Ps 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.

**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 before prescribing; online resources can streamline this process. Important considerations before prescribing include barriers to adherence and drug interactions.

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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). Most of these people are considered suitable for treatment in primary care. 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.

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. 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%. These two pangenotypic DAA treatment regimens are well tolerated. Side effects may include mild fatigue, headache or nausea. The two regimens are compared in the Table.

Who can treat chronic hepatitis C?
Any medical practitioner or authorised nurse practitioner can prescribe DAAs for treatment of chronic hepatitis C. 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/members/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>
<thead>
<tr>
<th>Formulation (daily dose)</th>
<th>Genotypes</th>
<th>Tablets per day</th>
<th>Treatment duration</th>
<th>Recommended relation with food</th>
<th>Renal impairment (eGFR &lt;30mL/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glecaprevir/pibrentasvir (300mg/120mg)</td>
<td>All</td>
<td>Three tablets orally once daily</td>
<td>8 weeks</td>
<td>With food</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir (400mg/100mg)</td>
<td>All</td>
<td>One tablet orally once daily</td>
<td>12 weeks</td>
<td>With or without food</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

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

DAA treatment is not recommended for women who are pregnant or breastfeeding. Women should also be advised to wait four weeks after the end of DAA treatment before becoming pregnant. If a woman who has started DAA treatment becomes aware that she is pregnant, treatment becomes invalid. If you are prescribed glecaprevir/ribavirin 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.

• If you are prescribed glecaprevir/ribavirin and you miss a dose, 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.
• 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.

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. 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


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

Are there any drug interactions?

Interactions between DAAs and other drugs that the patient takes must be assessed before DAAs are prescribed. 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). 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. 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.

Monitoring during treatment

It is not necessary to order routine investigations during the course of DAA treatment. 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.

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. 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). 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).

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.

3. RESOURCES FOR HEPATITIS C TREATMENT

- Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (www.ashm.org.au/HCV/)
- Hepatitis Australia (www.hepatitisaustralia.com)
- 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 DA A treatment. In addition, all patients who have not been cured by first-line DA A 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 DA A 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.

4. RECOMMENDED MONITORING FOR VIROLOGICAL RESPONSE FOR PANGENOTYPIC DAA REGIMENS

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).3

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References


Online CPD Journal Program

List at least two pangenotypic direct-acting antiviral regimens for hepatitis C.

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