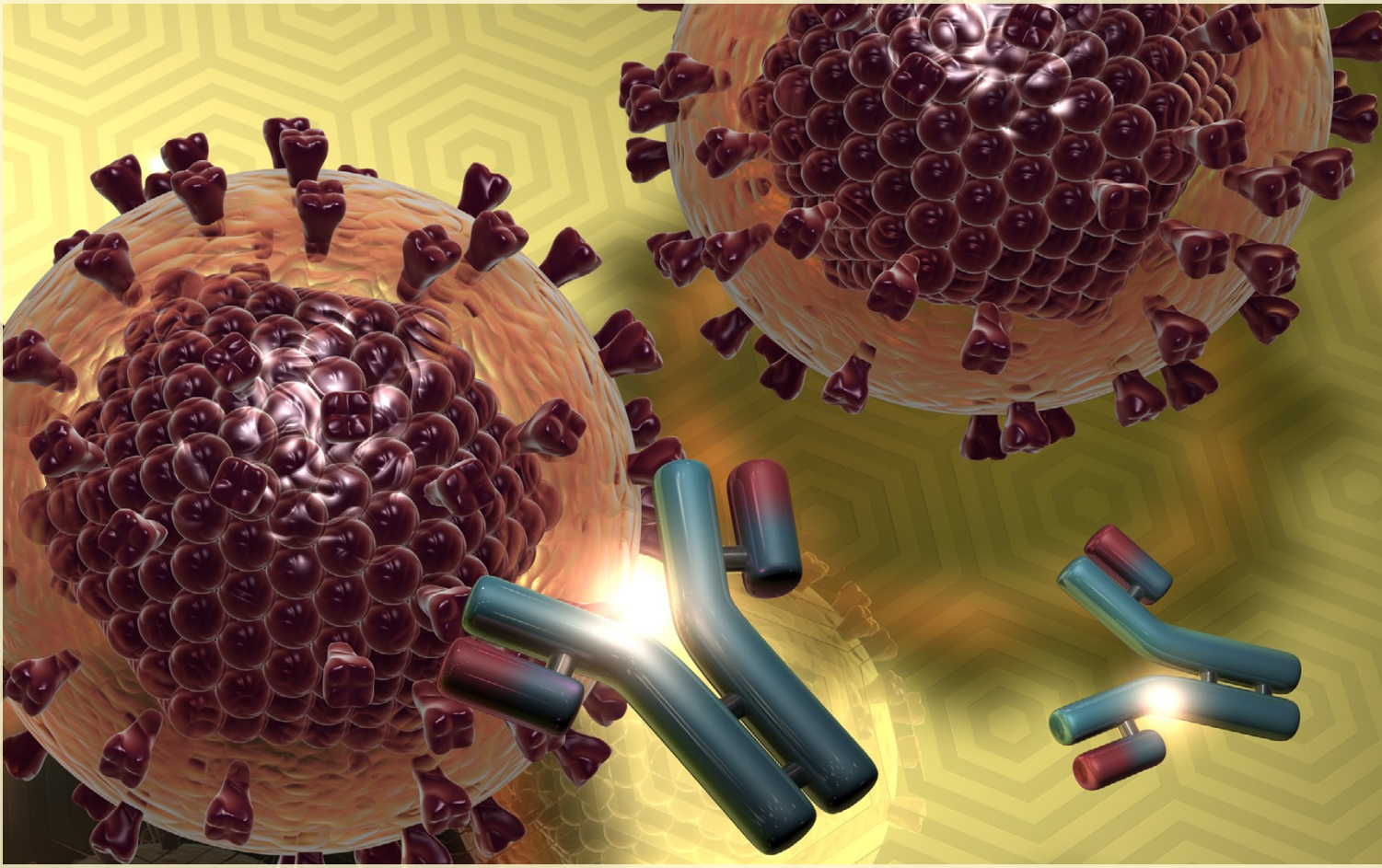
The treatment of hepatitis C has changed



Best Practice
Issue 77 SE September 2016

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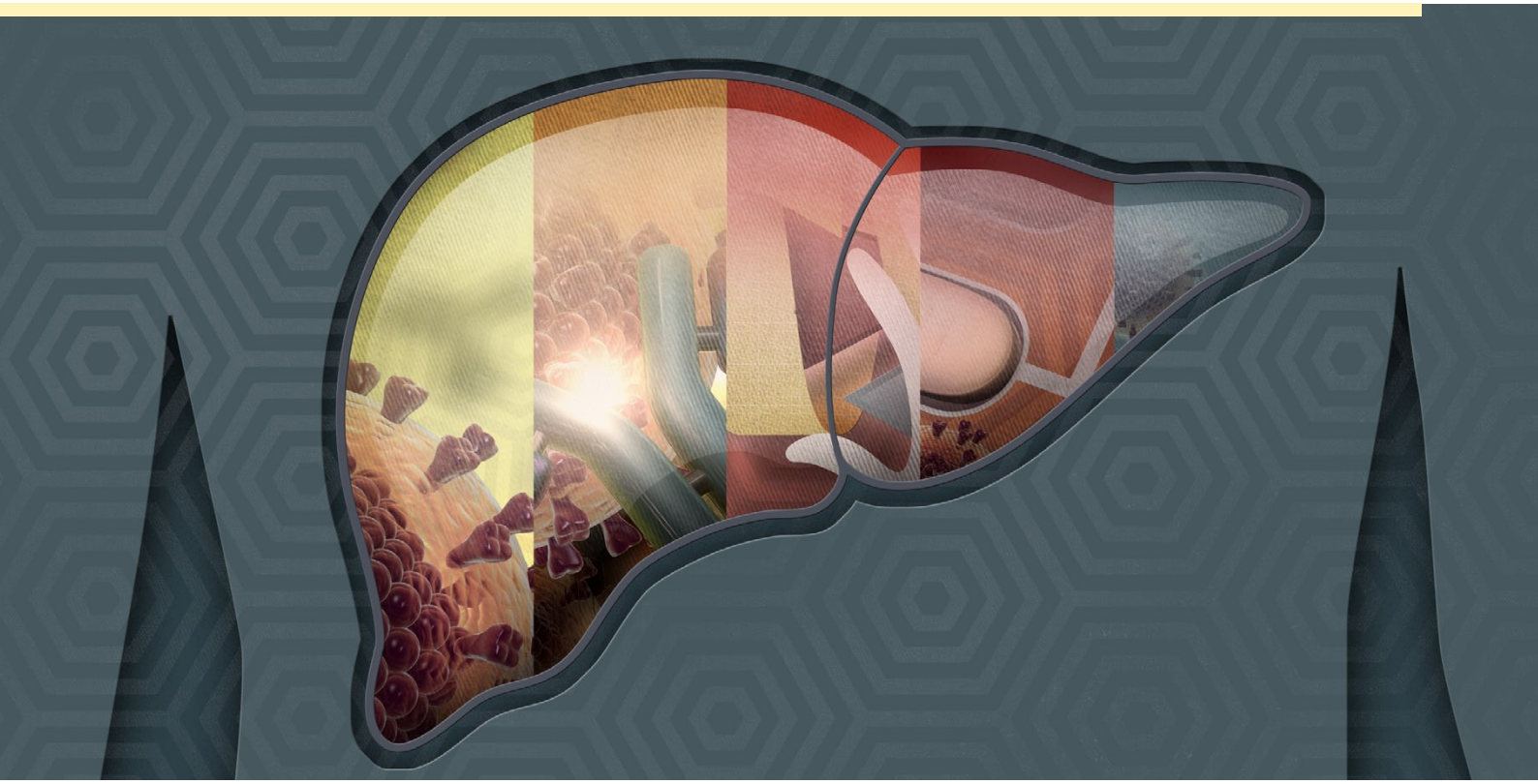


The treatment of **hepatitis C has changed**

Three new oral regimens for the treatment of hepatitis C, known as directly acting antiviral (DAA) medicines, are fully subsidised from 1 July, 2016:

- Viekira Pak (paritaprevir, ritonavir and ombitasvir with dasabuvir)
- Viekira Pak-RBV (the same combination with the addition of ribavirin)
- Harvoni (ledipasvir with sofosbuvir) for patients who meet the funding criteria

From 1 October, 2016, general practitioners will be able to prescribe Viekira Pak and Viekira Pak-RBV to treat patients infected with genotypes 1a and 1b of the hepatitis C virus (HCV). **Viekira Pak and Viekira Pak-RBV are only indicated for the treatment of patients with genotypes 1a and 1b**; approximately 55% of people with hepatitis C in New Zealand. It is important that prescribers **DO NOT** initiate Viekira Pak and Viekira Pak-RBV for patients with HCV genotypes 2,3,5 and 6, as treatment will not be effective and could lead to viral resistance which may limit the effectiveness of future treatment.

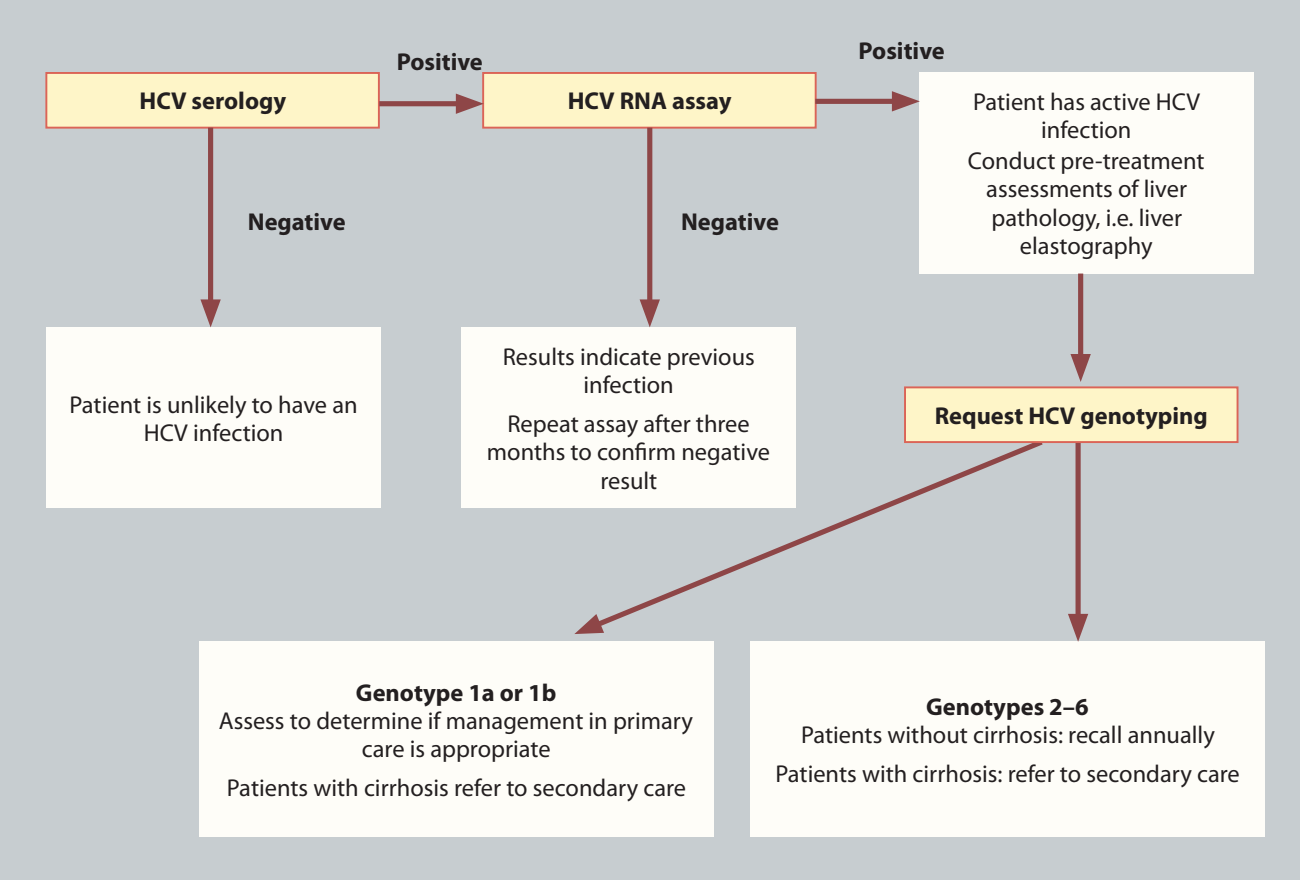
Harvoni will be available for patients with any genotype of HCV if they meet the funding criteria and the application is approved by the PHARMAC hepatitis C treatment panel. Due to the severity of disease in these patients it is expected that treatment with Harvoni will be initiated in secondary care.

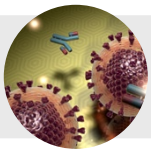
This resource provides prescribers in primary care with comprehensive guidance on the management of patients with hepatitis C. It is not intended to cover patients treated in secondary care who may have advanced disease and/or concurrent viral infections. Patients in secondary care are managed according to the New Zealand Society of Gastroenterology HCV treatment guidelines.

Acknowledgement: Thank you to **Dr Ed Gane,** Professor of Medicine, University of Auckland, Chief Hepatologist and Deputy Director of the New Zealand Liver Transplant Unit, **Dr Carol Atmore**, General Practitioner, Foxley Fellow, University of Otago and member or the National Hepatitis C Implementation Advisory Group and **Dr Steve Johnson**, Gastroenterologist and Senior Lecturer Dunedin School of Medicine for expert review of this article.

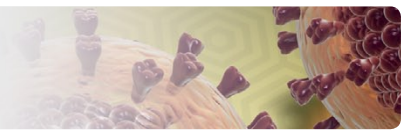
To safely manage patients with hepatitis C in primary care, general practitioners need to:

1. Test patients at high risk of infection





For further information see:
Testing for hepatitis C virus in patients at high risk of infection



2. Conduct pre-treatment assessments

Assess whether treatment in primary care is appropriate on the basis of liver pathology:

Treatment in primary care is appropriate for patients with ALL of the following:	Referral to secondary care is appropriate for patients who have ANY of the following:
■ Clinical examination does not suggest cirrhosis	■ Clinical examination consistent with cirrhosis
■ Scores of F0–F2 on liver elastography	■ Scores of F3–F4 on liver elastography
■ Laboratory results which do not suggest cirrhosis	■ Laboratory results consistent with cirrhosis

Liver elastography performed by Fibroscan or shear wave ultrasound is the preferred investigation for liver assessment in all patients with hepatitis C. In regions where access to these imaging technologies is limited the ratio of aspartate aminotransferase (AST) levels to platelet concentration (APRI) may be considered as a pragmatic alternative method to assess patients for the likelihood of cirrhosis.

Contraindications or situations where caution is required:

- Pregnancy
- Systemic vasculitis due to cryoglobulinaemia, which is associated with hepatitis C infection
- Co-infection with hepatitis B or HIV

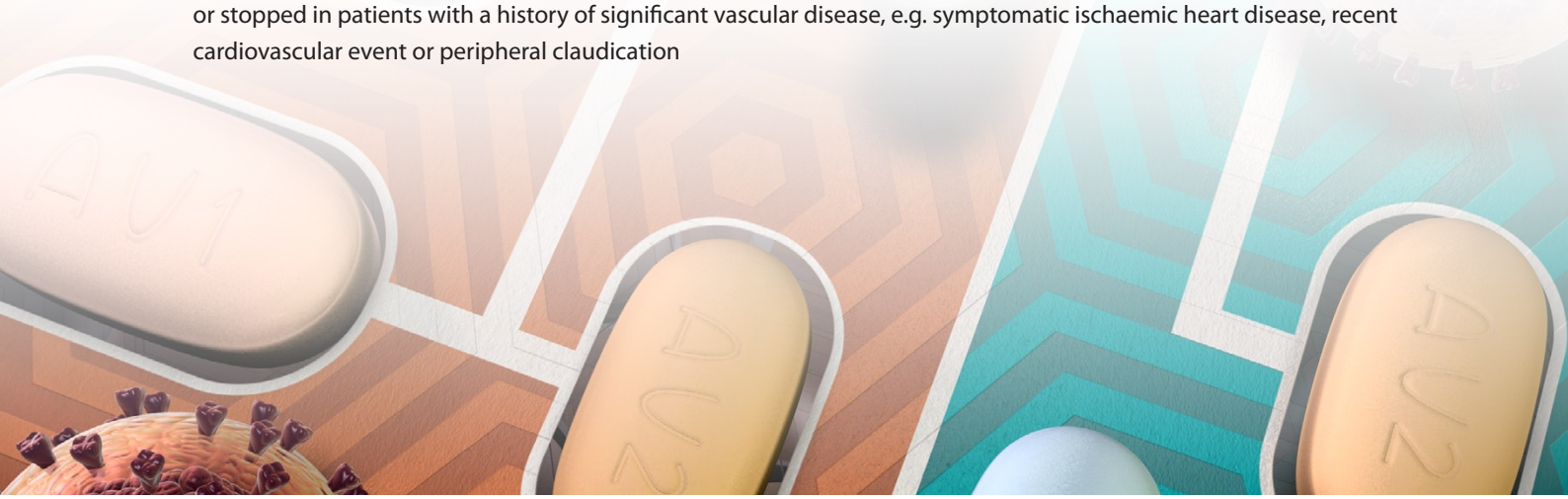
Viekira Pak-RBV should NOT be taken by patients with an eGFR < 30 mL/min/1.73 m^2. Prescribing of Viekira Pak-RBV to patients with an eGFR 30 – 50 mL/min/1.73m^2 routinely occurs in secondary care; these patients should be discussed with a gastroenterologist.

For further information see:
Pre-treatment assessment for patients with HCV genotype 1 infections

3. Prescribe Viekira Pak or Viekira Pak-RBV and monitor patients during treatment

Prescribe:	For patients with genotypes:
Viekira Pak-RBV for 12 weeks	1a
Viekira Pak for eight weeks	1b

- Assess the potential for medicine interactions prior to initiation: **www.hep-druginteractions.org/checker**
- Clinicians need to submit a distribution request form to PHARMAC for patients to receive funded Viekira Pak or Viekira Pak-RBV, see: **www.pharmac.govt.nz/assets/viekira-pak-form.docx**
- For patients taking ribavirin, dose depends on body weight:
  - Patients < 75 kg: 1000 mg ribavirin per day in two divided doses (400 mg in the morning + 600 mg at night)
  - Patients ≥ 75 kg: 1200 mg ribavirin per day in two divided doses (600 mg twice daily)
- Viekira Pak-RBV should NOT be taken by patients with an eGFR < 30 mL/min/1.73 m^2; patients with an eGFR 30 – 50 mL/min/1.73m^2 should be discussed with a gastroenterologist; dose reductions are recommended in patients with an eGFR 50 – 90 mL/min/1.73 m^2
- Patients taking ribavirin should use two forms of effective contraception during treatment and for six months after treatment has finished
- If haemoglobin levels fall below 100 g/L, ribavirin doses should be reduced in patients with no history of vascular disease or stopped in patients with a history of significant vascular disease, e.g. symptomatic ischaemic heart disease, recent cardiovascular event or peripheral claudication



	Patients taking Viekira Pak	Patients taking Viekira Pak + ribavirin*
Before treatment	Creatinine and electrolytes FBC LFTs INR HCV RNA assay**	
During treatment		
Week two	N/A †	FBC
Week four	N/A †	FBC
Week eight	N/A †	FBC
After treatment		
12 weeks after treatment#	HCV RNA assay LFTs	HCV RNA assay LFTs

* Ribavirin may cause elevation of uric acid; levels should be monitored in patients at risk of gout.

** Depending on when the test was last performed. For patients with a long-term infection, the HCV RNA assay is not necessary if it was performed in the last five years. HCV RNA assays during treatment are not necessary, however, they can be requested if patient adherence is a concern; most patients should achieve undetectable HCV RNA levels during treatment.

† For patients with cirrhosis the New Zealand Society of Gastroenterology guidelines recommend LFTs at weeks two, four and eight of treatment. However, for primary care patients, i.e. those without cirrhosis, no LFT testing is required during treatment.

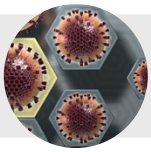
If the HCV RNA assay at 12 weeks after treatment is positive, patients should be discussed with a gastroenterologist. A negative result indicates cure.

For further information see:
Management of patients taking directly-acting antivirals (DAAs)

4. Ensure appropriate follow-up

Following treatment:

- At least nine out of ten patients should have undetectable HCV RNA 12 weeks after treatment, indicating cure
- Patients who have finished taking ribavirin should continue to use two forms of effective contraception for six months
- Patients without cirrhosis and with normal liver function tests do not require further follow-up
- Patients with cirrhosis should undergo monitoring, ideally every six months, for the development of hepatocellular carcinoma and where appropriate, oesophageal varices



For further information see:
Follow-up after treatment has finished

The treatment of **hepatitis C has changed**

Hepatitis C virus (HCV) was discovered in 1989. Until recently infected patients have been treated with interferon, a cytokine produced by immune cells in response to pathogens. Pegylated interferon, which has a longer half-life, and combination treatment with ribavirin, an antiviral which inhibits HCV via an unknown mechanism, have also been used.[1] These regimens involve long treatment courses, have high rates of adverse effects and successfully cure hepatitis C in only 40–80% of patients.[1, 2]

New antiviral medicines are now available

Directly acting antivirals (DAAs) are now available to treat patients with HCV including the newly subsidised oral medicines:

- Viekira Pak (paritaprevir, ritonavir and ombitasvir with dasabuvir)
- Viekira Pak-RBV (the same combination with the addition of ribavirin)
- Harvoni (ledipasvir with sofosbuvir) for patients who meet the funding criteria

These medicines target HCV proteins to inhibit replication and viral function, and are used in combination to target multiple pathways. These treatments have success rates of over 90%.[1]

Clinicians in primary care can prescribe new HCV medicines

From 1 July, 2016, infectious disease specialists, gastroenterologists and hepatologists in New Zealand have been able to prescribe subsidised Viekira Pak and Viekira Pak-RBV. From 1 October, 2016, any relevant prescriber, including general practitioners, will be able to initiate subsidised treatment with these medicines. Access to DAA regimens mean clinicians in primary care will be able to manage some patients with HCV infection without referral to secondary care, particularly those without cirrhosis, who comprise the majority of patients who are infected.[3]

Another DAA medicine combination, Harvoni (ledipasvir with sofosbuvir), is also subsidised from 1 July, 2016, for patients infected with any HCV genotype who meet the funding criteria. These patients have advanced liver complications, e.g. decompensated cirrhosis. Applications for subsidised Harvoni are likely to be made in secondary care and will be reviewed by the PHARMAC Hepatitis C Treatments Panel.[4]

Treatment indication depends on genotype

There are multiple genotypes of HCV. **Viekira Pak and Viekira Pak-RBV are indicated only for the treatment of patients**

infected with HCV genotypes 1a or 1b; approximately 55% of cases in New Zealand.[3,5] It is important that prescribers **DO NOT** initiate Viekira Pak and Viekira Pak-RBV for patients with HCV genotypes 2,3,5 and 6, as treatment will not be effective and could lead to viral resistance which may limit the effectiveness of future treatment.

The majority of patients with HCV infection have not been treated

It is estimated that 54 000 people in New Zealand are living with HCV infection, with half of those undiagnosed.[3] More than 90% of people infected have yet to receive treatment for hepatitis C.[3]

Due to under-treatment, the vast majority of people infected with HCV are at high risk of developing complications, e.g. hepatic fibrosis, cirrhosis and hepatocellular carcinoma, as well as transmitting the virus to others. Approximately 16% of patients infected with HCV develop cirrhosis after 20 years, increasing to 41% after 30 years.[6] In New Zealand, the number of cases of HCV-related hepatocellular carcinoma increased from 21 to 75 between 2008 and 2013, and HCV contributed to approximately half of liver transplants in adults in 2013.[3]

Treatment of HCV infection is often curative

Unlike human immunodeficiency virus (HIV) or herpes viruses, treatment of HCV can result in clearance of the virus, i.e. cure, rather than just viral suppression. This is because HCV cannot integrate into host DNA and has no hidden reservoirs.

A surge in patients wanting treatment may occur

The number of people accessing interferon treatment for HCV has decreased in recent years. In 2010, 700 patients received subsidised HCV treatment and there are reports that in 2015 the number of treated patients had fallen by more than two-thirds.[7] This decline is likely to be caused by several factors. Firstly, anticipation by patients and clinicians that DAA treatment regimens would soon be subsidised. Secondly, access to cheaper generic DAAs overseas, and thirdly, participation in clinical trials.[7–9]

With the new subsidy changes there is expected to be a surge in requests for antiviral treatment, as has been observed in Australia since subsidy of DAA regimens began in March, 2016.

Further information for patients and clinicians:

- Education for diagnosing and managing patients with hepatitis C in primary care from the Ministry of Health: **learnonline.health.nz/course/category.php?id=9**
- Information on training and treatment services available in New Zealand from the Ministry of Health: **www.health.govt.nz/our-work/diseases-and-conditions/hepatitis-c**
- Education for patients with hepatitis C from the Ministry of Health: **www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/hepatitis-c**
- New Zealand Society of Gastroenterology HCV treatment guidelines: **www.nzsg.org.nz**
- PHARMAC: **www.pharmac.govt.nz/medicines/my-medicine-has-changed/hepatitis-c-treatments**
- Australasian society for HIV, viral hepatitis and sexual health medicine: **www.ashm.org.au**

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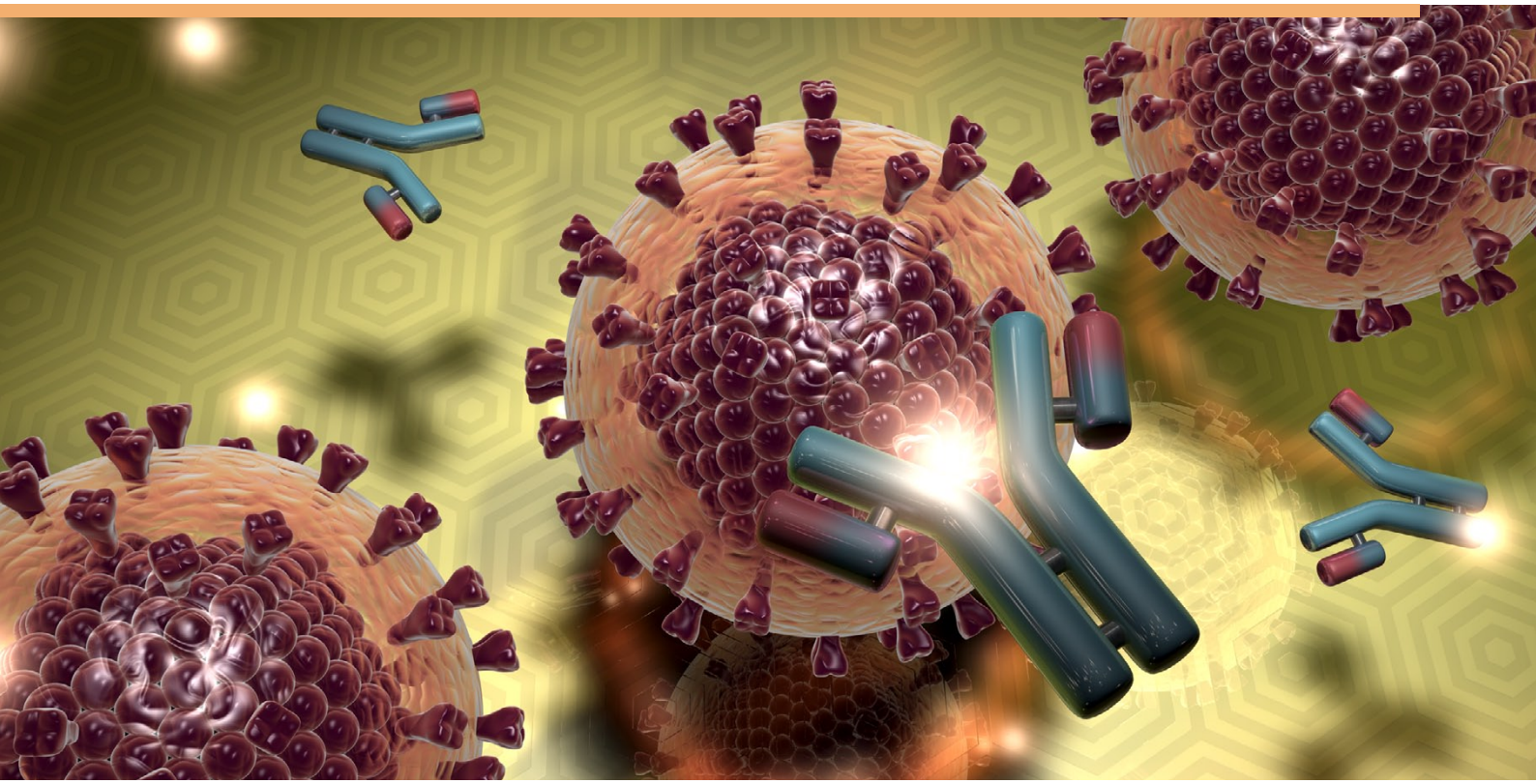


Testing for hepatitis C virus (HCV) in patients at high risk of infection

KEY PRACTICE POINTS

- Identify patients with HCV infection by testing those at high risk
- Testing begins with serology for anti-HCV antibodies
- Positive serology must be followed by an HCV RNA (PCR) assay
- HCV genotype testing is required as Viekira Pak and Viekira Pak-RBV are only indicated for the treatment of patients with genotype 1a and 1b infections

Who is at risk of HCV infection?

Hepatitis C infection occurs through exposure to infected blood or body fluids. The majority of newly acquired infections in New Zealand are from injectable drug use. Promoting the use of clean needles for people using injectable drugs is important to reduce new infections. If people using injectable drugs are not already receiving assistance, they should be referred to community alcohol and drug services (CADS) and a local needle exchange service.

For a list of needle exchange outlets, see: **www.needle.co.nz/outlet_summary.html/15**

Some patients with hepatitis C will have acquired iatrogenic infection from contaminated blood products, used in New Zealand prior to July 1992. Others may have become infected following medical or dental procedures, particularly if these were performed in countries with high HCV prevalence and/or poor infection control procedures.[1,2] Regions with high HCV prevalence include Eastern Europe, the Middle East, North Africa, Western and Central Sub-Saharan Africa, Central Asia and the Indian subcontinent.[1,2] People who have been incarcerated are also at high risk, due to the prevalence of HCV in the prison

population and the use of potentially contaminated tattooing equipment. Sexual transmission plays a minor role in the spread of hepatitis C and the risk is greatest for men who have sex with men, heterosexuals with multiple partners and sex workers, especially in association with injectable drug use.[3]

People cannot develop immunity to HCV. Therefore, anyone who has eradicated HCV infection either spontaneously or following antiviral treatment may be re-infected.

Initial infection is usually asymptomatic

The majority of people who contract HCV are asymptomatic in the acute stages of infection with only 25–30% of people noticing symptoms.[4] The symptoms of acute HCV infection are nonspecific and include:[4, 5]

- Fatigue
- Nausea
- Abdominal pain
- Muscle aches
- Jaundice

Substantially elevated alanine aminotransferase (ALT) levels, e.g. greater than ten times the upper limit of normal, occur two to eight weeks after infection.[6]

Viral clearance without treatment is possible

It is estimated that 20–25% of people infected with HCV clear the virus without medical intervention.[1] Females, younger patients, and patients who develop symptoms, such as jaundice, are more likely to achieve spontaneous viral clearance.[1]

The majority of patients develop long-term infection

Approximately three out of four people infected develop long-term HCV infection, placing them at increased risk of hepatic complications and making transmission of the virus more likely. Due to the slow disease process many people will be unaware of the infection. People who present with symptoms of liver disease may have acquired HCV at a younger age, and the source of infection may never be identified.

In people with long-term HCV infection the risk of cirrhosis increases with the duration of infection; 20–30% of patients develop cirrhosis after 20–30 years with 2–4% of these people per year developing hepatocellular carcinoma.[1, 2]

Opportunistic testing for patients at high risk of HCV infection

Identify the patients who are most likely to have been infected with HCV through their personal and maternal history.
Risk factors for HCV infection include:[1, 2, 7]

- Injectable drug use; 70–84% of patients with HCV in New Zealand have used injectable drugs[8]
- Receiving a blood transfusion or organ transplant in New Zealand prior to July, 1992
- Migration from or receiving health care in a region with high HCV prevalence
- Time spent in prison
- A tattoo, body piercing or alteration, e.g. scarification, performed in prison or in a country with a high prevalence of HCV
- History of acute hepatitis, jaundice, or abnormal liver function
- Being born to an HCV infected mother; mother to baby transmission occurs in approximately 5% of infected mothers[9]

It is recommended that all patients with these risk factors undergo testing for HCV infection.[1] In practice, a reasonable approach is to offer HCV testing to patients with risk factors and ensure that new patients with risk factors are identified on enrolment.

The HCV testing process

Diagnosing HCV infection typically involves three stages:

1. Serology for anti-HCV antibodies
2. HCV RNA by polymerase chain reaction (PCR), if serology is positive*
3. HCV genotyping, if HCV RNA is positive*

* Some laboratories may perform these as reflex tests

Additional tests for other forms of hepatitis and HIV are generally requested at the same time.

Testing starts with HCV serology

Serology is the first-line test for investigating HCV infection in the majority of patients (Figure 1). Antibodies to HCV may take up to six months to develop and only 50% of patients are likely to have positive serology during the acute stage of infection; delayed testing may be appropriate for these patients.[5] Discuss the limits of testing with patients with ongoing risk of infection, e.g. current injectable drug users, and the delay between infection and HCV antibody production.

Negative serology indicates the absence of HCV infection, unless the patient is immunosuppressed or they have an acute HCV infection.

Positive serology indicates either a current or previous HCV infection, or a false positive, and must be followed by an HCV RNA assay to determine if the patient has a current infection (see below).

HCV serology is not diagnostic for hepatitis C

Serology tests have a high sensitivity and specificity, although false positive results do occur. The proportion of false positive

results depends on the background prevalence of hepatitis C; in populations with a low prevalence, false positive results can account for up to 35% of positive results.[10] Testing patients without risk factors for HCV infection is therefore not recommended. Serology must be followed by HCV RNA testing to determine if the infection is current.[10]

If a patient has a positive serology and a negative HCV RNA test they are not currently infected and do not require treatment. False negatives are uncommon: it is estimated that 99% of patients with a long-term infection and detectable HCV RNA test positive for anti-HCV antibodies.[11]

A positive HCV RNA assay confirms current infection

An HCV RNA assay detects and quantifies viral RNA (Figure 1). In acute infection, HCV RNA can be detected within one to two weeks of exposure and levels increase two to eight weeks after infection.[6]

A positive result indicates current infection, either acute or long-term (see: "Testing in patients with acute HCV infection"). Patients should be informed of positive results in person and counselled about transmission prevention (see "Advice for patients to reduce the risk of HCV transmission"). The quantity of RNA at diagnosis (viral load) is also useful for monitoring progress later in treatment.

A negative HCV RNA assay indicates the patient does not have current infection and does not require treatment. Retesting of HCV RNA after three months is recommended to confirm the result as HCV RNA may be undetectable for brief periods during acute infections.[5]

HCV genotyping should be performed to determine if treatment is indicated

A positive HCV RNA test should be followed by HCV genotype testing; some laboratories may perform this test reflexively. The newly subsidised Viekira Pak DAA regimens are only indicated for the treatment of infections with HCV genotype 1 (Figure 1).

For patients previously diagnosed with HCV infection where subsidised DAA treatment is appropriate, an HCV RNA assay and HCV genotype should be requested if these have not been performed in the last five years.[13]

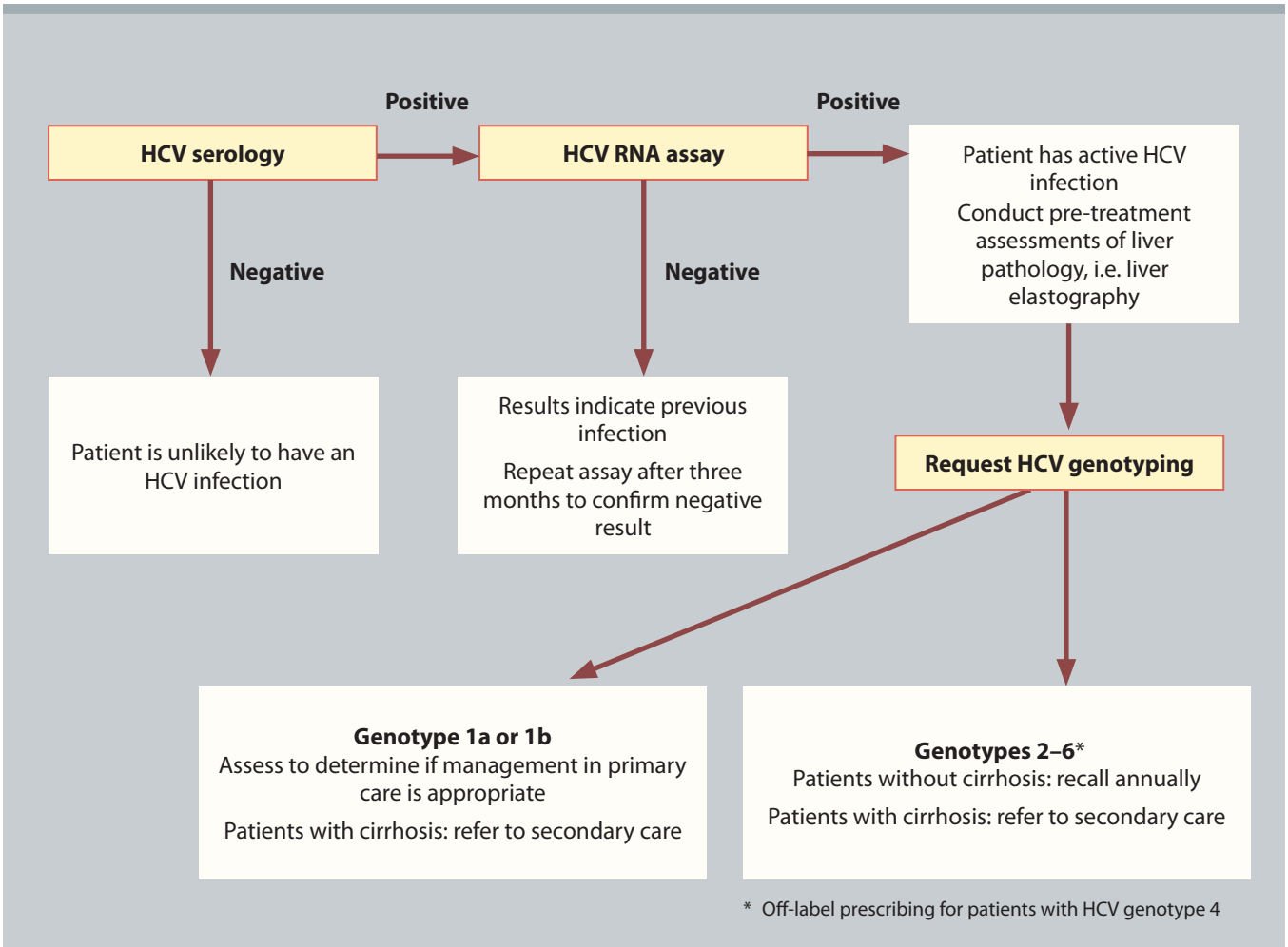


Figure 1: Testing patients for HCV infection and referral options based on HCV genotype.[12, 13]

In New Zealand, it is estimated that of those infected with HCV:[14]

- 55% have HCV genotype 1, which is subdivided into genotypes 1a and 1b
- 35% have genotype 3
- 8% have genotype 2
- 1% have genotypes 4 or 6

N.B. Genotype 5 was not detected in a New Zealand reference laboratory containing more than 2000 individual positive HCV test results

For patients infected with HCV genotype 1a or 1b, Viekira Pak-RBV or Viekira Pak, respectively, are now the first-line treatments once patients have been assessed to determine if management in primary care is appropriate (see: "Pre-treatment assessment for patients with HCV genotype 1 infections", page 15).[13]

For patients infected with HCV genotypes 2 to 6, interferon is no longer favoured as a treatment option. Neither Viekira Pak nor Viekira Pak-RBV is currently indicated for patients with HCV genotypes 2, 3, 5 or 6. Delaying treatment until other DAA medicines become available for these patients is recommended.[13, 15] **Patients with HCV genotypes 2, 3, 5 or 6 should not be treated with Viekira Pak or Viekira Pak-RBV**. In vitro data suggest these medicines will have reduced efficacy against HCV genotypes 2, 3, 5 and 6, and clinical trials are lacking.[17, 20, 21] Inappropriate prescribing of Viekira Pak or Viekira Pak-RBV may also lead to viral resistance which could limit the effectiveness of future treatment. Off-label use of the paritaprevir with ritonavir and ombitasvir and ribavirin (but not dasabuvir) components of Viekira Pak-RBV in patients with HCV genotype 4 is effective, however, these patients comprise a small minority of patients with HCV (see: "Off-label prescribing for patients with HCV genotype 4").

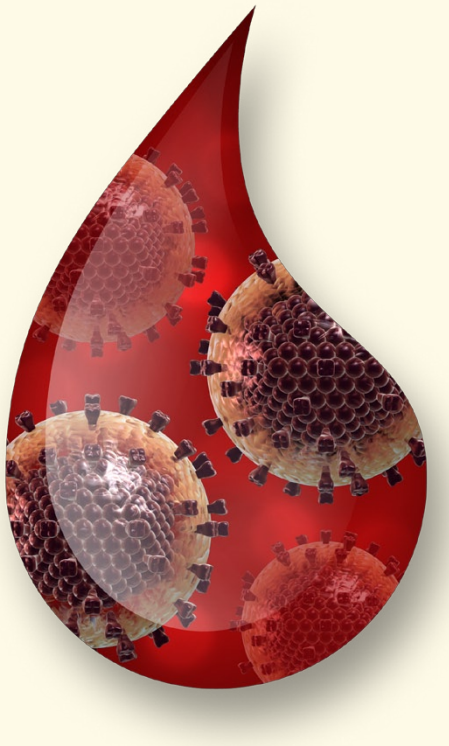
Recall patients for whom current subsidised treatment is unsuitable on an annual basis to reinforce lifestyle measures to avoid progression of liver disease, e.g. avoiding heavy alcohol or cannabis use, and to discuss any developments in DAA treatment.[13] Three-yearly assessments for liver cirrhosis, e.g. liver elastography, are recommended; patients who develop cirrhosis should be referred to secondary care.[13]

If patients with any HCV genotype have advanced liver disease or complications of HCV infection, they may be eligible for subsidised treatment with Harvoni (ledipasvir with sofosbuvir). These patients should be referred to secondary care for further assessment. For patients infected with HCV genotypes 2 to 6 where current subsidised treatments are not indicated and treatment delays are considered unacceptable, alternative options are listed in guidelines from the New Zealand Gastroenterology Society.[13] Referral to secondary care may be appropriate if patients wish to undergo interferon-based treatment.

Advice for patients to reduce the risk of HCV transmission

Information for patients infected with HCV is available from:

- Hepatitis Foundation of New Zealand: **www.hepatitisfoundation.org.nz/**
- Ministry of Health: **www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/hepatitis-c**
- A list of facilities involved in the New Zealand needle exchange programme is available from: **www.needle.co.nz/home_page.html/1**



Off-label prescribing for patients with HCV genotype 4*

Viekira Pak-RBV contains five medicines which are formulated into three tablets:[15]

- Paritaprevir with ritonavir and ombitasvir, co-formulated into a pink tablet
- Dasabuvir, in a beige tablet
- Ribavirin, in a blue tablet

The **paritaprevir, ritonavir and ombitasvir and ribavirin** components of Viekira Pak-RBV are effective in the treatment of patients with genotype 4 HCV infections although this is an unapproved indication. Patients with HCV genotype 4 and advanced liver disease may be eligible for treatment with Harvoni and should be referred to secondary care. Genotype 4 is estimated to account for only 0.5% of HCV infections in New Zealand.[14]

The three medicines in the pink tablet, paritaprevir, ritonavir and ombitasvir, and ribavirin,in the blue tablet, have been evaluated in a clinical trial in patients with HCV genotype 4. This study showed cure rates of 100% in patients treated with these three medicines and ribavirin, and 91% in patients treated with these three medicines without ribavirin.[16] Dasabuvir, in a beige tablet in Viekira Pak, was not included in this trial; in vitro data show this medicine is ineffective against HCV genotype 4.[17]

Prescribers and pharmacists can advise patients with genotype 4 HCV infections to take only the co-formulated paritaprevir, ritonavir and ombitasvir pink tablets and the blue ribavirin tablets from Viekira Pak-RBV. Dosing instructions for this modified regimen are shown in Table 1.

* If an approved medicine is prescribed outside of the approved indications, dose range or route of administration, this is an unapproved use of a medicine, also known as "off-label" prescribing.

Further information on the unapproved use of medicines is available from: "Upfront: Unapproved medicines and unapproved uses of medicines: keeping prescribers and patients safe", BPJ 51 (Mar, 2013).

Table 1: Off-label prescribing of modified Viekira Pak-RBV, for patients with HCV genotype 4 without cirrhosis.

	Morning	Evening
Viekira Pak + ribavirin (Viekira Pak-RBV) (Patients should discard the beige tablet)		
Patients with eGFR >90 mL/min/1.73 m²:		
Patients < 75 kg 1000 mg ribavirin	Four tablets: ■ Two combined paritaprevir/ritonavir/ombitasvir tablets, each containing 75 mg/50 mg/12.5 mg ■ Two ribavirin 200 mg tablets	Three tablets: ■ Three ribavirin 200 mg tablets
Patients ≥ 75 kg 1200 mg ribavirin	Five tablets: ■ Two combined paritaprevir/ritonavir/ombitasvir tablets, each containing 75 mg/50 mg/12.5 mg ■ Three ribavirin 200 mg tablets	Three tablets: ■ Three ribavirin 200 mg tablets
Patients with eGFR between 50–90 mL/min/1.73 m²:		
	Three tablets: ■ Two combined paritaprevir/ritonavir/ombitasvir tablets, each containing 75 mg/50 mg/12.5 mg ■ One ribavirin 200 mg tablet	One tablet: ■ One ribavirin 200 mg tablet

Conservative management is generally appropriate for acute infection

A watch and wait approach is reasonable for patients during the acute phase of infection, with ongoing HCV RNA testing for viral clearance and monitoring of liver function.[1] It is estimated that 20–25% of people infected with HCV clear the virus without medical intervention.[1] The majority of patients who clear the virus spontaneously do so within 12 weeks of infection.[6]

In the first few months of infection, viral RNA levels can fluctuate. Testing should continue for six months or until spontaneous clearance is confirmed or deemed unlikely. Patients are regarded as having cleared an HCV infection if there are at least two HCV RNA tests below the level of detection, performed at least one month apart.[1]

Acute HCV infection can be treated with interferon-based regimens, with a shorter duration, simpler treatment regimen and greater success rate than that used for long-term HCV infection; discussion with a gastroenterologist may be appropriate, e.g. if patients have more severe symptoms, hepatic impairment or co-infection with HIV.[1, 22]

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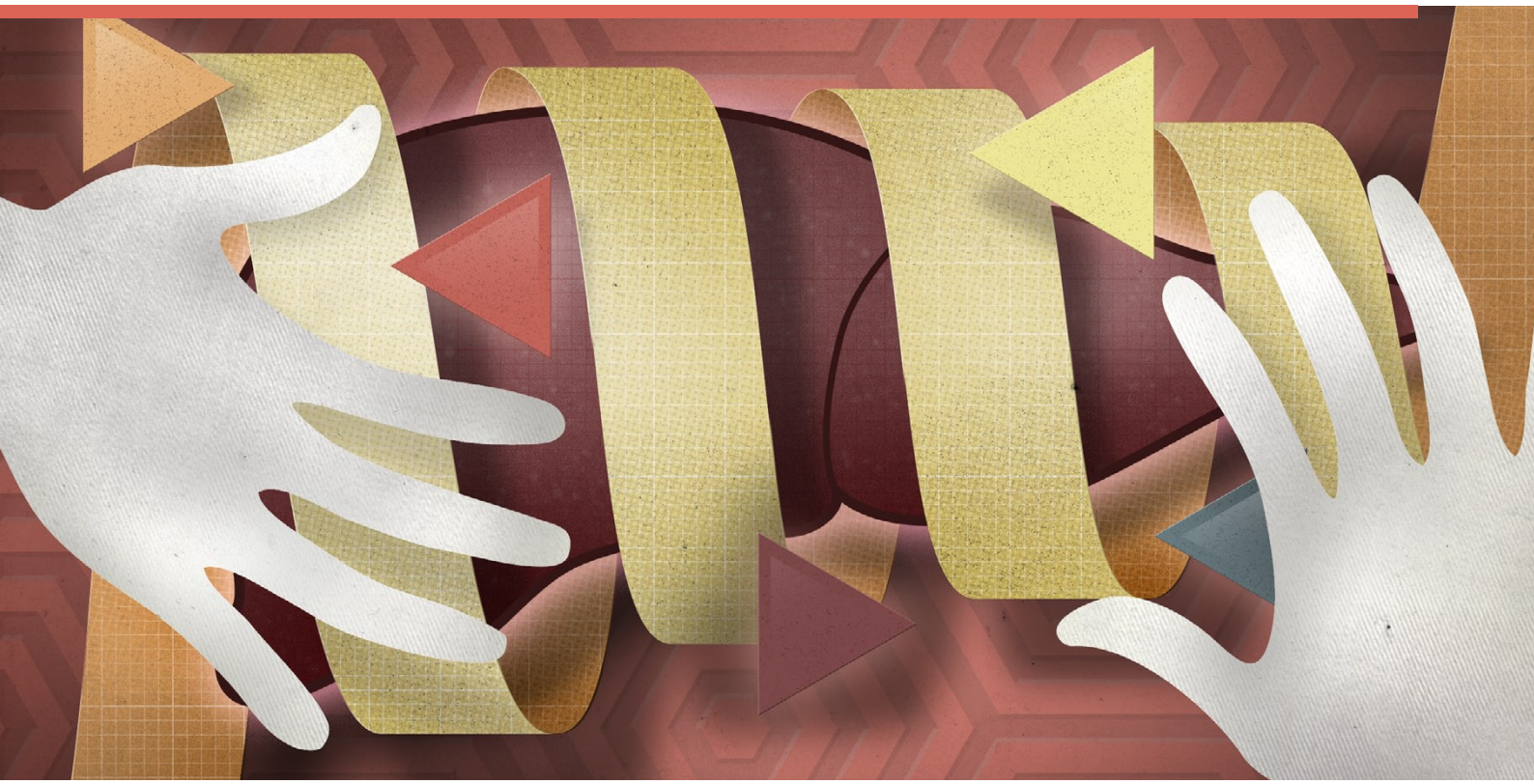

Pre-treatment assessment for patients with HCV genotype 1 infections

KEY PRACTICE POINTS

- Prior to treatment patients should be assessed for cirrhosis using clinical examination, laboratory tests and liver elastography scans which measure liver stiffness in response to ultrasound
- In regions where access to liver elastography is limited the ratio of aspartate aminotransferase (AST) levels to platelet concentration (APRI) may be considered as a pragmatic alternative method of assessment for cirrhosis
- Viekira Pak or Viekira Pak-RBV should NOT be taken by patients:[1]
  - Who are pregnant or have a partner who is pregnant
  - With decompensated, i.e. severe, cirrhosis
  - Who may have significant interactions with other medicines
- Viekira Pak-RBV should NOT be taken by patients with an eGFR < 30 mL/min/1.73 m^2; patients with an eGFR 30 – 50 mL/min/1.73m^2 should be discussed with a gastroenterologist; dose reductions are recommended in patients with an eGFR 50 – 90 mL/min/1.73 m^2

Discuss with a gastroenterologist or refer to secondary care patients with:

- Evidence of cirrhosis, which can include:
  - Clinical signs or symptoms, i.e. jaundice, abdominal pain and ascites
  - Laboratory findings, e.g. decreased serum albumin, elevated serum bilirubin, high INR (> 1.3)
  - Liver elastography results suggestive of severe fibrosis or cirrhosis (see below)
  - An APRI score ≥ 1.0
- Uncertain results from investigations for liver pathology
- Cryoglobulinaemia, an immune complex disorder which can result in systemic vasculitis
- eGFR < 50 mL/min/1.73 m^2
- Hepatitis B or HIV

Deciding whether treatment can be initiated in primary care

Patients with hepatitis C require pre-treatment assessment to establish if they can be safely treated in primary care with directly acting antivirals (DAAs). Pre-treatment assessment also indicates which patients require long-term monitoring once treatment has finished.

Laboratory tests and investigations recommended prior to starting treatment include:[1, 2]

- Liver elastography
- Full blood count
- Liver function including AST
- INR
- Renal function
- Hepatitis B and HIV
- Pregnancy test for women of reproductive age

If the patient has symptoms or signs consistent with systemic vasculitis then request a rheumatoid factor test, followed by cryoglobulins if positive.[3]

DAA regimens are safer in patients without liver impairment

Assessment of liver function **prior** to initiating treatment, is required as cirrhosis increases the risks of using Viekira Pak or Viekira Pak-RBV.[1] Viekira Pak is contraindicated in patients with decompensated cirrhosis or severe hepatic impairment and should be used with caution in compensated cirrhosis due to the potential for medicine-induced liver damage.[4, 5]

Assessing the presence of liver complications

A combination of clinical examination, laboratory tests and liver imaging (Table 1) is used to determine the severity of any liver disease.[1, 4]

In patients with long-term HCV infection DAA treatment should not be initiated until an assessment for the presence of cirrhosis has been performed.[1] This is because the risk of DAA treatment exacerbating underlying liver pathology in patients with cirrhosis is greater than the risk to the patient of untreated HCV infection, which has a slow progression.[1]

Liver elastography

Liver elastography performed by Fibroscan or shear wave ultrasound is the preferred investigation for detection of fibrosis or cirrhosis in all patients with HCV infection. It is strongly recommended that this investigation be conducted in all patients with hepatitis C, wherever possible, before treatment with DAA medicines is initiated. If liver elastography is performed after treatment with DAAs has begun changes to the liver are likely to make the result unreliable. In situations where the patient's HCV infection is known to be recent, e.g. in a patient with recent onset injectable drug use and previously negative serology, liver elastography is not necessary.[7]

The availability of liver elastography varies throughout the country. There are currently ten Fibroscan machines in New Zealand and portable machines are being purchased; clinicians are advised to contact a local radiology service to determine if this type of imaging is available in their DHB. In Northern DHBs, Fibroscans can be requested by general practitioners through e-referrals and the current waiting time is less than two weeks.

Elastography measures the velocity of a low-frequency wave which correlates with the degree of liver stiffness which is increased in patients with fibrosis.[4] Liver biopsy is typically

Table 1: Risk factors for cirrhosis based on clinical examination and patient history.[2, 4, 8–11]

Risk factors for cirrhosis include:	Features consistent with cirrhosis include:	Symptoms and signs of decompensated cirrhosis include:	Laboratory results consistent with cirrhosis are:
■ Duration of HCV infection of > 10 years ■ Male sex ■ A history of excessive alcohol consumption or heavy cannabis use ■ BMI ≥ 25 kg/m^2 ■ Type 2 diabetes ■ Other liver disease, e.g. non-alcoholic fatty liver disease	■ Signs of portal hypertension: splenomegaly or caput medusae (dilated superficial abdominal veins) ■ Spider naevi ■ Leukonychia (white spots on nails)	■ Jaundice ■ Ascites ■ Abdominal pain or tenderness on palpation, with fever or chills, which could indicate spontaneous bacterial peritonitis ■ Confusion ■ Dyspnoea, digital clubbing or cyanosis; symptoms and signs of hepatopulmonary syndrome ■ Variceal haemorrhage ■ Low platelet count	■ Decreased serum albumin ■ An INR > 1.3 ■ Elevated serum bilirubin, e.g. >20 micromol/L ■ An APRI ≥ 1.0 (cirrhosis cannot be excluded and referral to secondary care is recommended) ■ A score of F3–F4 on Fibrotest or Fibrosure (see below)

reserved for patients where there is uncertainty regarding the cause of cirrhosis detected with imaging.[4, 12]

Either a Fibroscan machine or an ultrasound machine capable of "shear wave" assessments is used to perform liver elastography.[1, 13] A standard liver ultrasound is inappropriate for liver assessment in patients with HCV infection. Elastography testing takes approximately ten minutes, with results available immediately.

Liver elastography results will report a score ranging from F0, no fibrosis, to F4, severe fibrosis (Table 2):[7]

- **Scores F0–F2 indicates treatment in primary care** with Viekira Pak or Viekira Pak-RBV is appropriate if there is no evidence of cirrhosis (Table 2)
- **Scores F3 or F4 indicate patients should be referred to secondary care**

The reliability of elastography is decreased or the scan may be unsuccessful in patients with:[12]

- Obesity
- Ascites
- A narrow intercostal space

For the small number of patients where liver elastography is unsuccessful, clinical examination and blood tests are used (see below) to determine if cirrhosis is present; discussion with a gastroenterologist may be necessary.[1]

Assessing liver pathology if liver elastography is not available

In some regions of New Zealand access to liver elastography may be limited. In these situations prescribers in primary care may consider calculating an APRI ratio as a pragmatic alternative method to assess patients for the likelihood of cirrhosis. This should only be considered, however, if patients are unable to access liver elastography.

APRI scores:[1]

- < 1.0 are consistent with a patient not having cirrhosis and clinicians in primary care should be confident that treatment can be initiated
- ≥ 1.0 indicate that the patient should be referred to secondary care as they may have cirrhosis

For example, a female patient with:

- A low platelet count of 120×10^9/L (reference range: $150–450 \times 10^9$/L) [10]

AND

- A mildly elevated AST value of 50 U/L (reference range 10–35 U/L) [10]
- Has an APRI score of:
  - APRI = AST as % of upper limit of normal/platelet count
  - = (50/35) × 100 / 120
  - = 1.43 × 100 / 120
  - = 1.19

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

The APRI score cannot be used to assess the likelihood of cirrhosis in patients with acute hepatitis as they often have elevated AST levels.[12]

Commercially available testing panels, e.g. Fibrotest and Fibrosure, may be used to assess serum fibrosis markers if imaging is not available. These tests are not, however, publicly funded and are not available at many laboratories in New Zealand.

Non-hepatic assessment prior to initiating DAA regimens

Ribavirin should not be used in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 and treatment options should be discussed with a gastroenterologist.[1] For patients with an eGFR of 30–50 mL/min/1.73 m^2 treatment with ribavirin may be appropriate and these patients should be discussed with a gastroenterologist. For patients with an eGFR between 50–90 mL/min/1.73 m^2 reductions in ribavirin dosing are required.

Table 2: Treating or referring on the basis of liver assessments[1, 7]

Treatment in primary care is appropriate for patients with ALL of the following:	Referral to a gastroenterologist is appropriate for patients with ANY of the following:
■ Clinical examination does not suggest cirrhosis	■ Clinical examination consistent with cirrhosis
■ Scores of F0–F2 on liver elastography	■ Scores of F3–F4 on liver elastography
■ Laboratory results which do not suggest cirrhosis	■ Laboratory results consistent with cirrhosis

Table 3: Examples of medicines which are contraindicated or should be used with caution in patients taking DAAs*.[1, 5, 17, 18]

Medicines which are contraindicated	Medicines that should be used with caution
■ Amiodarone ■ Atorvastatin ■ Carbamazepine ■ Clarithromycin ■ Colchicine; if patient has renal or hepatic impairment ■ Ergotamine and its derivatives ■ Ethinylestradiol-containing medicines ■ Fusidic acid (sodium fusidate) ■ Gemfibrozil ■ Midazolam ■ Phenobarbital ■ Phenytoin ■ Rifampicin ■ Quetiapine ■ Salmeterol ■ Sildenafil used continuously for the treatment of pulmonary arterial hypertension ■ Simvastatin ■ Triazolam ■ Triazole antifungals	■ Calcium channel blockers, e.g. amlodipine, diltiazem; dose reductions of these medicines may be necessary ■ Candesartan ■ Colchicine; patients with normal renal or hepatic function may require a reduction in colchicine dosing ■ Digoxin; consider more frequent monitoring of serum levels ■ Erythromycin ■ Fluticasone ■ Furosemide; dose reductions for this medicine may be necessary ■ Pravastatin; dose reductions for this medicine may be necessary ■ Rosuvastatin; dose reductions for this medicine may be necessary ■ Sildenafil used intermittently for erectile dysfunction; increased potential for adverse effects ■ Warfarin; consider more frequent monitoring of INR

* This table is not exhaustive; further information is available from: **www.hep-druginteractions.org/checker** and medicine data sheets[17, 19]

Patients with cryoglobulinaemia should be referred to secondary care

Long-term HCV infection can cause complications, including cryoglobulinaemia, leading to systemic vasculitis due to deposition of immune complexes in small blood vessels. Approximately 30% of patients with HCV infection will have circulating cryoglobulins, with approximately 10% of these patients developing systemic vasculitis.[14] The most common manifestation is a purpuric skin rash in the lower limbs, most evident in cold weather.[3] Renal impairment from glomerulonephritis and abdominal pain from enteric vasculitis are less common.[3] Testing for cryoglobulinaemia can begin with rheumatoid factor, and if positive, followed by testing for serum cryoglobulins.[3] Patients with cryoglobulinaemia should be discussed with a gastroenterologist as treatment with Harvoni may be appropriate.[4, 5]

Ribavirin causes anaemia, this is particularly important in patients with significant cardiovascular disease

An assessment for cardiovascular disease, including an ECG, is recommended in patients aged over 50 years prior to treatment with ribavirin.[4] Ribavirin causes anaemia in many patients and adverse effects may be greater in those with significant cardiovascular disease, e.g. symptomatic ischaemic heart disease, a recent cardiovascular event or peripheral claudication. Treatment and monitoring recommendations for patients who develop anaemia during ribavirin treatment differ for patients with and without cardiovascular disease (see: "Monitoring patient safety during treatment", page 22).

Are patients co-infected with hepatitis B or HIV?

Referral to secondary care is strongly recommended for all patients with HCV who are co-infected with either hepatitis B or HIV. There is the possibility that hepatitis B may be activated following treatment for HCV.[4, 5] Serious interactions may occur between DAAs and antiviral medicines used to treat HIV.

Ensure that patients' vaccinations against hepatitis A and B are up to date to reduce the progression of any liver disease.[15] Pneumococcal vaccination is recommended but not funded for individuals with chronic liver disease.[16]

DAA regimens are contraindicated during pregnancy

Ribavirin is a potent teratogen and should not be used if the patient, or their partner, is pregnant or at risk of becoming pregnant.[4, 5] There is a lack of safety data regarding treatment with Viekira Pak during pregnancy and contraception is recommended for male and female patients taking Viekira Pak with or without ribavirin.[4] For patients taking ribavirin, two forms of effective contraception, i.e. condoms plus another form of contraception, is recommended continuing for six months after treatment has finished.[4, 5] Increases in transaminases have been observed in females taking

DAA regimens and ethinylestradiol-containing medicines concurrently, i.e. for contraception, treatment of menopausal symptoms or osteoporosis prevention. Ethinylestradiol-containing medicines should be stopped prior to treatment and patients switched to an alternative medicine.[2, 4]

Patients who are pregnant should delay initiation of DAA treatment until breastfeeding has ceased as treatment is contraindicated due to a lack of safety data.[1]

Check potential medicine interactions prior to prescription

A number of important interactions are possible between Viekira Pak or ribavirin and other commonly prescribed medicines (Table 3), including statins and asthma or COPD medicines.

Paritaprevir, one of the medicines in Viekira Pak, is metabolised in the liver by CYP3A4. Viekira Pak also contains ritonavir, an inhibitor of CYP3A4, in order to boost the antiviral activity of paritaprevir. Therefore, co-administration of other medicines which are metabolised by CYP3A4 will result in increased plasma levels of these medicines.

St John's wort induces CYP3A4 and can reduce antiviral efficacy and patients should avoid taking supplements containing this herb.[5]

Prior to prescribing, check for potential medicine interactions with an online tool:

- The University of Liverpool hepatitis medicines interactions checker provides detailed information on potential interactions: **www.hep-druginteractions.org/checker**
  - Select "OBV/PTV/r+DSV" (Viekira Pak if "Trade" button selected) or "ribavirin" from the left hand panel
- The NZF interactions checker: **www.nzf.org.nz**
  - Select "Interactions" next to the search bar and search for medicine names, e.g. "ombitasvir+paritaprevir+ritonavir" or "dasabuvir" (Viekira Pak) or "ribavirin" and then other medicines
- Discussion with a gastroenterologist is recommended if patients have medicine interactions which cannot be avoided

In patients where a potential interaction with Viekira Pak has been identified, consider if the current regimen can be temporarily withdrawn, replaced with another medicine or the dose reduced.

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Management of **patients taking directly-acting antivirals (DAAs)**

KEY PRACTICE POINTS

- Patients with HCV infection take four tablets per day for Viekira Pak treatment, and six to ten tablets per day for Viekira Pak-RBV
- Fatigue, headache and nausea are the most common adverse effects experienced by patients
- Clinicians managing patients in primary care should monitor full blood counts for patients taking Viekira Pak-RBV; it is not uncommon for patients taking ribavirin to have haemoglobin levels fall to 90–95 g/L:
  - If haemoglobin levels fall below 100 g/L, ribavirin doses should be reduced and the ribavirin component of treatment withdrawn if levels fall below 85 g/L.
  - For patients with significant cardiovascular disease ribavirin should be withdrawn if haemoglobin levels fall below 100 g/L
  - Treatment with the Viekira Pak should continue for all patients if ribavirin is withdrawn

Ensuring optimal treatment for patients with HCV

Following successful treatment of HCV infection patients experience improvements in their quality of life including feelings of general wellbeing and improved physical health. Some patients may report benefits during treatment.[1] Clinicians should notice improved liver function tests at the end of treatment and can expect slowed progression or a reduction in fibrosis in the coming years. In patients with advanced liver disease, reductions in portal hypertension and splenomegaly may occur, as well as a 70% reduction in the risk of hepatocellular carcinoma and a 90% reduction in the risk of mortality from liver disease.[2–4] Patients with cirrhosis require monitoring once treatment has finished for complications such as hepatocellular carcinoma. Successful treatment reduces the incidence of non-hepatic complications, such as cryoglobulinaemia or non-Hodgkin lymphoma, and eliminates the risk of transmitting HCV to others.[2]

Initiating treatment in primary care

The HCV genotype determines whether the use of ribavirin is indicated:[5]

- HCV genotype 1a: Viekira Pak-RBV for 12 weeks
- HCV genotype 1b: Viekira Pak for eight weeks

Patients with HCV genotype 1a infection

Viekira Pak-RBV should be prescribed to all patients with HCV genotype 1a infections, where possible, to increase the likelihood that treatment will be curative. If patients infected with HCV genotype 1a have contraindications to ribavirin use, e.g. eGFR < 30 mL/min/1.73 m^2, Viekira Pak alone is a potential alternative. Patients with HCV genotype 1a infection who are treated with Viekira Pak alone have a cure rate of 90%, compared to 97% for patients also taking ribavirin.[6]

Patients with HCV genotype 1b infection

These patients can be treated in primary care with an eight week course of Viekira Pak. Previously, a 12 week course was recommended. However, a clinical trial involving 162 patients with HCV genotype 1b infection, without cirrhosis, was published in July, 2017 and reported that 98% of patients achieved a cure with an eight week course of treatment, similar to cure rates achieved with 12 weeks of treatment. Therefore, patients with HCV genotype 1b infection who are suitable candidates for treatment in primary care, i.e. have not previously undergone unsuccessful treatment for HCV and do not have evidence of cirrhosis, can now be prescribed an eight week course of Viekira Pak.[2]

How to prescribe Viekira Pak and Viekira Pak-RBV

Clinicians need to submit a distribution request form to PHARMAC for patients to receive funded Viekira Pak or Viekira Pak-RBV, see: **www.pharmac.govt.nz/assets/viekira-pak-form.docx.**

The form should include the patient's and clinician's details, which medicine regimen is being prescribed and the nearest accredited pharmacy for distribution (see below).

Clinicians should also provide patients with a prescription to present to the pharmacy when the medicine is dispensed.

Dispensing of Viekira Pak and ribavirin occurs at accredited pharmacies

Only accredited pharmacies can dispense funded Viekira Pak or Viekira Pak-RBV. Prescribers will be asked to specify on the form which accredited pharmacy the patient will collect the medicine from. PHARMAC will then arrange for delivery and the pharmacy will arrange a collection time with the patient.

For a list and map of accredited pharmacies, see: **www.viekira.co.nz/locations**

Alternatives are available for patients unable to access an accredited pharmacy

For patients who are unable to access an accredited pharmacy, medicines can be delivered to an appropriate alternative location, e.g. a general practice, for storage until collection. This is available by special arrangement: call PHARMAC on **0800-023-588 (option 3)** for details.

For further information on prescribing and distribution, see: **www.pharmac.govt.nz/medicines/my-medicine-has-changed/hepatitis-c-treatments/**

Treatment of HCV requires morning and evening dosing

Patients taking Viekira Pak will have four tablets per day (Table 1). The paritaprevir, ritonavir and ombitasvir are co-formulated into a single tablet, taken as two tablets in the morning, and dasabuvir is taken as a separate tablet, twice daily.

Patients taking Viekira Pak-RBV will have six to ten tablets per day (Table 1). If indicated, ribavirin is prescribed, twice daily, alongside Viekira Pak. Reductions in ribavirin dosing are required for patients with a eGFR < 90 mL/min/1.73m^2 due to the increased risk of adverse effects. Patients with an eGFR 30–50 mL/min/1.73m^2 should be discussed with a gastroenterologist . Ribavirin tablets are 200 mg each, and the total dose depends on body weight and renal function:

- Patients with an eGFR > 90 mL/min/1.73 m^2:
  - Patients < 75 kg: 1000 mg ribavirin per day in two divided doses (400 mg in the morning + 600 mg at night)
  - Patients ≥ 75 kg: 1200 mg ribavirin per day in two divided doses (600 mg twice daily)
- Patients with an eGFR between 50–90 mL/min/1.73 m^2 require reduced dosing to 200 mg ribavirin, twice daily. Ribavirin is contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Off-label prescribing of Viekira Pak-RBV to patients with an eGFR 30 – 50 mL/min/1.73m^2 routinely occurs in secondary care.

Mild adverse effects are common but treatment can be continued

The most common adverse effects experienced by patients taking Viekira Pak, with or without ribavirin, are:[6, 8, 9]

- Fatigue in up to 46% of patients
- Headache in up to 33% of patients
- Nausea in up to 24% of patients

Pruritis, insomnia, diarrhoea, fatigue and weakness each occur in 10–20% of patients. There is no specific guidance for

Table 1: DAA dosing regimens for HCV infections[7]

	Morning	Evening
Viekira Pak only		
	Three tablets: ■ Two combined paritaprevir/ritonavir/ombitasvir tablets, each containing 75 mg/50 mg/12.5 mg ■ One dasabuvir 250 mg tablet	One tablet: ■ One dasabuvir 250 mg tablet
Viekira Pak + ribavirin (Viekira Pak-RBV)		
Patients with eGFR >90 mL/min/1.73 m²:		
Patients < 75 kg 1000 mg ribavirin	Five tablets: ■ Two combined paritaprevir/ritonavir/ombitasvir tablets, each containing 75 mg/50 mg/12.5 mg ■ One dasabuvir 250 mg tablet ■ Two ribavirin 200 mg tablets	Four tablets: ■ One dasabuvir 250 mg tablet ■ Three ribavirin 200 mg tablets
Patients ≥ 75 kg 1200 mg ribavirin	Six tablets: ■ Two combined paritaprevir/ritonavir/ombitasvir tablets, each containing 75 mg/50 mg/12.5 mg ■ One dasabuvir 250 mg tablet ■ Three ribavirin 200 mg tablets	Four tablets: ■ One dasabuvir 250 mg tablet ■ Three ribavirin 200 mg tablets
Patients with eGFR between 50–90 mL/min/1.73 m²:		
	Four tablets: ■ Two combined paritaprevir/ritonavir/ombitasvir tablets, each containing 75 mg/50 mg/12.5 mg ■ One dasabuvir 250 mg tablet ■ One ribavirin 200 mg tablet	Two tablets: ■ One dasabuvir 250 mg tablet ■ One ribavirin 200 mg tablet

managing adverse effects in patients taking DAAs and patients can generally be encouraged to persevere with treatment. In clinical trials of Viekira Pak, with or without ribavirin, a maximum of 2% of patients stopped treatment due to adverse effects.[6, 8, 9] Patients should immediately contact a health professional if they develop signs of hepatotoxicity including, fatigue, weakness, loss of appetite, nausea, vomiting, or jaundice.[2, 10]

Patients may drink up to two standard alcoholic drinks per day while taking Viekira Pak, however, those with evidence of severe fibrosis or cirrhosis should be advised to avoid alcohol.[11] During treatment the potency of some recreational drugs will be increased due to changes in hepatic metabolism, increasing the risk of overdose.[7, 12]

Monitoring patient safety during treatment

A full blood count and liver function test should be requested before treatment with Viekira Pak or Viekira Pak-RBV is initiated (Table 2). In patients being managed in primary care **monitoring of liver function during treatment is not required in patients without cirrhosis**. Any elevations in

Table 2: Recommended testing in primary care for patients without cirrhosis before, during and after treatment for HCV infection adapted from[7,11,13]

	Patients taking Viekira Pak	Patients taking Viekira Pak + ribavirin*
Before treatment	Creatinine and electrolytes FBC LFTs INR HCV RNA assay**	
During treatment		
Week two	N/A †	FBC
Week four	N/A †	FBC
Week eight	N/A †	FBC
After treatment		
12 weeks after treatment#	HCV RNA assay LFTs	HCV RNA assay LFTs

* Ribavirin may cause elevation of uric acid; levels should be monitored in patients at risk of gout.[14]

** Depending on when the test was last performed. For patients with a long-term infection, the HCV RNA assay is not necessary if it was performed in the last five years.[7] HCV RNA assays during treatment are not necessary, however, they can be requested if patient adherence is a concern; most patients should achieve undetectable HCV RNA levels during treatment.

† LFTs are not routinely required in patients without cirrhosis, i.e. those managed in primary care. LFTs are recommended by the New Zealand Society of Gastroenterology guidelines at weeks two, four and eight of treatment as this guidance includes patients with cirrhosis who are managed in secondary care.

If the HCV RNA assay at 12 weeks after treatment is positive, patients should be discussed with a gastroenterologist.[7] A negative result indicates cure.

Table 3: Monitoring and dosing recommendations during ribavirin treatment[14]

Patients without vascular disease	
If haemoglobin levels fall to 85–100 g/L	Reduce ribavirin dose to 600 mg, daily (200 mg in the morning and 400 mg at night)
If haemoglobin levels fall to < 85 g/L	Stop ribavirin treatment; continue Viekira Pak Monitor patient every two weeks – haemoglobin levels should return to normal after treatment is withdrawn.
Patients with significant vascular disease*	
If haemoglobin levels fall to < 100 g/L	Stop ribavirin treatment; continue Viekira Pak Monitor patient every two weeks – haemoglobin levels should return to normal after treatment is withdrawn.

* Significant vascular disease includes e.g. recent myocardial infarction or transient ischaemic attack, symptomatic ischaemic heart disease or peripheral claudication

liver enzymes are likely to be mild, transient and will not affect patient management. Patients taking Viekira Pak-RBV require monitoring of haemoglobin at weeks two, four and eight of treatment. More frequent testing may be required for some patients if adverse effects such as anaemia develop.

Ribavirin often causes mild anaemia

Mild haemolytic anaemia is common in patients taking ribavirin and typically resolves within four weeks of stopping treatment.[5] The clinical significance of anaemia is determined by the overall health of the patient. Reductions in ribavirin dosing are necessary if the patient's haemoglobin falls to < 100 g/L (Table 3).[7] If the patient's haemoglobin level falls to < 85 g/L then treatment with ribavirin should be stopped.[14] Extra caution is required in patients with significant vascular disease, e.g. recent myocardial infarction, stroke or transient ischaemic attack, symptomatic ischaemic heart disease or peripheral claudication (Table 3);[7] ribavirin should be withdrawn if the patient's haemoglobin level falls by > 20 g/L.[14] In clinical trials, patients who required dose reductions of ribavirin due to anaemia had the same rates of cure as patients who maintained the same dosing throughout treatment.[9, 15]

The average reduction of haemoglobin in patients taking Viekira Pak + ribavirin is reported to be 24 g/L.[11] Only 3–7% of patients are likely to need their ribavirin dose lowered due to haemoglobin levels falling below 100 g/L.[6, 8, 9]

If ribavirin is withdrawn patients should be instructed to continue with the Viekira Pak component of treatment.

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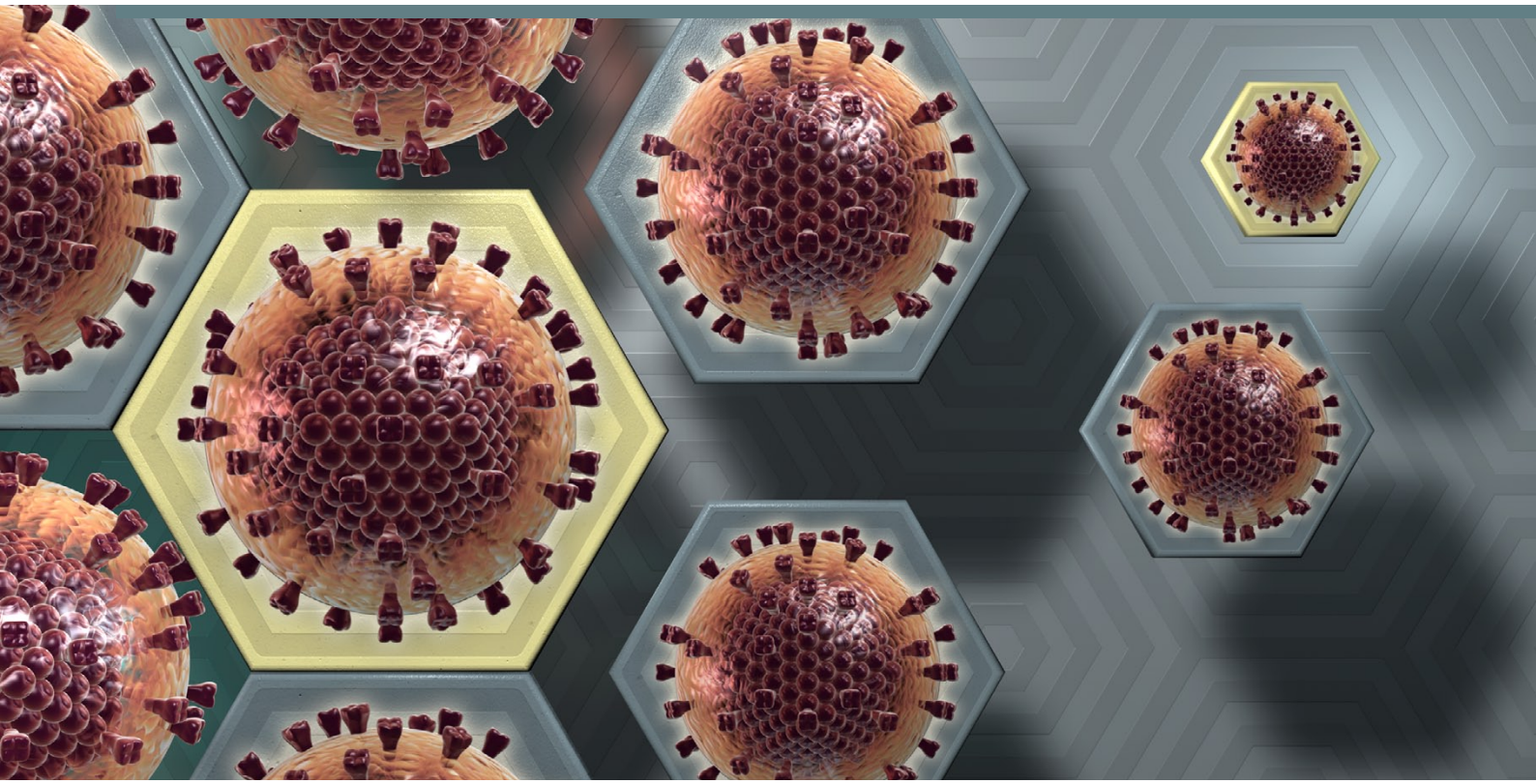

Follow-up after treatment is completed

KEY PRACTICE POINTS

- Patients who have taken ribavirin should continue to use two forms of effective contraception for six months following treatment
- At least nine out of ten patients should have undetectable HCV RNA 12 weeks after finishing treatment, indicating HCV infection has been cured
- Patients without cirrhosis and with normal liver function tests following treatment do not require further follow-up
- Patients with cirrhosis should undergo monitoring, ideally every six months, for the development of hepatocellular carcinoma and where appropriate, oesophageal varices

Identifying patients who require monitoring

Completion of treatment with Viekira Pak, with or without ribavirin, is likely to be successful in at least nine out of ten patients with either HCV genotype 1a or 1b. Undetectable HCV RNA with a PCR assay 12 weeks after treatment indicates cure.[1]

When requesting HCV RNA testing at 12 weeks, remind patients who have taken ribavirin of the need to use two forms of effective contraception for six months following treatment. Patients who discontinued an ethinylestradiol-containing contraceptive may switch back to these medicines two weeks after finishing treatment.[2]

Patients who have virologic failure during treatment or relapse post-treatment should be discussed with a gastroenterologist.[2]

Follow-up testing of liver disease after treatment of HCV infection

After successful treatment, patients with normal liver function tests and without cirrhosis do not require additional follow-up.[1] For patients without cirrhosis, but with ongoing raised liver

function results, other causes of elevated liver enzymes may need to be investigated. This could include other medicines, over-the-counter supplements, alcohol or recreational drug use, non-alcoholic fatty liver disease or inherited conditions, e.g. haemochromatosis.[1]

In patients with cirrhosis, liver ultrasound and alpha fetoprotein (AFP) tests at six-monthly intervals are recommended to assess for hepatocellular carcinoma.[3, 4] Patients with cirrhosis with low platelet counts or evidence of portal hypertension on ultrasound should also have an endoscopy every one to two years to assess for oesophageal varices.[4]

For further information on helping patients with alcohol misuse, see: **www.bpac.org.nz/BPJ/2016/May/alcohol.aspx**

Post-treatment monitoring for patients at high risk of re-infection

Patients who continue to use injectable drugs or have other ongoing risk factors should be monitored for HCV infection with annual HCV RNA tests.[1] In patients who have been successfully treated for HCV infection, serology cannot be used to test for re-infection as the majority of patients remain seropositive for years following successful treatment.[5] The presence of HCV antibodies, however, does not confer immunity to re-infection. Discussion with a gastroenterologist is recommended if patients become re-infected.

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