- What is the genotype of the infecting HCV? (This requirement may be removed in the future owing to the availability of pangenotypic agents.)

1. PRETREATMENT ASSESSMENT OF PEOPLE WITH CHRONIC HEPATITIS C VIRUS (HCV) INFECTION[1]*

History

- Estimated duration of HCV infection
- Previous HCV treatment: date, regimen and response
- Cofactors for liver disease progression: alcohol intake, marijuana use, virological cofactors (HIV, hepatitis B virus), diabetes, obesity
- If ribavirin treatment is planned then note any history of ischaemic heart disease or cardiovascular risk factors
- Vaccinations against hepatitis A and B viruses
- 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 RNA PCR testing
- HCV genotype†
- Consider HCV RNA level (quantitative)†
- Hepatitis B virus serology (HBsAg, anti-HBc, anti-HBs§), HIV, hepatitis A serology

Investigations

- Full blood examination, liver function tests, urea and electrolytes, eGFR, INR
- Pregnancy test for women with childbearing potential
- Liver fibrosis assessment, for example
  - transient elastography (e.g. FibroScan), shear wave elastography or acoustic radiation force impulse (ARFI) imaging
  - serum biomarker (APRI, Hepascore, ELF test, FibroGENE¶)
- Liver ultrasound examination should be performed in people with cirrhosis to exclude hepatocellular carcinoma (within three months before starting DAAs)
- ECG should be performed if ribavirin therapy is planned and patient is over 50 years of age or has cardiac risk factors

Abbreviations: anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; APRI = aspartate aminotransferase to platelet ratio index; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; ELF = enhanced liver fibrosis; HBsAg = hepatitis B surface antigen; INR = international normalised ratio.

* Adapted from Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018). Melbourne: Gastroenterological Society of Australia; 2018 (www.asid.net.au/documents/item/1208).[1]

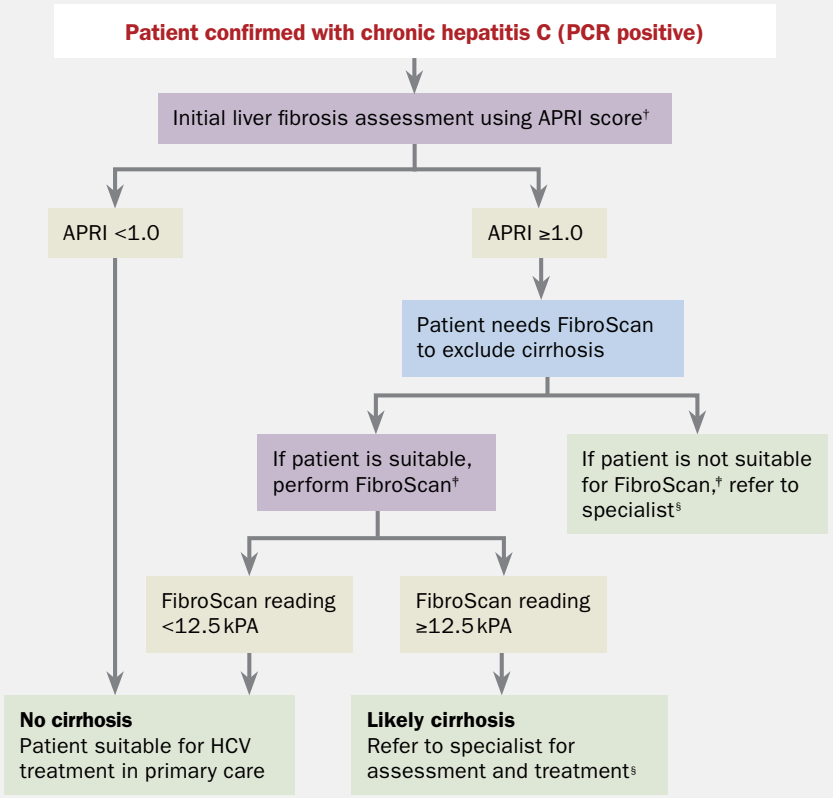
† HCV genotyping is a PBS criterion; it is important before prescribing elbasvir plus grazoprevir or sofosbuvir plus ledipasvir.

† HCV RNA level is important for determining eligibility for eight-week treatment duration with sofosbuvir plus ledipasvir.

§ All three tests for hepatitis B virus may be requested if the clinical notes indicate acute or chronic hepatitis.

¶ FibroGENE is a gene-based model for staging liver fibrosis; a FibroGENE calculator is available online (www.fibrogene.com/viral_hepatitis.html).

PATHWAYS TO LIVER FIBROSIS ASSESSMENT IN PRIMARY CARE FOR PATIENTS WITH HEPATITIS C[2]*



Abbreviations: APRI = aspartate aminotransferase to platelet ratio index; PCR = polymerase chain reaction.

* Adapted from Burnet Institute Eliminate Hepatitis C Partnership. Eliminate hepatitis C partnership practice support toolkit. Melbourne: Burnet Institute; 2018 (https://ecpartnership.org.au/toolkit).[2]

† An APRI calculator is available at: www.hepatitisc.uw.edu/page/clinical-calculators/apri

‡ FibroScan is not approved for use in people younger than 18 years, pregnant women, people with ascites and people with a pacemaker or implantable defibrillator. FibroScan and APRI results should be interpreted in conjunction with a full clinical picture by a trained clinician.

§ Appropriate specialists include gastroenterologists, hepatologists and infectious disease physicians, depending on local referral processes.

- Is the patient coinfected with HIV or hepatitis B virus (HBV)?
- Are there any potential drug interactions between the patient's current medication and the DAAs?
- Has the patient previously been treated for hepatitis C?
- What is the patient's renal function?

An important part of the pretreatment assessment is determining the presence of advanced liver disease. Patients with cirrhosis require specialist referral and may need changes to the standard treatment regimen.

It is also important to address potential psychosocial barriers to treatment during the assessment process. Current active injecting drug use is not a contraindication to hepatitis C treatment. However, some patients may need support to stabilise drug and alcohol use or to establish adherence support services before treatment.

Vaccinations

All susceptible patients with hepatitis C should be offered vaccinations against hepatitis A and B viruses. These vaccinations are subsidised for patients with liver disease and those who are at high risk of infection in some jurisdictions.

Liver fibrosis assessment

Liver fibrosis assessment is important to determine whether the patient has cirrhosis (Flowchart).[2] Although all patients are eligible for treatment, regardless of their cirrhosis status, the presence of cirrhosis determines the need for referral for specialist care and influences treatment regimen and duration in some cases, as well as follow up after treatment.[1] Most patients do not have advanced liver disease and can be treated easily in primary care.

The two most widely used noninvasive methods for assessing liver fibrosis are:

- the aspartate aminotransferase (AST) to platelet ratio index (APRI)
- transient elastography, including FibroScan.

Current active injecting drug use is not a contraindication to hepatitis C treatment

AST to platelet ratio index

The APRI has been developed as a simple serum biomarker for assessing fibrosis using results from a full blood count and liver function test. The APRI is calculated from the AST level and platelet count. APRI calculators are readily available online (e.g. www.hepatitisc.uw.edu/page/clinical-calculators/apri). Alternatively, the APRI can be calculated using the formula shown in the Figure. An APRI result of 1.0 or more indicates possible cirrhosis; the patient should be referred for further assessment including transient elastography. An APRI result less than 1.0 suggests that cirrhosis is unlikely and further evaluation for cirrhosis is usually not necessary unless clinically indicated; the patient can proceed on the treatment pathway.

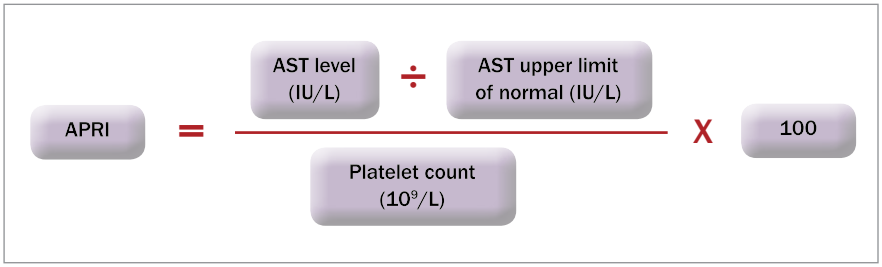


Figure. Formula for the aspartate aminotransferase (AST) to platelet ratio index (APRI).

Transient elastography

Transient elastography measures the stiffness of the liver, which is used to assess liver fibrosis. Threshold levels can determine the presence of cirrhosis. FibroScan is the most extensively validated and widely available method of transient elastography. It uses a series of short, pulsed, low-frequency sound waves and is similar to an abdominal ultrasound examination in terms of patient experience. FibroScan takes a trained operator (usually a nurse or doctor) 10 to 15 minutes to perform. GPs can refer patients to a liver clinic for a FibroScan. In some areas, specialist hepatology nurses offer FibroScan clinics in the community.

A FibroScan reading of 12.5 kPa or higher indicates a high likelihood of cirrhosis.[3] The patient requires referral to a specialist for management and regular monitoring for complications of cirrhosis, including hepatocellular carcinoma. Patients with a FibroScan result of less than 12.5 kPa are generally suitable for DAA therapy in primary care.

A FibroScan reading of 12.5 kPa or higher indicates a high likelihood of cirrhosis. The patient requires referral to a specialist

Alternative methods for evaluating liver stiffness are offered by some radiology services as an add-on to a liver ultrasound examination. They include shear wave elastography and acoustic radiation force impulse (ARFI) imaging. These methods are convenient but less well validated in identifying fibrosis in the presence of chronic hepatitis C.[1]

Risk factors and signs of cirrhosis

Other clinical information should be collected to determine a patient's risk of cirrhosis. This includes their clinical risk factors for cirrhosis and signs of advanced liver disease on physical examination (Box 2). A comprehensive patient assessment is needed because the APRI and FibroScan may not detect cirrhosis in all patients.

Drug interactions

DAAs can interact with many medications. Common examples include proton pump inhibitors, statins, ethinylestradiol and antiepileptic medications such as carbamazepine and phenytoin. The potential for interactions depends on the specific DAA. The University of Liverpool in the UK has developed a comprehensive tool for checking potential drug interactions (available online at: www.hep-druginteractions.org).

When to refer

Most patients with hepatitis C can receive DAA therapy safely in primary care (see the case study in Box 3 and the Table). Patients with cirrhosis, complex comorbidities or who have received previous failed DAA therapy should be referred for specialist care (Box 4).[1,2]

Appropriate specialists are those who have expertise in treating patients with viral hepatitis. This includes gastroenterologists, hepatologists, infectious diseases physicians and sexual health physicians, depending on the indication for the referral and local pathway (including telehealth or other videoconferencing consultations for GPs and patients in rural or remote areas who have limited access to specialist care).

Psychosocial assessment

When determining patient readiness for DAA therapy, GPs must take account of comorbidities, lifestyle and social issues. Major psychiatric disorders such as schizophrenia or ongoing drug use (including injecting drug use) and alcohol use or being homeless can pose challenges to adherence for patients but are not contraindications to treatment. It is important to optimise the patient's health when they are considering treatment.

2. RISK FACTORS FOR CIRRHOSIS AND SIGNS OF ADVANCED LIVER DISEASE

Clinical risk factors for cirrhosis[1]

- Male sex
- Older age when infected
- More than 20 years of HCV infection
- Comorbidities including:
  - diabetes
  - metabolic syndrome
  - coinfection with hepatitis B virus or HIV
  - obesity
  - excessive alcohol consumption

Physical signs of advanced liver disease

- Leukonychia
- Spider naevi
- Palmar erythema
- Gynaecomastia
- Hepatic flap
- Foetor
- Splenomegaly or hepatomegaly
- Oedema
- Ascites
- Jaundice
- Encephalopathy

3. CASE STUDY: A NEW PATIENT WITH A HEPATITIS C RISK FACTOR

Michelle is a fit and active woman aged 49 years who recently transferred to your practice because her previous GP retired. In your initial consultation, you take a medical history, including Michelle's current medications. She has asthma and mild gastric reflux. Her current medications include budesonide/formoterol fumarate dihydrate 200/6 two inhalations twice daily, salbutamol as required and methadone 40 mg daily.

You start a conversation with Michelle about her methadone treatment. She reports that she injected heroin between the ages of 14 and 35 years. She commenced methadone treatment when she was 35 and has not injected drugs for the past 10 years. She has no current or past history of significant alcohol use. You ask if she has ever been tested for hepatitis C and she reports that a previous GP told her she had been exposed to the virus but she is unsure if she has a current infection. She has not previously received antiviral therapy.

You order a comprehensive set of pathology investigations. The results show that Michelle has current hepatitis C with elevated aspartate aminotransferase (AST) and alanine aminotransferase levels (Table).

You calculate Michelle's AST to platelet ratio index (APRI) score using her AST and platelet levels:

$$APRI = [(53/40)/255] \times 100 = 0.52.$$

An APRI of 0.52 indicates a low likelihood of cirrhosis. Michelle has evidence of past cleared hepatitis B virus (HBV) infection but is not currently coinfected with HBV or HIV. She has normal renal function and has not been previously treated for hepatitis C. You decide that it is appropriate for Michelle to receive antiviral treatment in primary care.

Treatment and monitoring will be covered in the next article in this series.

TABLE. MICHELLE'S TEST RESULTS

Test	Result (reference range)
AST (U/L)	53 (<40)
ALT (U/L)	60 (<40)
Bilirubin (mcmol/L)	20 (4 to 20)
Platelets (x 10^9 cells/L)	255 (150 to 400)
eGFR (mL/min/1.7 m^2)	97 (>90)
HCV RNA	Viral load 3,100,000 IU/mL, genotype 3
Hepatitis B serology	Anti-HBs and anti-HBc positive, HBsAg negative
HIV	Negative
Hepatitis A total antibody	Negative
Pregnancy test	Negative
Full blood count, urea and electrolytes, INR, fasting glucose level, body mass index	Within reference range

Abbreviations: ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; INR = international normalised ratio.

4. PATIENT CIRCUMSTANCES THAT REQUIRE REFERRAL TO A SPECIALIST[2]

Liver related

- Advanced fibrosis or cirrhosis (FibroScan liver stiffness score ≥12.5 kPa)
- Persistently abnormal liver function test results after treatment

Coinfections and comorbidities

- HCV-HIV coinfection
- HCV-HBV coinfection
- Complex comorbidities
- Renal impairment (eGFR less than 50 mL/min/1.73 m^2)

Treatment related

- Failed first-line DAA therapy
- Complex drug-drug interactions
- Experienced major adverse events during treatment

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

5. RESOURCES ON HEPATITIS C MANAGEMENT FOR HEALTHCARE PROVIDERS AND PATIENTS

Gastroenterological Society of Australia (GESA)
Hepatitis C treatment resources for medical practitioners (www.gesa.org.au/resources/hepatitis-c-treatment/):

- **Consensus statement:** *Australian recommendations for the management of hepatitis C virus infection* (September 2018)
- **Wallchart for GPs:** *Clinical guidance for treating hepatitis C virus infection: a summary* (also at: http://cart.gesa.org.au/membes/files/Resources/Hepatitis%20C/GP_algorithm_Sep_Oct_edit2018.pdf); this summarises the clinical guidance for treating hepatitis C, including a pre-treatment assessment form
- **Request form:** *Remote consultation request for initiation of hepatitis C treatment*
- **Video:** *A practical guide to prescribing the new hepatitis C antiviral drugs in general practice*

Hepatitis Australia
A range of hepatitis C resources and information (www.hepatitisaustralia.com/Pages/Category/hepatitis-c)

Eliminate Hepatitis C (EC) Partnership
Resources for primary care providers:

- **EC Practice Support Toolkit** (https://ecpartnership.org.au/toolkit): includes resources to promote hepatitis C testing, treatment and follow up developed specifically for GPs and other primary care providers
- **Other resources** (https://ecpartnership.org.au/resources)

Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)

- **Links to hepatitis C training, information and resources** (www.ashm.org.au/HCV)
- **REACH-C checklist** (www.reach-c.ashm.org.au)

This may include initiating opioid substitution therapy before starting treatment and referral to support services as required.

More intensive adherence support may need to be organised before treatment. This will be covered in more detail in the next article in the series.

Conclusion

The role of GPs in managing patients with hepatitis C and preparing them for DAA treatment is crucial to the hepatitis C elimination effort in Australia. Resources on hepatitis C management for healthcare providers and patients are shown in Box 5. If left untreated, people with hepatitis C will be at increased risk of developing cirrhosis and associated complications, including liver failure and hepatocellular carcinoma. Preparation for hepatitis C treatment involves a few straightforward steps. Most people diagnosed with hepatitis C can be assessed and treated in primary care, giving GPs an exciting opportunity to offer their patients a cure. MT

Acknowledgement

The authors gratefully acknowledge the contribution to this work of the Victorian Operational Infrastructure Support Program received by the Burnet Institute.

References

1. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018). Melbourne: Gastroenterological Society of Australia; 2018. Available online at: www.asid.net.au/documents/item/1208 (accessed July 2019).
2. Burnet Institute Eliminate Hepatitis C Partnership. Eliminate hepatitis C partnership practice support toolkit. Melbourne: Burnet Institute; 2018. Available online at: https://ecpartnership.org.au/toolkit (accessed July 2019).
3. Hepatitis C Virus Infection Consensus Statement Working Group. Clinical guidance for treating hepatitis C virus infection: a summary. (September 2018). Melbourne: Gastroenterological Society of Australia; 2018.

COMPETING INTERESTS: Ms Layton, Dr Richmond, Dr Oliver-Landry, Dr Howell: None.
Dr Baker has received clinical trial funding and conference sponsorship and serves on the advisory Board for AbbVie, Gilead and MSD.
Associate Professor Owen has received travel assistance from Abbvie, Gilead and ViiV Healthcare.
Associate Professor Matthews has received research grants from Gilead and AbbVie.
Dr Doyle receives funding for investigator-initiated research or consulting from AbbVie, Bristol-Myers Squibb, Gilead and MSD.

Eliminating hepatitis C

Part 3. Curing hepatitis C in general practice

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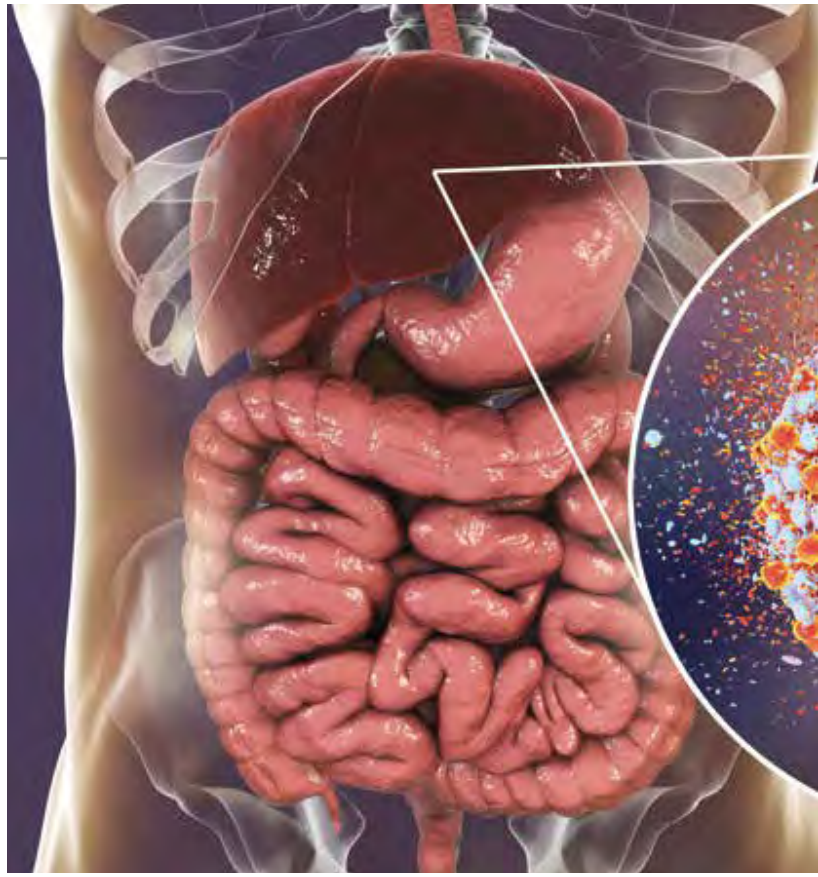
Most patients with hepatitis C are treated with pangenotypic direct-acting antivirals (DAAs) such as sofosbuvir/velpatasvir and glecaprevir/pibrentasvir. GPs experienced in the management of hepatitis C can prescribe DAAs independently. Others must consult with a specialist before prescribing; online resources can streamline this process. Important considerations before prescribing include barriers to adherence and drug interactions.

KEY POINTS

- Most people with hepatitis C can be treated with direct-acting antiviral (DAA) therapy in primary care.
- Pangenotypic DAA regimens that are well tolerated and effective against all hepatitis C genotypes include sofosbuvir/velpatasvir and glecaprevir/pibrentasvir.
- GPs who are experienced in the management of hepatitis C can prescribe DAAs independently, whereas others must consult with a specialist by phone, fax or email before DAA prescribing; online resources are available to facilitate this process.
- Considerations before prescribing DAAs include barriers to adherence and interactions between DAAs and prescribed medications and other drugs the patient takes.
- Clinical support, tools and resources to help GPs treat hepatitis C are available online.



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GPs can treat most people living with hepatitis C using direct-acting antivirals (DAAs). These medications are highly effective, with few side effects, and can cure more than 95% of individuals after a full course of DAA therapy. Curing an individual's infection can significantly reduce their risk of developing liver disease and liver cancer, and reduce onward transmission, moving Australia towards the WHO goal of hepatitis C elimination.

This is the third article in a series on eliminating hepatitis C. Previous articles discussed how to identify your patients with hepatitis C and how to assess them in preparation for DAA treatment.[1,2] This article focuses on initiating treatment in general practice.

MedicineToday 2019; 20(11 Suppl): 16-20
First published: MEDICINE TODAY 2019; 20(8): 20-26
Updated November 2019

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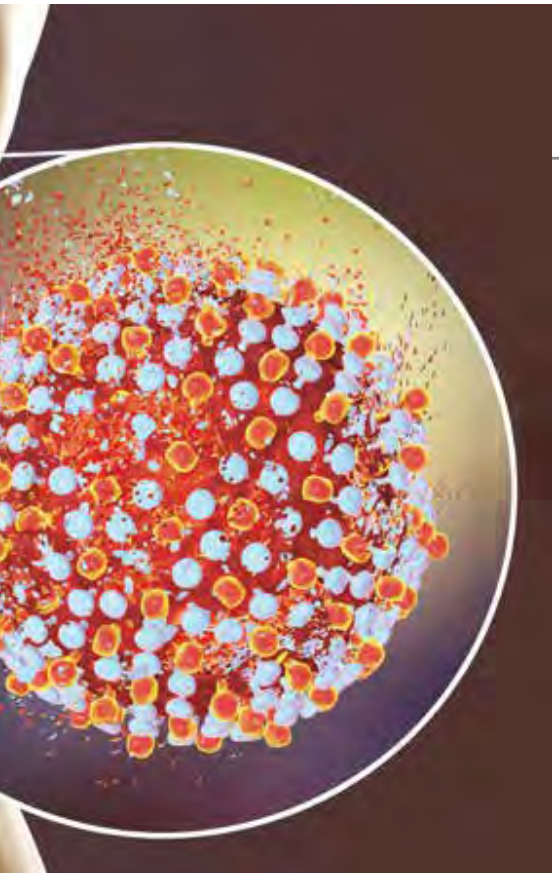

Why treat hepatitis C in general practice?

More than 70,000 people with hepatitis C in Australia have been treated and cured since DAAs became available in this country. However, an estimated 165,000 people in Australia are still living with hepatitis C (projections based on a published model and updated MBS and PBS data).[3] Most of these people are considered suitable for treatment in primary care.[4] To eliminate hepatitis C as a public health threat in Australia, it is crucial that GPs engage in hepatitis C management for all people living with hepatitis C, including people who inject drugs. Providing hepatitis C treatment in general practice promotes treatment uptake, especially among marginalised populations.[5]

What treatments are available?

Although multiple DAAs are approved in Australia, 85% of all patients are now treated with pangenotypic DAA regimens that are effective against all hepatitis C genotypes.[6] This article focuses on two pangenotypic DAA regimens:

- fixed-dose combination sofosbuvir/velpatasvir
- fixed-dose combination glecaprevir/pibrentasvir.

Both sofosbuvir/velpatasvir and glecaprevir/pibrentasvir have cure rates higher than 95%.[4] These two pangenotypic DAA treatment regimens are well tolerated. Side effects may include mild fatigue, headache or nausea.[4] The two regimens are compared in the Table.[4]

Who can treat chronic hepatitis C?

Any medical practitioner or authorised nurse practitioner can prescribe DAAs for treatment of chronic hepatitis C.[7] However, there are some provisos:

- Medical practitioners who are not experienced in the management of hepatitis C must consult with a specialist (gastroenterologist, hepatologist or infectious diseases physician) before prescribing DAAs.
- Medical practitioners and authorised nurse practitioners experienced in the management of hepatitis C can prescribe DAAs independently.
- Although most people with hepatitis C can be treated by nonspecialists, a selected minority need specialist treatment, as described below.

How do you consult with a specialist?

If GPs are not experienced in hepatitis management then they are required to consult with an experienced specialist. GPs can do this directly by phone, fax or email. This consultation process is one of the ways GPs can gain enough experience to prescribe independently.

Local HealthPathways have been created by Primary Health Networks to support GPs and authorised nurse practitioners to consult with specialists. The HealthPathways websites include key clinical information and details of local referral pathways, designed for use in primary care. GPs can access their local HealthPathways website via their Primary Health Network.

Some practitioners use the Gastroenterological Society of Australia (GESA) consultation request form (http://cart.gesa.org.au/membes/files/Resources/Hepatitis%20C/Remote_consultation_form_updated_Sep_2018.pdf), which can be sent to the local specialist team. As the recommended DAA regimens have changed over time, it is important to ensure prescribers use the most current version of the consultation form.

An online portal, Reach-C, can also be used to obtain a response from a specialist within 24 hours (https://reach-c.ashm.org.au).

TABLE. PANGENOTYPIC DAA REGIMENS FOR PEOPLE WITH HEPATITIS C WHO ARE TREATMENT-NAÏVE WITH NO CIRRHOSIS[4]

Formulation (daily dose)	Genotypes	Tablets per day	Treatment duration	Recommended relation with food	Renal impairment (eGFR <30 mL/min/1.73 m^2)
Glecaprevir/pibrentasvir (300 mg/120 mg)	All	Three tablets orally once daily	8 weeks	With food	No dose adjustment required
Sofosbuvir/velpatasvir (400 mg/100 mg)	All	One tablet orally once daily	12 weeks	With or without food	Not recommended

Abbreviation: eGFR = estimated glomerular filtration rate.
Adapted from Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018).[4]

1. ADVICE FOR PATIENTS TAKING SOFOSBUVIR/VELPATASVIR OR GLECAPREVIR/PIBRENTASVIR

- Take your tablets around the same time each day
- If you are prescribed sofosbuvir/velpatasvir and you miss a dose, take the missed dose as soon as possible unless it is almost time for the next dose. Do not take a double dose to make up for a missed dose[9]
- If you are prescribed glecaprevir/pibrentasvir and you miss a dose, if it is less than 18 hours late, take the missed dose with food as soon as possible. If it is more than 18 hours late, wait until the next dose. Do not take a double dose to make up for a missed dose[10]
- Treatment is usually very well tolerated. If side effects occur, they are usually mild and manageable, including fatigue, headache and nausea.
- You can pick up your medication one month at a time. The pharmacy may require 24 hours notice.
- If you miss a few days, talk to your doctor rather than stopping treatment

Important considerations before prescribing DAAs

Is the patient suitable for treatment in primary care?

The overwhelming majority of patients with hepatitis C can be treated in general practice. Patient populations who require referral for specialist management were discussed in the previous article in this series.[2] They include people with advanced fibrosis or cirrhosis, hepatitis B or HIV coinfection, complex comorbidities, renal impairment, failed first-line DAA treatment or complex drug interactions.[8]

DAA treatment is not recommended for women who are pregnant or breastfeeding.[9,10] Women should also be advised to wait four weeks after the end of DAA treatment before becoming pregnant.[4] If a woman who has started DAA treatment becomes aware that she is pregnant, it is recommended that treatment is stopped.

Are there any barriers to adherence?

To maximise the likelihood of achieving a cure, it is important that the patient adheres to the treatment course. It is crucial to consider psychosocial issues that may pose barriers to medication adherence and to develop a collaborative plan to support treatment adherence. Ongoing drug and alcohol use is not a contraindication to DAA treatment. People with hepatitis C who are suitable for treatment in primary care can continue to consume alcohol as per NHMRC guidelines (no more than two standard drinks on any day) while receiving DAA treatment.[11] It may be helpful to offer treatment such as opioid substitution therapy (OST) before DAA treatment.

The overwhelming majority of patients with hepatitis C can be treated in general practice

The Australasian Hepatology Association (AHA) consensus guidelines provide recommendations about adherence support for people with hepatitis C who are receiving DAA treatment.[12] The AHA guidelines describe 24 recommendations that encourage a patient-centred approach. Further information about supporting adherence can be found in the EC Partnership Practice Support Toolkit (https://ecpartnership.org.au/system/resource/80/file/EC_Partnership_Toolkit.pdf).[8]

In addition to adherence strategies, it can be helpful to provide advice about taking DAA medications (Box 1).[9,10]

Are there any drug interactions?

Interactions between DAAs and other drugs that the patient takes must be assessed before DAAs are prescribed.[4] Other drugs include prescribed medications, over-the-counter preparations, complementary and alternative medicines and recreational drugs.

Drug interactions can be easily checked using the free University of Liverpool HEP Drug Interactions website and app (www.hep-druginteractions.org).[13] Pangenotypic DAA regimens should never be dose adjusted; however, patient medications for other medical conditions may need to be adjusted in the presence of DAAs, as directed by the University of Liverpool website. The website offers detailed advice about options, including dose reduction, switching or stopping the interacting drug. DAA selection may also be influenced by potential drug interactions. The website includes some complementary medications and recreational drugs.

Problematic drug interactions are an indication for specialist referral or consultation.

The DAA prescription

PBS authority is required for hepatitis C treatment. Patients must be aged over 18 years.[7] The telephone number to obtain an authority is 1800 888 333. The PBS operator will ask for the patient's hepatitis C genotype and cirrhosis status. Authority will be given for the entire treatment course. Requirements for prescribing may change, so prescribers should ensure their knowledge is up to date.

A case study that illustrates treatment of a patient with hepatitis C in general practice is shown in Box 2. Useful resources for hepatitis C treatment are shown in Box 3.[2,13]

Monitoring during treatment

It is not necessary to order routine investigations during the course of DAA treatment.[3] However, many doctors see their patient after the first month to review treatment adherence, side effects and patient concerns. The current recommendations for investigations before and after DAA treatment are shown in Box 4.[14]

End of treatment – what next?

Hepatitis C cure is assessed 12 weeks after completion of DAA treatment. This involves a repeat HCV RNA PCR test and liver function tests. If the HCV RNA PCR result is negative then the patient is cured. It is not essential for the HCV PCR test to be performed exactly 12 weeks after

treatment – any PCR after this point is reliable at proving treatment has been successful; however, a test any earlier may occasionally be inaccurate as relapse can occur for up to 12 weeks after treatment. If liver function test results remain abnormal despite cure of hepatitis C, the patient should be evaluated for another cause of liver disease.

Nobody is immune to hepatitis C; the patient can be reinfected if re-exposed. People at risk of reinfection should be screened at least annually with an HCV RNA PCR test (as they will most likely remain positive for HCV antibodies indefinitely). They should also be provided with access to harm reduction, such as a needle and syringe program or opioid substitution therapy.[4] Any HCV RNA detected after a confirmed successful hepatitis treatment course (i.e. a negative HCV PCR result at least 12 weeks after treatment) is consistent with reinfection in a person with ongoing risks.

2. CASE STUDY: A PATIENT TREATED WITH DAAS IN GENERAL PRACTICE

Presentation

Michelle is a fit and active 49-year-old woman who recently transferred to your care because her previous GP retired. You reviewed Michelle a week ago and diagnosed chronic hepatitis C virus (HCV) infection (see part 2 in this series).[2] She has returned today to commence hepatitis C treatment.

Pretreatment assessment

During the previous consultation, you confirmed HCV genotype 3 and calculated Michelle's APRI score to be 0.52, indicating a low likelihood of cirrhosis. Michelle is not coinfected with either hepatitis B virus or HIV, has normal renal function and has not been previously treated for hepatitis C. Therefore, you decided it is appropriate for you to prescribe direct-acting antivirals (DAAs) and manage her treatment. Before prescribing DAA treatment, you also discussed with Michelle the importance of medication adherence and explore potential barriers.

Choosing a DAA regimen

On completion of the pretreatment assessment, you determine that Michelle is eligible for treatment with either sofosbuvir/velpatasvir for 12 weeks or glecaprevir/pibrentasvir for eight weeks. You assess potential drug interactions between each of these two regimens and Michelle's current medications using the University of Liverpool HEP Drug Interactions website (www.hep-druginteractions.org/). Her other medications are budesonide/formoterol fumarate dihydrate 200/6 two inhalations twice daily, salbutamol as required and methadone 40 mg daily. The website shows no potential drug interactions (Figure).[13]

As no drug interactions are identified, you discuss with Michelle which option she prefers: one tablet daily for 12 weeks or three tablets once daily for eight weeks. You also discuss the potential side effects and explain that there are no differences in efficacy or side effect profile between the two regimens. The only differences are pill burden, treatment duration and the nature of drug-drug interactions.

Prescribing a DAA

You follow your local HealthPathways and consult with a specialist via a consultation form. After receiving approval from your local specialist (the time needed for this process depends on the local service and may range from 24 hours to two weeks), you telephone the PBS to obtain PBS authority and arrange a DAA prescription.

As Michelle is premenopausal, you explain to her the importance of not becoming pregnant during treatment and the need for contraception. You advise her to ask anyone who prescribes any medication for her while she is taking the DAA to check for drug interactions and to contact your practice if there are any issues. You also warn her about the possibility of interactions with over-the-counter and complementary and alternative medicines and recreational drugs.

You remind Michelle to take her medication regularly and to touch base with you if any issues arise. You explain that she can fill the DAA prescription at any pharmacy, but they will require 24 hours' notice. You brainstorm with her some adherence strategies, including a visit part way through treatment.

Finally, you explain to Michelle that you will see her at least 12 weeks after she finishes DAA treatment to review her blood tests and confirm whether she has been cured as expected.

Figure. Drug interaction report for Michelle's DAA therapy options and other medications, from the University of Liverpool HEP drug interactions checker (www.hep-druginteractions.org/checker).[13]

3. RESOURCES FOR HEPATITIS C TREATMENT

- **Gastroenterological Society of Australia (GESA) hepatitis C treatment resources** (www.gesa.org.au/resources/hepatitis-c-treatment)
- **Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018)** (http://cart.gesa.org.au/membes/files/Resources/Hepatitis%20C/hepatitis_C_virus_infection_consensus_statement_Sep_2018.pdf)
- **Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine** (www.ashm.org.au/HCV/)
- **Hepatitis Australia** (www.hepatitisaustralia.com)
- **EC Partnership Toolkit** (https://ecpartnership.org.au/system/resource/80/file/EC_Partnership_Toolkit.pdf)
- **Remote consultation form** (http://cart.gesa.org.au/membes/files/Resources/Hepatitis%20C/Remote_consultation_form_updated_Sep_2018.pdf)
- **Reach-C online portal to obtain a specialist response** (https://reach-c.ashm.org.au)
- **HEP drug interactions checker** (www.hep-druginteractions.org)

Some individuals will require ongoing care following DAA treatment. In addition, all patients who have not been cured by first-line DAA treatment should be referred to a specialist. Post-treatment care will be discussed in the next article in this series.

Conclusion

GPs can treat and cure over 95% of people with chronic hepatitis C after a full course of DAA therapy. Treatment options can be tailored for the individual patient, and clinical support resources are available for GPs. Curing hepatitis C can be life-changing for patients and rewarding for GPs. Treating patients with hepatitis C in general practice is also crucial to achieving the WHO's hepatitis C elimination goals. MT

4. RECOMMENDED MONITORING FOR VIROLOGICAL RESPONSE FOR PANGENOTYPIC DAA REGIMENS[14]*

Week 0: Pre-treatment blood tests, including HCV RNA PCR (quantitative), liver function tests

Week 12 post-treatment (assessment for sustained virological response): HCV RNA PCR (qualitative), liver function tests

Abbreviation: HCV = hepatitis C virus.

* Certain populations may require more intensive monitoring (see Australian recommendations for the management of hepatitis C virus).[4]

Acknowledgement

The authors gratefully acknowledge the contribution to this work of the Victorian Operational Infrastructure Support Program received by the Burnet Institute.

References

1. Draper B, Layton C, Doyle J, et al. Eliminating hepatitis C: Part 1. Finding your patients with hepatitis C. Med Today 2019; 20(6): 34-40.
2. Layton C, Richmond J, Baker D, et al. Eliminating hepatitis C: Part 2. Assessing your patient for antiviral treatment. Med Today 2019; 20(7): 24-32.
3. Scott N, Sacks-Davis R, Wade A, et al. Australia will need to increase testing to achieve hepatitis C elimination. Med J Aust 2019. In press.
4. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018). Melbourne: Gastroenterological Society of Australia; 2018. Available online at: www.asid.net.au/documents/item/1208 (accessed August 2019).
5. Wade AJ, Doyle JS, Gane E, et al. Outcomes of treatment for hepatitis C in primary care compared to hospital-based care: a randomised controlled trial in people who inject drugs. Clin Infect Dis 2019 Jun 22. pii: ciz546. doi: 10.1093/cid/ciz546. [Epub ahead of print]
6. Kirby Institute. Monitoring hepatitis C treatment uptake in Australia. Issue 10 June 2019. Sydney: UNSW, Kirby Institute; 2019.
7. Pharmaceutical Benefits Scheme. General statement for drugs for the treatment of hepatitis C. Canberra: Australian Government Department of Health; 2018. Available online at: www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c (accessed August 2019).
8. Burnet Institute Eliminate Hepatitis C Partnership. Eliminate Hepatitis C Partnership Practice Support Toolkit. Melbourne: Burnet Institute; 2018.
9. Gilead Sciences. Australian product information – EPCLUSA (sofosbuvir/velpatasvir) v3.0 (21 June 2019). Melbourne: Gilead Sciences; 2019.
10. AbbVie. Australian product information – MAVIRET (glecaprevir/pibrentasvir) tablets. Version 3. 5 July 2019. Sydney: AbbVie; 2019.
11. NHMRC. Australian guidelines to reduce health risks from drinking alcohol. Canberra: NHMRC; 2009.
12. Richmond JA, Sheppard-Law S, Mason S, Warner SL. The Australasian Hepatology Association consensus guidelines for the provision of adherence support to patients with hepatitis C on direct acting antivirals. Patient Prefer Adherence 2016; 10: 2479-2489. Available online at: www.dovepress.com/articles. php?article_id=30472 (accessed August 2019).
13. University of Liverpool. HEP drug interactions. Interaction checker. Available online at: www.hep-druginteractions.org (accessed August 2019).
14. Gastroenterological Society of Australia (GESA). Clinical guidance for treating hepatitis C virus infection: a summary. GESA; 2018. Available online at: www.gesa.org.au/resources/hepatitis-c-treatment/ (accessed August 2019).

COMPETING INTERESTS: Dr Purcell, Ms Accadia, Dr Allard: None. Dr Wade has received funding for investigator-initiated research from AbbVie. Associate Professor Strasser has received honoraria for advisory board participation and speakers fees from Gilead, AbbVie, MSD, BMS, Norgine, Bayer, Ipsen, Eisai, Pfizer and Astellas.
Dr Read has received honoraria and travel expenses for speaking from Gilead and MSD, and institutional research funding from Gilead.
Dr Baker has received clinical trial funding and conference sponsorship and serves on the advisory board for AbbVie, Gilead and MSD.
Dr Pedrana receives funding for investigator-initiated research from AbbVie, Gilead and MSD.
Dr Doyle receives funding for investigator-initiated research or consulting from AbbVie, Bristol-Myers Squibb, Gilead and MSD.

PEER REVIEWED FEATURE

Eliminating hepatitis C

Part 4. Ongoing care after hepatitis C treatment

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Most patients who receive direct-acting antiviral treatment for hepatitis C are cured. The need for and nature of ongoing clinical care after treatment depends on whether cure has been achieved, the presence of cirrhosis or persistently abnormal liver function test results and ongoing risk of reinfection with hepatitis C virus.

KEY POINTS

- **Over 95% of patients are cured after a full course of DAA treatment.**
- **Patients with persistent liver function test abnormalities after DAA treatment need specialist referral for further investigation.**
- **Patients with cirrhosis need specialist referral and lifelong monitoring for complications such as hepatocellular carcinoma.**
- **Past infection does not result in immunity to hepatitis C, so patients should be counselled about the risk of reinfection and importance of harm reduction.**
- **Harm reduction is an effective approach to reduce hepatitis C risk, including access to clean needles, syringes and other injecting equipment, and opioid substitution therapy.**
- **Patients at risk of reinfection should be offered at least annual hepatitis C virus RNA PCR testing in the knowledge that they are eligible for retreatment if reinfected.**

In Australia, over 70,000 people living with hepatitis C have received direct-acting antiviral (DAA) treatment, and GPs are writing an increasing proportion of all DAA prescriptions.[1,2] Primary care is crucial to management of people after they have received DAA treatment for hepatitis C.

This is the fourth article in a series about treatment of patients with hepatitis C in general practice. Previous articles outlined how to identify patients with hepatitis C, their assessment and treatment with DAAs.[3-5] This article focuses on general practice care of patients after DAA treatment. This includes recommended care of those who have been cured of hepatitis C, the small proportion who are not cured, those with cirrhosis and those with ongoing risk factors for reinfection.

MedicineToday 2019; 20(11 Suppl): 21-25
First published: MEDICINE TODAY 2019; 20(9): 36-42
Updated November 2019

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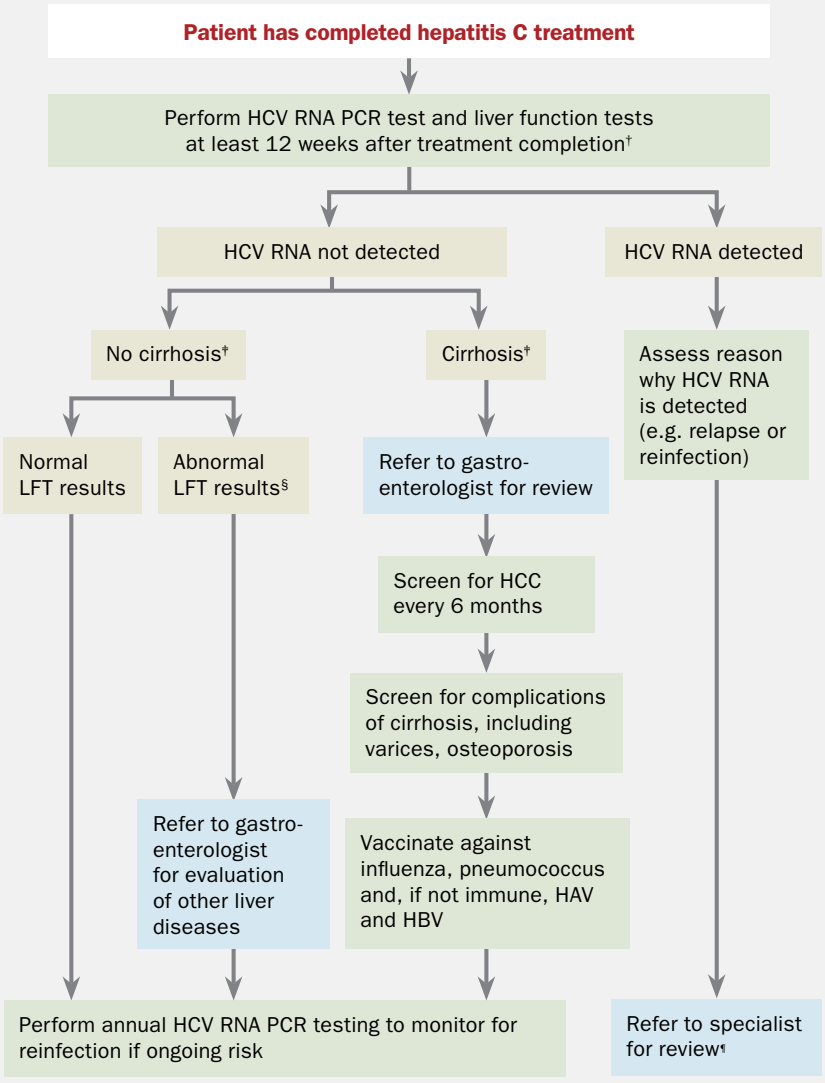
Determining treatment outcome

Over 95% of patients with chronic hepatitis C are cured after a full course of DAA treatment. Hepatitis C virus (HCV) RNA testing is required to determine treatment success or failure (or subsequent reinfection).

A patient is defined as cured of hepatitis C if HCV RNA is no longer detected by a PCR test on a blood sample taken at least 12 weeks after completing the DAA treatment course.[6] Cure is also referred to as a sustained virological response at 12 weeks (SVR12).

FOLLOW-UP CARE OF PATIENTS AFTER HEPATITIS C TREATMENT WITH DIRECT-ACTING ANTIVIRALS[8]*



Abbreviations: HAV = hepatitis A virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; LFT = liver function test; PCR = polymerase chain reaction.

* Adapted from Burnet Institute Eliminate Hepatitis C Partnership. Eliminate hepatitis C partnership practice support toolkit. Melbourne: Burnet Institute; 2018 (https://ecpartnership.org.au/toolkit).[8]
† HCV RNA PCR determines whether the patient is currently infected with HCV.
† Liver fibrosis assessment should be completed before commencing treatment to determine whether patient has cirrhosis.
§ Abnormal LFT results: alanine aminotransferase ≥30 U/L (men) or ≥19 U/L (women).
¶ Suitable specialists include gastroenterologists, hepatologists and infectious disease physicians. Patients will need to see a gastroenterologist for any liver-related follow up (persistent abnormal LFTs, HCC screening, oesophageal varices monitoring) and can see another specialist for relapse and reinfection assessment.

Advice for patients who are cured

After successful treatment, it is important to inform patients of the following:

- Antibodies against HCV will most likely remain detectable long term. These antibodies represent the body's immune response to the virus and reflect exposure, not active infection.
- Past infection does not result in immunity and the presence of HCV antibodies does not prevent reinfection. People who continue to engage in behaviours that put them at risk can be reinfected with HCV.

People who inject drugs should be reminded that practising harm reduction will help minimise the risk of reinfection (see below). Men who have sex with men should be reminded about safe sexual practices to minimise the risk of reinfection. It is also worth mentioning that HIV pre-exposure prophylaxis with tenofovir–emtricitabine does not protect against HCV infection.

For people who continue to be at risk of HCV reinfection, HCV RNA testing by PCR should be offered at least annually (note that the MBS funds one HCV RNA PCR test per 12-month period).[7] This is also an opportunity to discuss harm reduction measures. There is no indication for repeat hepatitis C antibody testing, as the result will most likely continue to be positive. It is important to let people know that they can be retreated if they are reinfected.

Clinical follow up

The recommended follow up for patients after hepatitis C DAA treatment is shown in the Flowchart.[8] The need for ongoing clinical follow up is determined by several factors:[6]

- whether hepatitis C has been cured
- the degree of liver fibrosis present before DAA treatment

- liver function test results 12 weeks after treatment is completed
- ongoing exposure to risk factors.

Follow up of a patient who is cured is described in Box 1.

Patients who are cured

Patients without cirrhosis and with normal liver function

Most people currently living with hepatitis C in Australia do not have cirrhosis.[9] No further clinical follow up of hepatitis C is needed for those without cirrhosis who:

- achieve a cure
- have normal liver function test results after treatment, and
- are not at risk of reinfection.

Other comorbidities and risk factors may contribute to the development of liver disease, such as excessive alcohol use and fatty liver disease/metabolic syndrome. These people should be encouraged to maintain a healthy lifestyle, including smoking cessation, safe alcohol consumption, maintaining a healthy weight, healthy diet and exercise. They should also be encouraged to avoid reinfection through harm reduction practices. Patients who have not received hepatitis A and hepatitis B vaccinations should be offered them.[10]

Patients without cirrhosis but with abnormal liver function results

Patients without cirrhosis who have abnormal liver function test results after treatment (alanine aminotransferase [ALT] ≥30 U/L [men] or ALT ≥19 U/L [women]) may have comorbid liver disease. Routine investigations for liver disease can be initiated by the GP. These patients should be referred to a gastroenterologist for further investigation and management.

Patients with cirrhosis

Patients who were diagnosed with cirrhosis before DAA treatment would usually have been referred to a specialist at that time. After DAA treatment, they will require ongoing management of their liver disease by a gastroenterologist and should be referred if not already receiving specialist care.

Patients who are not cured

About 5% of patients who complete a full treatment course do not achieve cure of hepatitis C with initial DAA therapy. Possible reasons include:

- viral resistance to the DAAs used
- presence of advanced liver disease.

Patients who are not cured should be referred to a gastroenterologist or infectious disease specialist who is experienced in the management of hepatitis C for further assessment and potential retreatment. Retreatment of a patient after DAA treatment failure may require a specific salvage regimen but generally has a good outcome.[11]

Hepatitis C virus reinfection

People with ongoing risk factors for infection are at risk of reinfection with HCV. The main risk groups in Australia are:

- people who inject drugs – most new HCV infections occur in this group[6]
- men who have sex with men, particularly those who are HIV-positive
- people in custodial settings
- people who have received a tattoo or body piercing in an unsterile setting.

Treatment of HCV reinfection

Patients with HCV reinfection should be retreated to prevent both progression of liver disease and transmission of HCV to others. Importantly, people with reinfection are eligible for PBS-subsidised DAA therapy. Those with clear reinfection – for example, HCV RNA detected after confirmed SVR12 or a different HCV genotype detected – can be treated as if they are treatment-naïve.[6]

Further, patients with HCV reinfection should be invited to bring in or refer their sexual or injecting partners (who may have been the reinfection source) for treatment. They should also be offered advice and support to reduce their infection risk.

Reducing risk of reinfection for people who inject drugs

People who inject drugs are at ongoing risk of HCV infection. Three simple hepatitis C harm reduction messages are:

1. CASE STUDY: FOLLOW UP AFTER DAA TREATMENT

Presentation

Michelle is a fit and active 49-year-old woman. About six months ago, you diagnosed her with chronic hepatitis C and prescribed a pangenotypic direct-acting antiviral (DAA) regimen (see part 3 in this series).[5] It is now 12 weeks since the scheduled completion of her DAA course and you send her a text message reminder to see you.

Michelle attends and reports that she completed the DAA treatment. She experienced mild headaches and nausea in the first few weeks of treatment but was able to cope. She forgot the tablets on only two days during the whole course.

Management

You order a hepatitis C virus (HCV) RNA PCR test (qualitative) and liver function tests. Michelle returns a week later to receive her results, which show:

- HCV RNA PCR – not detected
- liver function tests – normal range.

These results indicate that Michelle is cured of hepatitis C. Because she had no evidence of cirrhosis before DAA treatment and her liver function results are within the normal range after treatment, she does not require any follow up related to hepatitis C.

You take the opportunity to remind Michelle that being cured of hepatitis C does not mean she is immune to reinfection. She is no longer injecting drugs and is currently using methadone opioid substitution therapy. However, you remind her to have an HCV RNA PCR test if she is exposed to new risks in the future.

You also explain to Michelle that even though her hepatitis C is cured, her HCV antibody results will most likely remain positive. This does not mean she has a current HCV infection. Finally, you explain there are other causes of liver disease, such as excessive alcohol use and excess weight, and it is important to maintain a healthy lifestyle.

2. USEFUL RESOURCES FOR GPS AND PATIENTS AFTER HEPATITIS C TREATMENT

- Hepatitis C treatment resources for healthcare providers are available from Gastroenterological Society of Australia (GESA; www.gesa.org.au/resources/hepatitis-c-treatment). These include:
  - *Australian recommendations for the management of Hepatitis C virus infection: a consensus statement* September 2018
  - Wallchart for GPs: *Clinical guidance for treating hepatitis C virus infection: a summary*
- Resources for patients and healthcare providers are available from Hepatitis Australia, including downloadable information for patients (https://www.hepatitisaustralia.com)
- *Eliminate hepatitis C (EC) practice support toolkit:* developed for primary care practitioners, the toolkit contains resources to promote hepatitis C testing and treatment and to encourage people to remain engaged in high-quality hepatitis C care (https://ecpartnership.org.au/toolkit)
- *Safer using tips:* two resources from Harm Reduction Victoria provide information on safer use of drugs, with specific reference to reducing hepatitis C transmission (https://docs.wixstatic.com/ugd/ebb8bf_61a57e28de614edea74585d8951275fb.pdf, https://docs.wixstatic.com/ugd/ebb8bf_f26901243d6f4c4295d46010e8d90088.pdf)
- *Removing barriers: it's easy as 1, 2, 3* webpage from Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) includes steps to reduce stigma and discrimination in your practice (http://removingbarriers.ashm.org.au)

- Use sterile injecting equipment and do not share any injecting equipment
- Encourage injecting partners to be tested and treated
- Remind people they can be retreated if they are reinfected.

TABLE. RECOMMENDED SURVEILLANCE FOR CIRRHOSIS COMPLICATIONS[6,15]

Condition	Test	Frequency
Hepatocellular carcinoma	Liver ultrasound examination	Six-monthly
Oesophageal varices	Gastroscopy	Individualised by gastroenterologist according to Baveno VI criteria[16]
Osteoporosis	DXA Vitamin D level	Two-yearly Six-monthly
Other monitoring	Liver function tests, full blood count, urea, electrolytes, creatinine, INR/prothrombin time, others as required	Based on individual circumstances and gastroenterologist's opinion

Abbreviation: DXA = dual emission x-ray absorptiometry.

Harm reduction is an effective approach to reduce hepatitis C risk. It includes providing access to clean needles, syringes and other injecting equipment and opioid substitution therapy (OST). Informative harm reduction resources for people who inject drugs are readily available on the internet and provide easily accessible information on topics such as safe injecting practices and OST (Box 2). GPs can play an active role in harm reduction by:

- offering OST within their practice or discussing pathways to access
- discussing safer injecting behaviours.

GPs are also recommended to offer HCV RNA PCR testing at least annually to people who inject drugs to screen for HCV reinfection, as previously discussed.

People who inject drugs may have other comorbidities requiring long-term care. A trusting and lasting relationship with a GP is very important for this patient group.[12] People who inject drugs often report experiencing stigma and discrimination from healthcare providers, which can be a significant barrier to seeking health advice and treatment.[13] Resources for primary care staff to help raise awareness about stigma and discrimination are available from the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (Box 2).[14]

Hepatitis C-related cirrhosis

Liver cirrhosis is a significant complication that occurs in about two to three of every 10 people with chronic hepatitis C, generally after longstanding (20 to 30 years) infection.[6] People with cirrhosis remain at risk of complications of liver disease such as hepatocellular carcinoma (HCC), even after being cured of hepatitis C.

Follow up for patients with cirrhosis

Patients with cirrhosis require lifelong follow up (Table).[6,15,16] They should be referred to a gastroenterologist for specialist care. In particular, all patients with cirrhosis require HCC surveillance with six-monthly targeted liver ultrasound examinations. The GP should also provide hepatitis A and B, influenza and pneumococcal vaccinations to all patients with cirrhosis in accordance with Australian immunisation guidelines.[10]

Shared models of care with open lines of communication between the GP and specialist can facilitate safe and effective management of patients with cirrhosis. This includes timely adherence to screening programs, safe prescribing of medications when liver dysfunction is present and early identification of decompensating liver function. Shared models of care can be supported through initiation of chronic disease care plans, team care arrangements and case conferencing.

Rural and remote GPs

Patients in a rural or remote area may not always be able to access a gastroenterologist. In this situation, the GP may need to take greater responsibility for co-ordinating care and may organise screening and monitor the patient's liver function in collaboration with the specialist (Table).[6,15,16] Co-ordination of care can be facilitated through a good relationship with a specialist in the regional centre, use of telemedicine and case conferencing.

Conclusion

After hepatitis C treatment with DAAs, all patients need follow up by their GPs. Over 95% of patients are cured after a full course of DAA treatment and will not need further hepatitis C treatment (see the Case study in Box 1). A small proportion of patients will require further management, and GPs can play a valuable role in their ongoing care in partnership with specialists. Patients at risk of reinfection will also need support to reduce their risk as well as regular HCV RNA testing by PCR. MT

Acknowledgement

The authors gratefully acknowledge the contribution to this work of the Victorian Operational Infrastructure Support Program received by the Burnet Institute.

References

1. Kirby Institute. Monitoring hepatitis C treatment uptake in Australia. Issue 10, June 2019. Sydney: Kirby Institute, UNSW Sydney; 2019. Available online at: https://kirby.unsw.edu.au/report/monitoring-hepatitis-c-treatment-uptake-australia-issue-10-june-2019 (accessed September 2019).
2. Doyle JS, Scott N, Sacks Davis R, Pedrana AE, Thompson AJ, Hellard ME. Treatment access is only the first step to hepatitis C elimination: experience of universal anti viral treatment access in Australia. Aliment Pharmacol Ther 2019; 49: 1223-1229.
3. Draper B, Layton C, Doyle J, et al. Eliminating hepatitis C: Part 1. Finding your patients with hepatitis C. Med Today 2019; 20(6): 34-40.
4. Layton C, Richmond J, Baker D, et al. Eliminating hepatitis C: Part 2. Assessing your patient for antiviral treatment. Med Today 2019; 20(7): 24-32.
5. Purcell T, Wade A, Accadia L, et al. Eliminating hepatitis C: Part 3. Curing hepatitis C in general practice. Med Today 2019; 20(8): 20-26.
6. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement. Melbourne: Gastroenterological Society of Australia; 2018.
7. Department of Health. Hepatitis C MBS items table. Canberra: Department of Health; last updated August 2018. Available online at: www1.health.gov.au/internet/main/publishing.nsf/Content/path-comp-hep-table (accessed September 2019).
8. Burnet Institute Eliminate Hepatitis C Partnership. Eliminate hepatitis C partnership practice support toolkit. Melbourne: Burnet Institute; 2018. Available online at: https://ecpartnership.org.au/toolkit (accessed September 2019).
9. Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2018. Sydney: Kirby Institute; 2018. Available online at: https://kirby.unsw.edu.au/report/hiv-viral-hepatitis-and-sexually-transmissible-infections-australia-annual-surveillance (accessed September 2019).
10. Australian Technical Advisory Group on Immunisation (ATAGI). Australian immunisation handbook. Canberra: Australian Government Department of Health; 2018. Available online at: https://immunisationhandbook.health.gov.au (accessed September 2019).
11. Papaluca T, Sinclair M, Gow P, et al. Retreatment with elbasvir, grazoprevir, sofosbuvir ± ribavirin is effective for GT3 and GT1/4/6 HCV infection after relapse. Liver Int 2019 Jul 29. doi: 10.1111/liv.14201. [Epub ahead of print]
12. Cornford C, Close H. The physical health of people who inject drugs: complexities, challenges, and continuity. Br J Gen Pract 2016; 66: 286-287.
13. Australian Injecting and Illicit Drug Users League (AIVL). 'We live with it almost every day of our lives': an AIVL report into experiences of stigma and discrimination. Canberra: AIVL; 2015.
14. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Removing barriers; it's easy as 1, 2, 3. Available online at: http://removingbarriers.ashm.org.au/ (accessed September 2019).
15. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Decision making in HCV. Sydney: ASHM; 2019. Available online at: https://www.ashm.org.au/products/product/Decision-Making-in-HCV (accessed September 2019).
16. de Franchis R; Baveno VI Faculty. Expanding consensus in portal hypertension. Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015; 63: 743-752.

COMPETING INTERESTS: Ms Chan, Dr Gooey, Dr Greenwood-Smith, Dr Chaney, Dr Howell: None. Professor Hellard receives funding support from Gilead Sciences, AbbVie and Bristol-Myers Squibb for investigator-initiated research.
Dr Baker has received clinical trial funding and conference sponsorship and serves on the advisory board for AbbVie, Gilead and MSD.
Dr Pedrana receives funding for investigator-initiated research from AbbVie, Gilead and MSD.
Dr Doyle receives funding for investigator-initiated research or consulting from AbbVie, Bristol-Myers Squibb, Gilead and MSD.

Eliminating hepatitis C

Part 5. Practical steps in your practice

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For most people with chronic hepatitis C, treatment with direct-acting antivirals (DAAs) is simple and easily incorporated into primary care. GPs can help in the push to eliminate hepatitis C by 2030 through strategies to eliminate hepatitis C from their own practices. This includes finding their patients with hepatitis C, assessing, treating and following up after DAA therapy.

KEY POINTS

- GPs can help achieve the goal of eliminating hepatitis C in Australia by 2030 through 'microelimination' in their own practices.
- Since 2016, over 6000 Australian GPs have treated patients with direct-acting antiviral (DAA) therapy.
- For most people with chronic hepatitis C, treatment with DAA therapy is simple and easily incorporated into primary care.
- Patients can be tested for hepatitis C, assessed, treated and followed up for cure in four GP visits, with an optional fifth visit during treatment.
- Ongoing care for patients after DAA therapy includes care of comorbidities and strategies to prevent and detect reinfection in those with ongoing risk.

Australia aims to eliminate hepatitis C by 2030. The contribution of GPs is essential to achieving this goal, and Australian GPs are leading the world in treating their patients with hepatitis C in primary care. Since direct-acting antivirals (DAAs) became available in March 2016, over 6000 GPs have treated one or more people living with hepatitis C.[1] GPs are also treating an increasing proportion of patients.[2] At the same time, there have been steady improvements in assessment and therapy, which have made the treatment pathway even more straightforward.[3]

This is the final article in the series on eliminating hepatitis C. Previous articles have reviewed patient testing, assessment, treatment and follow up after DAA treatment.[4-7] This article summarises practical ways for GPs to eliminate hepatitis C in their individual practices.

Microelimination in your practice

A useful approach for GPs to help achieve the goal of eliminating hepatitis C is 'microelimination'. This is the concept that we as GPs can focus on pursuing hepatitis C elimination in our own

MedicineToday 2019; 20(11 Suppl): 26-32
First published: MEDICINE TODAY 2019; 20(9): 36-46
Updated November 2019

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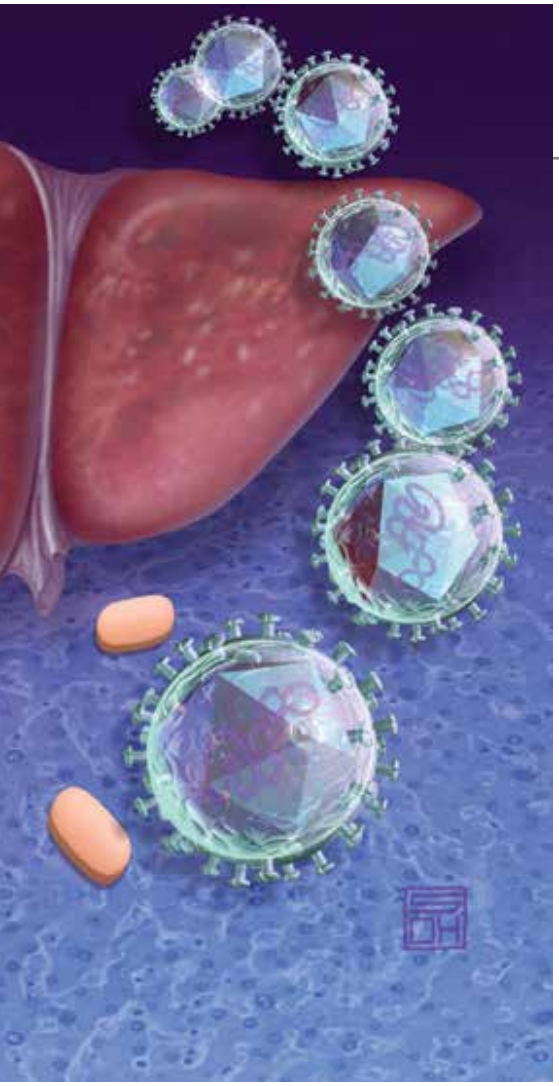

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practice or community.[8] This involves some planning to tailor an approach for our individual clinic. An example of a hepatitis C microelimination plan is shown in Box 1.[9]

Eliminating hepatitis C involves four steps: finding patients with hepatitis C, assessing, treating and following up. These steps can be achieved in four patient visits, with an optional fifth visit during treatment, as summarised in Box 2. Depending on patient circumstances, medical practitioners experienced in hepatitis C management may be able to achieve the steps in three visits.

Find patients with hepatitis C

There are two main groups of people with hepatitis C who need DAA treatment:[10]

- people who are undiagnosed (estimated to be about 20%)
- those who have been diagnosed previously with hepatitis C but remain untreated.

Both groups are important to reach.

1. EXAMPLE OF A HEPATITIS C MICROELIMINATION PLAN*[9]

General

- Develop a practice plan or policy to test for and treat hepatitis C
- Support doctors and practice nurses to attend a hepatitis C training course or to undertake online courses
- Make the waiting area 'hepatitis friendly' by providing information booklets in appropriate languages
- Consider possible barriers to patients, such as stigma and discrimination, and consider whether specific training is needed
- Consider choosing a lead doctor or nurse to co-ordinate the hepatitis C elimination plan

Finding hepatitis C

- Develop a testing and screening policy for your practice
- Promote your practice as offering hepatitis C treatment, for example on the practice website
- Set up a template for test batteries on practice computers, for example bloodborne virus testing: HCV antibody, HIV antibody, HBsAg, anti-HBc, anti-HBs
- Include reflexive testing for HCV RNA in the template; for example 'If HCV antibody +ve then perform HCV RNA PCR test'
- Implement a policy to ask all new patients if they would like bloodborne virus screening
- Offer bloodborne virus screening to existing patients after risk assessment
- Audit the existing patient database to review all patients with known hepatitis C to determine their treatment status
- Consider using a software tool such as POLAR or PenCat to conduct a practice audit. Training and support may be available from the local Primary Health Network

Assessment

- Review staff training, for example in fibrosis assessment with the APRI score
- Set up a template for test batteries for patients with hepatitis C as per the guidelines: HCV genotype, HBV (HBsAg, anti-HBc, anti-HBs), HIV antibody, HAV antibody, FBC, LFT, UEC, INR, beta-hCG
- Establish links to tertiary centres when further assessment is needed and not available in the community (e.g. FibroScan)

Treatment

- Access current treatment guidelines:
  - *Australian recommendations for the management of hepatitis C virus infection: a consensus statement*[3]
  - Local Health Pathways
- Establish links with a dispensing pharmacy regarding stocking direct-acting antivirals (DAAs)
- Prepare an HCV-specific GP management plan
- Review adherence support if needed

Follow up

- Review recall systems and establish practice policy about recording hepatitis C and cirrhosis
- Establish a system to review the GP management plan
- Support patients to reduce reinfection: discuss opioid substitution treatment and needle and syringe programs
- Set up recall systems for patients who are at risk of reinfection after SVR to retest annually with HCV RNA (PCR)
- Set up recall systems for patients with cirrhosis to undertake six-monthly liver ultrasound examinations to screen for hepatocellular carcinoma and ensure linkage to specialist care

Abbreviations: anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; APRI = aspartate aminotransferase to platelet ratio index; beta-hCG = beta human chorionic gonadotrophin; FBC = full blood count; HAV = hepatitis A virus; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LFT = liver function tests; UEC = urea, electrolytes, creatinine; SVR = sustained virological response.

* Based on the Burnet Institute Eliminate Hepatitis C Partnership. EC Partnership practice support toolkit (2018).[9]

Patients who are undiagnosed

Your approach to testing for hepatitis C will depend on your practice profile. One approach is to test everyone. Universal testing (or screening) is recommended as part of antenatal screening in Australia.[11] GPs working in high-prevalence practices, such as in homeless health or opioid

2. FOUR-VISIT PLAN FOR HEPATITIS C TREATMENT*

Visit 1. Find
- Obtain informed consent
- Undertake bloodborne virus screening, including reflexive HCV RNA PCR testing

Visit 2. Assess
- Discuss results; if positive for HCV RNA then proceed to pretreatment assessment
- Prepare a General Practice Management Plan (GPMP) and Team Care Arrangement (TCA) if indicated

Visit 3. Treat
- Assess APRI score, check for drug interactions, determine treatment, prescribe DAA, discuss adherence

Visit 3a. On treatment (optional)
- After one month of treatment, review side effects and adherence
- Provide pathology form for an SVR test (HCV RNA PCR, liver function tests) for next visit

Visit 4. Follow up
- Twelve weeks after treatment is completed, check HCV RNA PCR and liver function test results
- Review GPMP (TCA)

Abbreviations: APRI = aspartate aminotransferase to platelet ratio index; DAA = direct-acting antiviral; HCV = hepatitis C virus; SVR = sustained virological response.

* This plan could be completed in three to five visits depending on patient circumstances and medical practitioner experience.

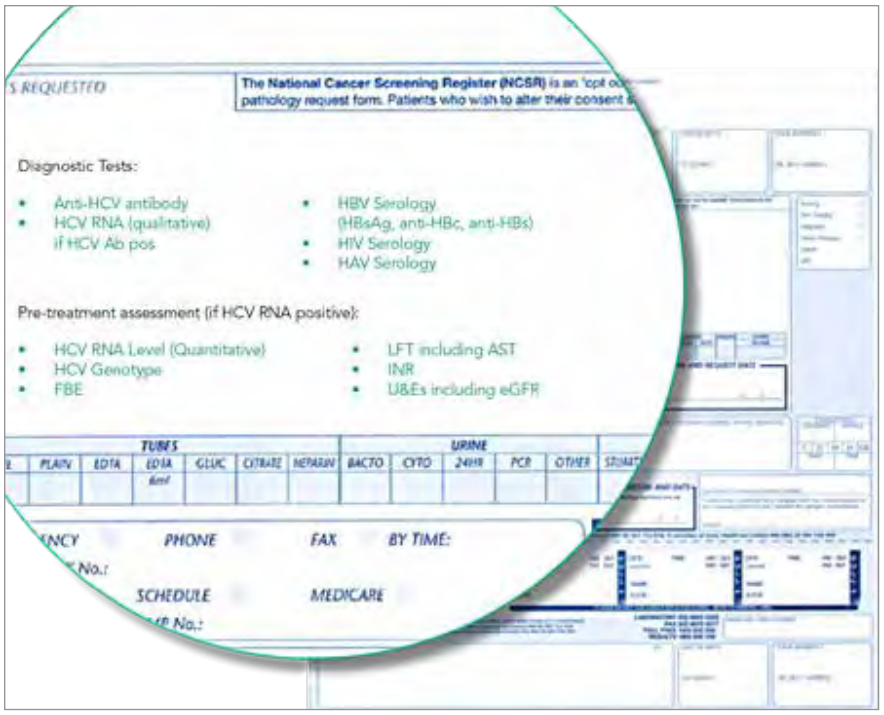


Figure 1. Bloodborne virus screen and pretreatment assessment for patients with hepatitis C.[9] Note that the quantitative hepatitis C virus RNA PCR test is optional. A pregnancy test should also be performed if indicated.

substitution therapy, might consider offering testing to all patients.

Otherwise, testing for hepatitis C is generally based on risk, as discussed in Part 1 of this series.[4] Sometimes, risk factors for hepatitis C may be difficult to identify during a busy GP consultation. In addition, for many patients, risk factors may have occurred in the distant past, such as a period of injecting drug use in their youth.

Most GPs take a social history from new patients, and this is an opportunity to enquire sensitively about risk factors such as current or past injecting drug use, along with recording demographic variables such as country of birth and sexual behaviour. This information is also crucial for establishing whether there is a need to test for bloodborne viruses such as hepatitis B virus and HIV along with hepatitis C, which can all be performed as part of 'a new patient screen'. Tests included in bloodborne virus screening are shown in Figure 1.[9]

Existing patients also need to be tested for hepatitis C. There are many opportunities for testing as part of general health checks, sexual health screens, pre-travel check-ups and antenatal screening.

Patients with hepatitis C can also be found by searching the practice management system. Third-party tools such as POLAR (https://outcomehealth.org.au/polar.aspx) and PenCat (https://help.pencs.com.au/dashboard.action) can help find patients with potential risk factors (e.g. abnormal liver function test results) for testing. Advice on using these tools can be obtained from your local Primary Health Network.

Patients who are diagnosed but not treated

Most people living with hepatitis C have been previously diagnosed. This group of patients includes those who have declined treatment and others who are not engaged in regular medical care. Many people living with hepatitis C belong to marginalised populations and may have limited contact with the health-care system. They are also an important group to engage and to support into treatment. A GP outreach project, the Kombi Clinic, that aims to engage and support people with hepatitis C, especially marginalised populations, into treatment is described in Box 3.

Assess patients

Assessment of patients was covered in Part 2 of this series.[5] The initial test to diagnose hepatitis C is a hepatitis C antibody test. If the result is positive then current infection needs to be confirmed with a qualitative hepatitis C virus (HCV)

RNA PCR test. If this result is positive then it is followed by HCV genotyping.

Other recommended blood tests after diagnosis of chronic hepatitis C are shown in Figure 1. They include tests:

- to detect hepatitis A, hepatitis B and HIV infection (if not already performed)
- to assess renal and liver function
- to exclude pregnancy.

The most complex part of pretreatment investigation is assessing for advanced liver disease. Patients with cirrhosis need specialist referral and may require changes to the treatment regimen. Most patients do not have cirrhosis and can be treated easily in general practice.

Steps in patient assessment for advanced liver disease are shown in the Flowchart.[9] A simple assessment that can be performed with the results of a full blood count and liver function testing is the aspartate aminotransferase to platelet ratio index (APRI). APRI calculators are available online (e.g. www.hepatitisc.uw.edu/page/clinical-calculators/apri). If the APRI score is less than 1.0 then cirrhosis is unlikely, and the patient can be treated without further investigation (see the case study in Box 4). If the APRI score is 1.0 or more then the patient needs further assessment.

The most useful next investigation is transient elastography, such as FibroScan. In many parts of Australia, this investigation can be performed by a specialist nurse at the GP clinic or local hospital (Figure 2).

Treat with DAAs

Hepatitis C treatment is straightforward, as described in Part 3 of this series.[6] DAA therapy for hepatitis C became available in March 2016 and has continued to evolve. Treatment options are based on the national guidelines, *Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018)*.[3]

The choice of DAA medication depends on:

- HCV genotype
- presence of cirrhosis
- presence of hepatitis B or HIV coinfection
- patient's renal function
- potential drug interactions and
- patient or provider preference.

Potential drug interactions can be checked using the University of Liverpool's online interaction checker (www.hep-druginteractions.org/checker).

There are two regimens that can be used for any HCV genotype (pangenotypic). Their characteristics are summarised in the Table.

Minimal monitoring is required during treatment. Many medical practitioners see the patient after four weeks to check on adherence and side effects, but pathology testing is no longer generally needed.

GPs who are not experienced in hepatitis C treatment need to have the treatment plan signed off by a specialist (gastroenterologist, hepatologist or infectious diseases physician). They can communicate with the specialist by telephone, email or fax. A proforma can be used, such as:

- *Remote consultation request for initiation of hepatitis C treatment* form from the Gastroenterological

3. THE KOMBI CLINIC: ENGAGING AND SUPPORTING PEOPLE WITH HEPATITIS C INTO TREATMENT

The Kombi Clinic is a mobile hepatitis C diagnostic and treatment clinic run by Brisbane GPs Matt Young and Joss O'Loan. They take the clinic, housed in a 1975 pine lime-coloured Kombi van, to drug rehabilitation centres, hostels, homeless shelters and the streets of South East Queensland. The clinic has a team of four: two GPs, a phlebotomist and a registered nurse who performs transient elastography scans (FibroScans).

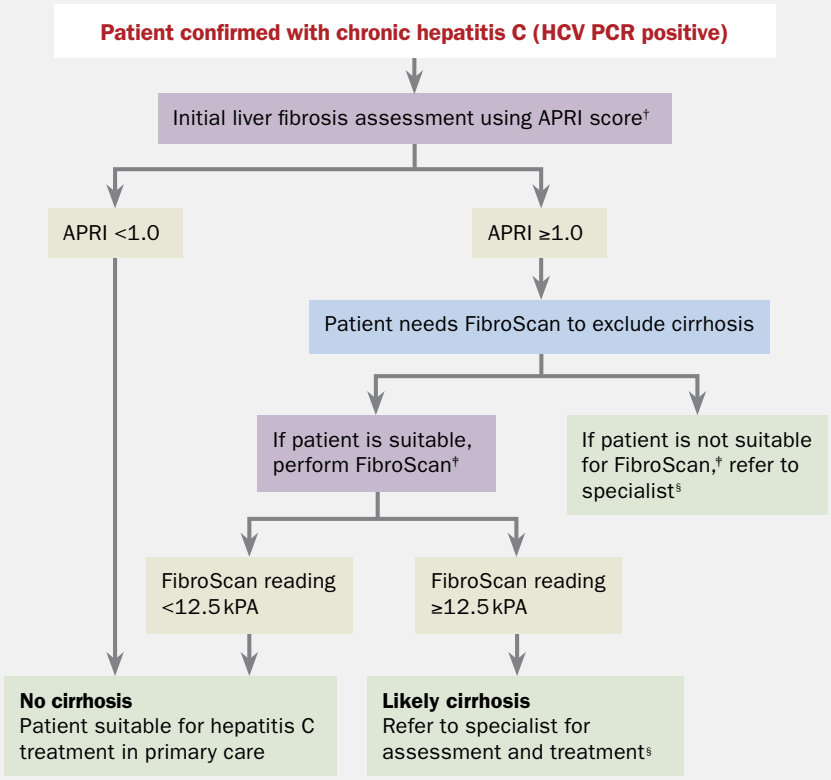
'Destigmatising hepatitis C and intravenous drug use by rocking up in a Kombi, wearing loud pink flamingo Hawaiian shirts and cranking out the rock 'n' roll is vital', said GP Matt Young. 'It helps engage people who have been marginalised by mainstream, more formally dressed medical professionals.'

The clinic also embeds medical students, registrars and other GPs to encourage their learning 'the ropes' of hepatitis C eradication.

Figure. Clinic staff Joss O'Loan, Mim O'Flynn, Matt Young and Christie Hoger outside the Kombi Clinic.

Photo courtesy of Andrea Macleod, City North News, Brisbane, Qld.

PATHWAYS TO LIVER FIBROSIS ASSESSMENT IN PRIMARY CARE FOR PATIENTS WITH HEPATITIS C[9*]



Abbreviations: APRI = aspartate aminotransferase to platelet ratio index; PCR = polymerase chain reaction.

* Adapted from Burnet Institute Eliminate Hepatitis C Partnership. EC partnership practice support toolkit (2018).[9]
† An APRI calculator is available at: www.hepatitisc.uw.edu/page/clinical-calculators/apri

‡ FibroScan is not approved for use in people younger than 18 years, pregnant women, people with ascites and people with a pacemaker or implantable defibrillator. FibroScan and APRI results should be interpreted in conjunction with a full clinical picture by a trained clinician.
§ Appropriate specialists include gastroenterologists, hepatologists and infectious disease physicians, depending on local referral processes.

Society of Australia (http://cart.gesa.org.au/membes/files/Resources/Hepatitis%20C/Remote_consultation_form_updated_Aug_2017.pdf)
- Reach-C interactive webpage (https://reach-c.ashm.org.au).

Follow up

Follow up of patients is essential after DAA treatment, as described in Part 4 of this series.[7] The key date for follow up is 12 weeks after completion of therapy. A negative HCV RNA PCR result at this time indicates hepatitis C cure, termed a sustained virological response (SVR12). This is truly a 'miracle of modern medicine' and a delightful message to convey to a patient.

Patients who are cured and have normal liver function test results and early liver disease need no further follow up, unless there is ongoing exposure to HCV, such as continuing injecting drug use. If liver function test results continue to be raised, indicating liver disease, or the patient has been diagnosed with cirrhosis then they need specialist review.

Patients with cirrhosis need lifelong monitoring with six-monthly liver ultrasound examinations because of the risk of hepatocellular carcinoma. Monitoring can be done by the GP or specialist. Built-in recall systems in GP software are helpful for this.

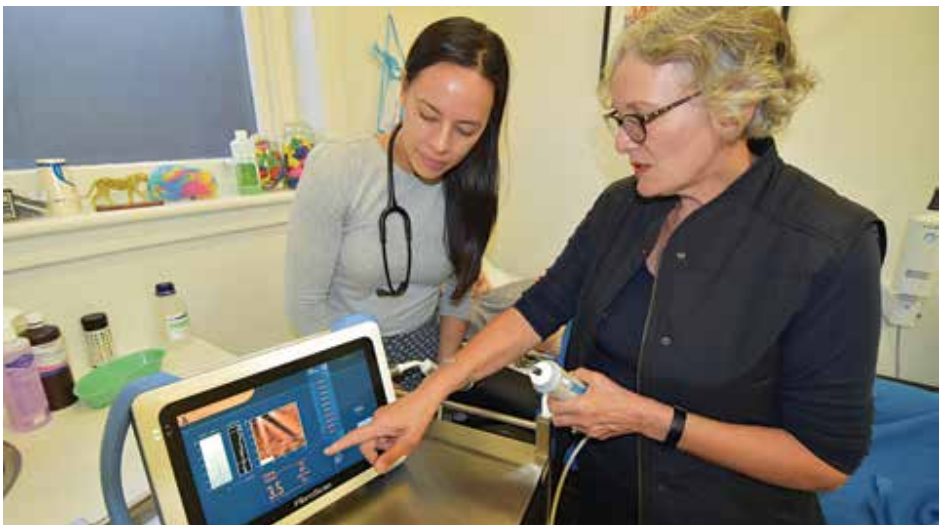


Figure 2. Hepatology nurse specialists can provide support to GPs managing patients with hepatitis C, performing mobile FibroScan assessments and giving advice to patients around treatment. Here, hepatitis nurse specialist Dianne How Chow advises GP registrar Jacqueline Nicholson on FibroScan results of a patient presenting for hepatitis C treatment.

HCV reinfection is possible as past infection does not provide any immunity to reinfection. Patients with an ongoing risk of HCV infection (e.g. continuing injecting drug use) need regular HCV RNA PCR tests at least once a year as long as they remain at risk. Note that the HCV antibody test will most likely give positive results for life, and this test is thus not useful for monitoring for reinfection and does not need to be repeated.

Complete patient care

Most people living with hepatitis C have comorbidities.[12] These can be:

- hepatitis C-related, such as cirrhosis, liver failure and type 2 diabetes
- associated with hepatitis C acquisition, such as injecting drug use and imprisonment
- associated with marginalisation and poverty, such as smoking, alcohol abuse and mental illness.

These problems require ongoing GP care and sometimes referral to other healthcare workers.

Some health problems that are more common in people living with hepatitis C are listed in Box 5. These health problems will probably persist after curative treatment of hepatitis C and impact on quality of life. Patient engagement in hepatitis C care can provide an opportunity to consider other health problems. Patients should be offered appropriate health screening according to the guidelines of the Royal Australian College of General Practitioners.[13]

Preventing reinfection is important. This may include offering opioid substitution therapy and encouraging safer injecting (e.g. needle and syringe exchange). It is also helpful to encourage patients to support their partner and friends to access hepatitis C treatment, which will also reduce the likelihood of reinfection.

4. CASE STUDY: A PATIENT WITH A PAST DIAGNOSIS OF HEPATITIS C

Presentation

Tim is a 48-year-old new patient to your practice. He has heard from a friend that you 'know something about hepatitis C'. He reports that he was diagnosed with hepatitis C in the early 1990s after a car accident and blood transfusion when he was overseas. He has not done anything about it in the past but is now keen to have treatment. He is well apart from mild asthma treated with a regular inhaled corticosteroid and as-required inhaled salbutamol. He smokes about 10 cigarettes daily and drinks two to four beers on an average day.

Assessment

You order hepatitis C virus (HCV) genotyping and standard pathology tests. Results show that Tim is infected with HCV genotype 1. His AST to platelet ratio index (APRI) calculated with an online calculator is 0.609 (Figure). Hepatitis B serology indicates he is immune to hepatitis B. All other test results are normal.

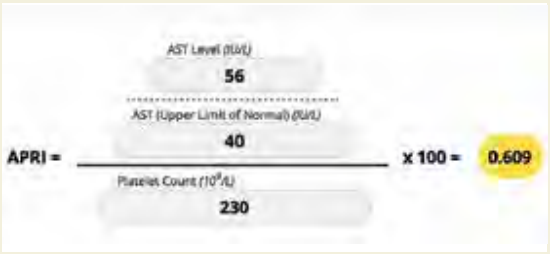


Figure. APRI result for Tim from an online calculator (www.hepatitisc.uw.edu/page/clinical-calculators/apri).

Management

You check for any potential drug interactions between Tim's current medication and hepatitis C direct-acting antiviral (DAA) therapy at the University of Liverpool online checker (www.hep-druginteractions.org/checker). As you are a new DAA prescriber, you complete and submit the Reach-C interactive form with the suggestion that Tim could be treated with either of the two pangenotypic DAA regimens. You receive a response the following day confirming your choice of DAA.

At Tim's next visit you discuss with him the results of the blood tests and his preference between the two DAA regimens. After telephoning the PBS for a PBS authority, you write Tim a DAA prescription and advise him that the pharmacy will likely need 24 hours' notice to fill the prescription.

Follow up

Tim returns to see you 12 weeks after he completes DAA treatment. He reports taking almost all doses of the DAA with mild nausea as the only adverse effect. You order an HCV RNA PCR test, which is negative, and liver function tests, which have normal results.

Tim is delighted when you tell him that he is cured and does not need any further follow up. As part of his long-term care you discuss his smoking and alcohol use.

Treating hepatitis C around Australia

GP referral to a specialist is a longstanding model, and referral is appropriate for patients with advanced liver disease or major comorbidities, such as chronic

TABLE. PANGENOTYPIC DAA REGIMENS FOR PEOPLE WITH HEPATITIS C WHO ARE TREATMENT-NAÏVE WITH NO CIRRHOSIS[3]*

Formulation (daily dose)	Tablets per day	Treatment duration	Recommended relation with food	Renal impairment (eGFR <30 mL/min/1.73 m²)
Glecaprevir/pibrentasvir (300 mg/120 mg)	Three once daily	8 weeks	With food	No dose adjustment required
Sofosbuvir/velpatasvir (400 mg/100 mg)	One once daily	12 weeks	With or without food	Not recommended

Abbreviation: eGFR = estimated glomerular filtration rate.
* Adapted from Hepatitis C Virus Infection Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018).[3]

5. COMMON COMORBIDITIES IN PATIENTS WITH HEPATITIS C

Social
- Poverty
- Imprisonment
- Unemployment
- Homelessness

Physical
- Smoking, chronic obstructive pulmonary disease (COPD)
- Type 2 diabetes
- Cardiovascular disease
- Obesity
- Lung and other smoking-related cancers
- Liver cancer

Mental health
- Alcohol dependency
- Opioid and amphetamine dependency
- Depression
- Psychosis

6. HEPATITIS C TREATMENT IN RURAL AND REMOTE AREAS

Outside major centres, GPs often have to manage patients with all stages of hepatitis C, including cirrhosis, because of the lack of specialists. Rural GP Annie Balcomb has established a dedicated viral hepatitis clinic within a busy general practice in Orange, NSW, and treated over 150 patients with hepatitis C, including 30% with compensated cirrhosis. She collaborates with specialists via telephone and email as needed. Her success rates for treatment of patients with cirrhosis are the same as those of tertiary centres.

'Many specialists are supportive of GPs in rural and remote communities and keen to see patients with cirrhosis treated', said Dr Balcomb. 'Reach out for support if you cannot get the patient to a specialist.'

Figure. Rural GP Annie Balcomb.

hepatitis B or HIV infection. However, treatment of chronic hepatitis C for most people is now simple and can be easily incorporated into primary care. Less experienced GPs can obtain specialist support and advice on a treatment plan by contacting a specialist by telephone, by email using the Reach-C proforma or by fax using the GESA proforma.

Rural GPs may need to manage all stages of diagnosis and treatment of hepatitis C, including the care of patients with cirrhosis (Box 6). GP outreach models have also been developed, in which GPs provide assessment and care in the community, as described above (Box 3).

Conclusion

Australian GPs are leading the world in curing hepatitis C. GPs can treat and cure most people living with hepatitis C with well-tolerated DAA therapy. Finding and treating patients with hepatitis C is straightforward and fits well with the skills that GPs use every day. Curing hepatitis C is rewarding for the treating doctor as well as life-changing for the patient. Eliminating hepatitis C from your practice is a great step towards hepatitis C elimination in Australia. MT

References

1. Hajarizadeh B, Dore G. Kirby Institute, UNSW Sydney, NSW. Unpublished data.
2. Kirby Institute. Monitoring hepatitis C treatment uptake in Australia. Issue 9, July 2018. Sydney: Kirby Institute, UNSW Sydney; 2018. Available online at: https://kirby.unsw.edu.au/report/monitoring-hepatitis-c-treatment-uptake-australia-issue-9-july-2018 (accessed October 2019).
3. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018). Melbourne: Gastroenterological Society of Australia, 2018. Available online at: http://www.hepcguidelines.org.au/wp-content/uploads/2018/11/hepatitis-C-virus-infection-a-consensus-statement-Sep-2018-1.pdf (accessed October 2019).
4. Draper B, Layton C, Doyle J, et al. Eliminating hepatitis C: Part 1. Finding your patients with hepatitis C. Med Today 2019; 20(6): 34-40.
5. Layton C, Richmond J, Baker D, et al. Eliminating hepatitis C: Part 2. Assessing your patient for antiviral treatment. Med Today 2019; 20(7): 24-32.
6. Purcell T, Wade A, Accadia L, et al. Eliminating hepatitis C: Part 3. Curing hepatitis C in general practice. Med Today 2019; 20(8): 20-26.
7. Chan K, Gooey M, Hellard M, et al. Eliminating hepatitis C: Part 4. Ongoing care after hepatitis C treatment. Med Today 2019; 20(9): 36-42.
8. Lazarus JV, Safreed-Harmon K, Thursz MR, et al. The micro-elimination approach to eliminating hepatitis C: strategic and operational considerations. Semin Liver Dis 2018; 38(3): 181-192.
9. Burnet Institute Eliminate Hepatitis C Partnership. EC Partnership practice support toolkit. Melbourne: Burnet Institute; 2018. Available online at: https://ecpartnership.org.au/toolkit (accessed October 2019).
10. Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2018. Sydney: Kirby Institute; 2018. Available online at: https://kirby.unsw.edu.au/report/hiv-viral-hepatitis-and-sexually transmissible-infections-australia-annual-surveillance (accessed October 2019).
11. Australian Government Department of Health. Clinical practice guidelines: pregnancy care. Canberra: Australian Government Department of Health; 2019.
12. Louie KS, St Laurent S, Forssen UM, Mundy LM, Pimenta JM. The high comorbidity burden of the hepatitis C virus infected population in the United States. BMC Infect Dis 2012; 12: 86.
13. Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th ed, updated. Melbourne: RACGP; 2018. Available online at: www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/red-book (accessed October 2019).

COMPETING INTERESTS: Dr Baker has received clinical trial funding and conference sponsorship and serves on the advisory board for AbbVie, Gilead and MSD. Dr Balcomb has received funding and conference sponsorship from Gilead and AbbVie. Dr O'Loan has received funding and conference sponsorship from Gilead and MSD. Dr Howell: None.

Online resources on hepatitis C for Australian GPs

Useful sources of information and resources for GPs managing patients with hepatitis C are summarised in the Box.

Major sources of information and resources on hepatitis C

- **Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)**
  www.ashm.org.au/HCV
- **Gastroenterological Society of Australia (GESA)**
  https://www.gesa.org.au/resources/hepatitis-c-treatment
- **Hepatitis Australia**
  https://www.hepatitisaustralia.com

Clinical resources

- ***Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018)***
  www.gesa.org.au/resources/hepatitis-c-treatment
- ***National HCV testing policy***
  http://testingportal.ashm.org.au/hcv
- ***Initiating hepatitis C testing: talking testing***
  www.latrobe.edu.au/__data/assets/pdf_file/0005/972239/Talking-Testing-Hepatitis-C.pdf
- **HEP drug interactions checker**
  www.hep-druginteractions.org
- **Remote consultation request**
  - *Remote consultation request for initiation of hepatitis C treatment form*
    www.gesa.org.au/resources/hepatitis-c-treatment
  - REACH-C interactive form
    https://reach-c.ashm.org.au
- **Wallchart for GPs: *Clinical guidance for treating hepatitis C virus infection: a summary***
  www.gesa.org.au/resources/hepatitis-c-treatment
- **HealthPathways in the local area** – specific information about hepatitis C treatment and referral in your area

Training

- **ASHM training courses (face-to-face, webinar and online), and other useful links**
  https://ashm.org.au/HCV/training
- **Video: *8 easy steps to improve hepatitis C treatment in your practice, Dr Nada Andric, 12.08.2018***
  https://vimeo.com/299336284
- **Video: *A practical guide to prescribing the new hepatitis C antiviral drugs in general practice*** (GESA)
  www.gesa.org.au/resources/hepatitis-c-treatment

General practice resources

- **Eliminate Hepatitis C (EC) Partnership Practice Support Toolkit** – resources to promote hepatitis C testing, treatment and follow up developed specifically for GPs and other primary care providers
  https://ecpartnership.org.au/toolkit
- ***Starting the conversation*** – tips for introducing hepatitis C testing to patients
  https://ecpartnership.org.au/system/resource/78/file/Starting_the_conversation_WEBSITE.pdf
- ***Getting someone ready for treatment*** – tips for discussing treatment readiness
  https://ecpartnership.org.au/system/resource/77/file/Getting_someone_ready_for_treatment_FINAL.pdf
- **Wallchart for GPs: *Clinical guidance for treating hepatitis C virus infection: a summary*** (see above)
- **GP Pledge (Aus GPs End Hep C)**
  www.ashm.org.au/HCV/Aus-GPs-End-Hep-C
- **Other resources**
  https://ecpartnership.org.au/resources

Patient information and support

- **Hepatitis Australia**
  Hepatitis information: Hepatitis C
  www.hepatitisaustralia.com/Pages/Category/hepatitis-c
- **ASHM** – written and audio patient information in 22 languages
  All good? Get facts. Get checked. Now you're all good
  http://allgood.org.au
- **State-based hepatitis peak bodies and national and state-based harm reduction organisations, including Harm Reduction Victoria and NSW Users and AIDS Association** – resources include *Safer using tips* (Harm Reduction Victoria)
  https://docs.wixstatic.com/ugd/ebb8bf_61a57e28de614edea74585d8951275fb.pdf
  and
  https://docs.wixstatic.com/ugd/ebb8bf_f26901243d6f4c4295d46010e8d90088.pdf

Overcoming stigma and discrimination

- ***Removing barriers: it's easy as 1, 2, 3*** (ASHM)
  http://removingbarriers.ashm.org.au