Hepatitis C management in primary care has changed

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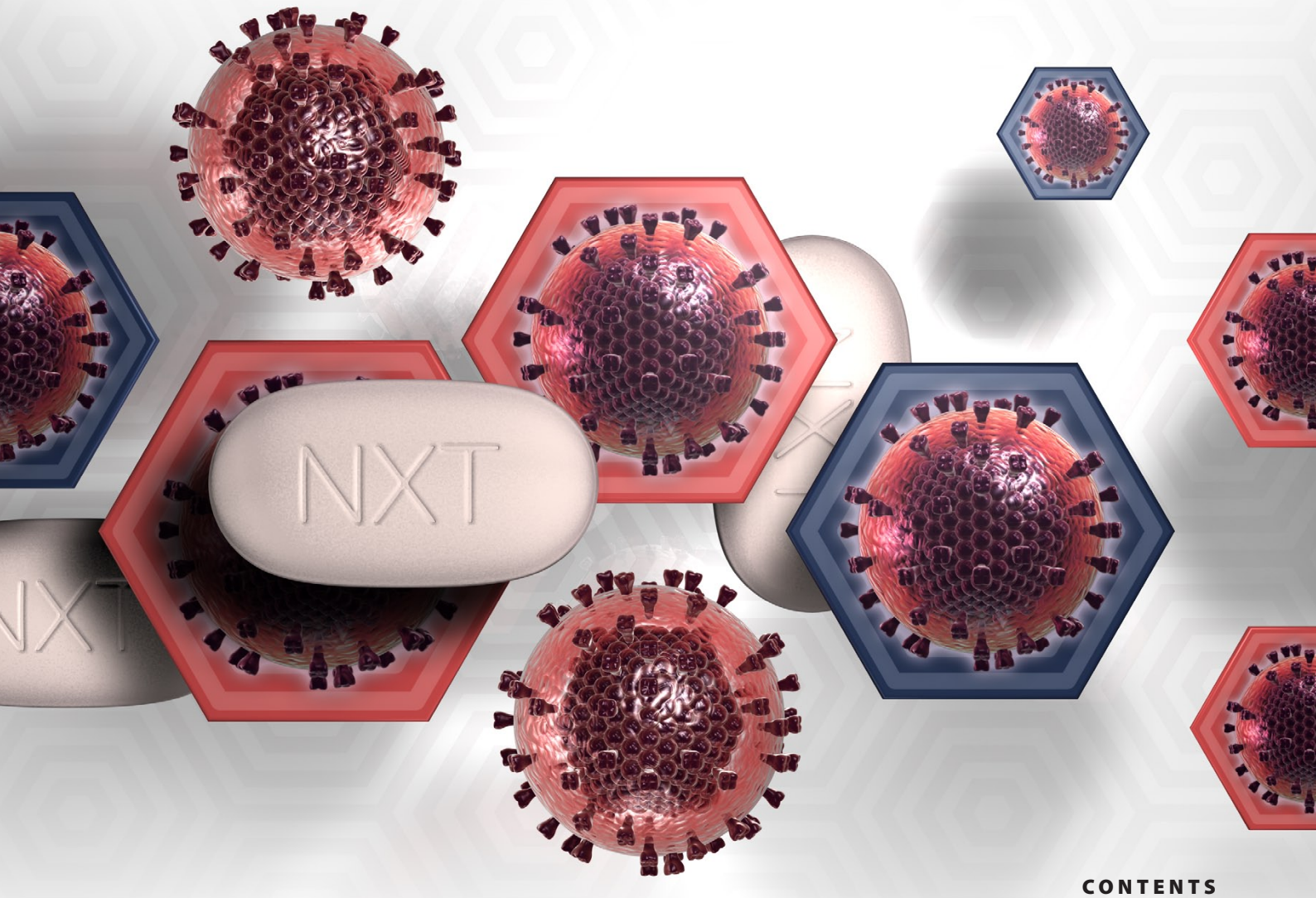

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Hepatitis C management in primary care: an overview

A new direct-acting antiviral (DAA) oral regimen for the treatment of hepatitis C, glecaprevir + pibrentasvir (Maviret) will be subsidised without restriction from 1 February, 2019 and will replace Viekira Pak* regimens, which are being delisted.[1] General practitioners have been able to prescribe Viekira Pak and Viekira Pak-RBV since 1 October, 2016, to treat patients infected with HCV genotypes 1a and 1b (approved indications) and genotype 4 (unapproved indication). Glecaprevir + pibrentasvir can be prescribed to patients with hepatitis C virus (HCV) infection due to any of the HCV genotypes.

* Viekira Pak (paritaprevir, ritonavir and ombitasvir with dasabuvir); Viekira Pak-RBV (the same combination with the addition of ribavirin)

More patients can now benefit from treatment

There are approximately 50,000 people with chronic HCV infection in New Zealand who could benefit from subsidised treatment with glecaprevir + pibrentasvir.[2]

In New Zealand, approximately 56% of HCV infections are caused by genotype 1, approximately 35% due to genotype 3 and 8% due to genotype 2.[3] Genotypes 4 and 6 together account for less than 2% of HCV infections, and genotype 5 does not appear to be present in New Zealand.[3] All patients with HCV infection without evidence of cirrhosis can now be treated in primary care with subsidised glecaprevir + pibrentasvir, including patients with less severe disease due to genotypes 2, 3, and 6, who were previously ineligible for subsidised treatment.

Treatment with glecaprevir + pibrentasvir is shorter and simpler for clinicians and patients than Viekira Pak regimens

Glecaprevir + pibrentasvir is taken as a once daily regimen of three tablets, for eight weeks, regardless of HCV genotype. Viekira Pak regimens required patients to take six to ten tablets per day, with morning and evening dosing, for eight to twelve weeks, depending on patient characteristics and HCV genotype.

HCV genotype testing is no longer required

Glecaprevir + pibrentasvir can be prescribed to patients infected with any HCV genotype, therefore genotype testing prior to initiating treatment is no longer required.

Treatment with ribavirin is no longer required

Patients with genotype 1a infection previously required the addition of ribavirin to their treatment regimen (Viekira Pak-RBV). The use of ribavirin is associated with adverse effects such as anaemia and requires strict use of two forms of contraception during and for six months following treatment due to its teratogenic potential. Ribavirin is not required for patients with genotype 1a infection receiving glecaprevir + pibrentasvir treatment.

Patients should present prescriptions for glecaprevir + pibrentasvir to an enrolled pharmacy

Prescriptions for glecaprevir + pibrentasvir should be given to the patient to present to a pharmacy, as is typically the case for most medicines subsidised in the community. Similar to the arrangements that have been in place for Viekira Pak regimens, glecaprevir + pibrentasvir will be available at enrolled pharmacies.[4] There is no co-payment required from patients for glecaprevir + pibrentasvir prescriptions. For patients prescribed Viekira Pak regimens or Harvoni, prescriptions need to be sent directly to PHARMAC.

From 1 February, 2019, a list of pharmacies enrolled to dispense glecaprevir + pibrentasvir will be available at: **www.marivet.co.nz**

An online training module for pharmacies who wish to enrol is available at: **www.abbviecarepharmacy.co.nz**

Viekira Pak regimens will be delisted

From 1 February, 2019, Viekira Pak and Viekira Pak-RBV will no longer be subsidised.[4] Patients who have already begun treatment with these regimens before this date can continue treatment and finish their prescribed course of medicines.[1] Patients who have already been prescribed a Viekira Pak regimen, but have not presented to an enrolled pharmacy to start their course of treatment, will be able to present to an accredited pharmacy between 1 February, 2019 and 30 April, 2019 to start treatment and receive their prescribed course of Viekira Pak regimen.[4] Patients who have previously been treated with Viekira Pak regimens and have no evidence of HCV viral activity after treatment do not need to be re-treated with glecaprevir + pibrentasvir.

Patients initiating HCV treatment on or after 1 February, 2019 should be prescribed glecaprevir + pibrentasvir.[1]

Ledipasvir + sofosbuvir (Harvoni) continues to be subsidised for patients with advanced disease

Ledipasvir + sofosbuvir is subsidised for patients who meet Special Authority criteria, including patients with advanced liver complications, e.g. decompensated cirrhosis or awaiting a liver transplant. Applications for subsidised ledipasvir + sofosbuvir are likely to be made in secondary care and will be reviewed by the PHARMAC Hepatitis C Treatments Panel.

Guidance for primary care has been updated to reflect subsidy changes

This resource provides prescribers in primary care with comprehensive guidance on the management of patients with hepatitis C (Figure 1). 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.

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

1. Test patients at high risk of infection
2. Conduct pre-treatment assessments
3. Monitor and follow-up patients prescribed glecaprevir + pibrentasvir

Further information for patients and clinicians:

- 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**
- Information for patients with hepatitis C from the Ministry of Health: **www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/hepatitis-c**
- PHARMAC information on HCV medicines: **www.pharmac.govt.nz/medicines/my-medicine-has-changed/hepatitis-c-treatments**
- Information on the diagnosis and management of hepatitis B: **www.bpac.org.nz/2018/hepb.aspx**

This article is available online at: **www.bpac.org.nz/2019/hepc**

HCV testing

- HCV serology*
- HCV RNA assay or HCV core antigen assay

If positive

Pre-treatment assessment to exclude cirrhosis or complicating factors

- Clinical examination for symptoms and signs
- Laboratory tests for liver disease, hepatitis B, HIV and pregnancy
- Non-invasive liver assessment:
  - APRI calculation
  - Liver elastography (Fibroscan) if available
- Check for medicines interactions:
  - New Zealand Formulary (NZF) interactions checker: **www.nzf.org.nz**
  - OR University of Liverpool HCV medicines interactions checker: **www.hep-druginteractions.org**

If treatment in primary care is appropriate

Prescribe glecaprevir + pibrentasvir

- Patients will need to collect their medicine from an enrolled pharmacy
- Alternative arrangements can be made if collection from an enrolled pharmacy is not possible

Treatment lasts eight weeks

Follow-up patients after four weeks of treatment to assess adverse effects

After treatment has finished

- Test for cure with an HCV RNA assay or HCV antigen assay conducted 12 weeks after treatment has finished. Order liver function tests at the same time.
- Refer patients to a gastroenterologist if test results are positive 12 weeks after treatment has finished
- Patients with cirrhosis require long-term monitoring for the development of hepatocellular carcinoma
- No further follow-up for HCV complications is required for patients without cirrhosis and with normal liver function tests after treatment
- If patients have ongoing abnormal liver function tests, consider other possible causes
- Annual HCV RNA assays or HCV core antigen assays are recommended for patients with ongoing risk factors, e.g. people who inject drugs. Previous infection does not confer immunity.

* It is anticipated that HCV core antigen assays will become available for routine testing at some stage during 2019. HCV core antigen assays can be used instead of HCV RNA assays to test for current chronic HCV infection. When they become available, HCV core antigen assays will be performed as reflex tests in patients with positive HCV serology.

Figure 1: Diagnosis and management of HCV infection in primary care

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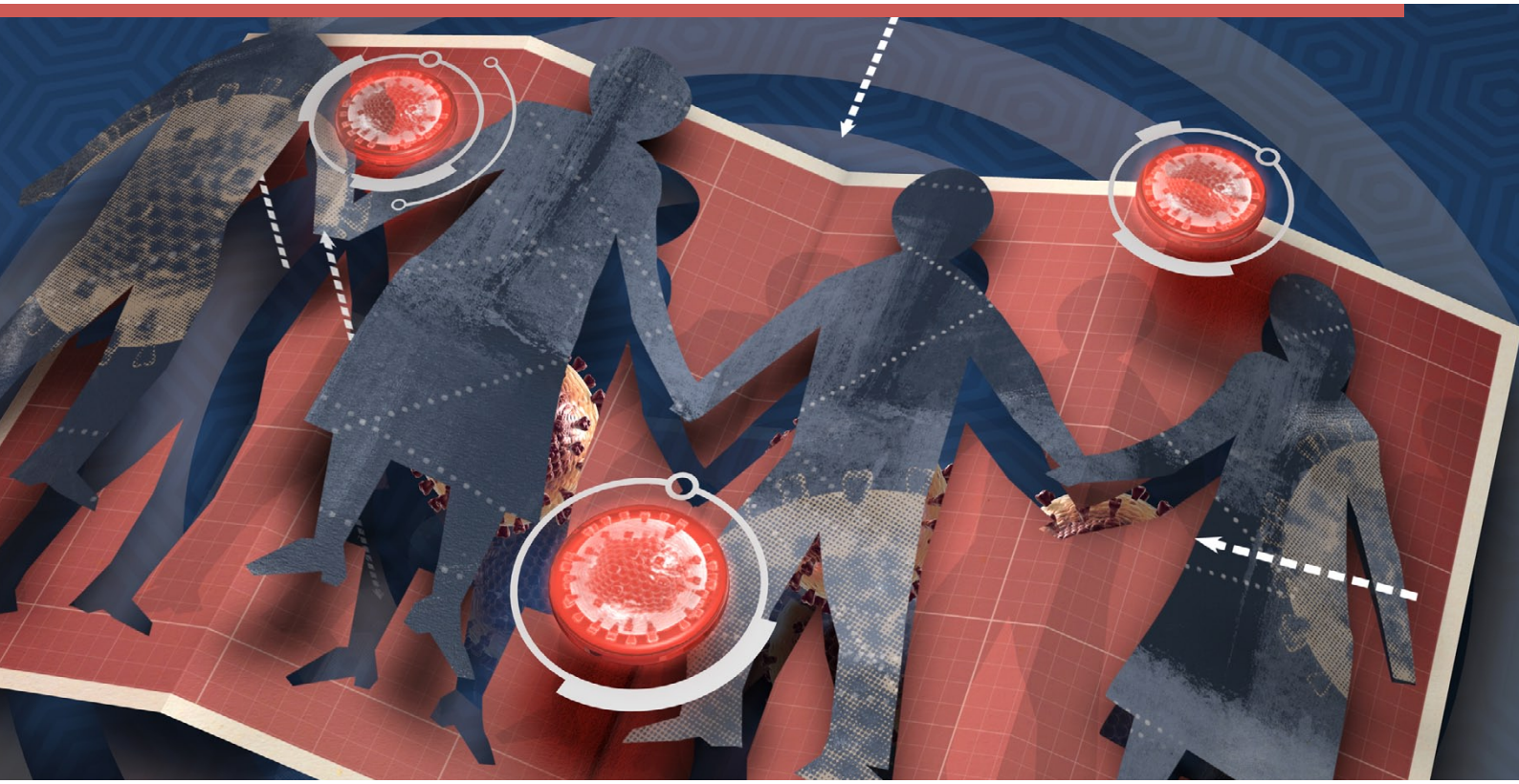

Testing for hepatitis C virus (HCV) in patients at high risk of infection

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 assay or HCV core antigen assay
- HCV RNA quantitation and HCV genotype testing are no longer required

Who is at risk of HCV infection?

Hepatitis C infection occurs through exposure to infected blood or body fluids.[1] The majority of newly acquired infections in New Zealand are from injectable drug use.[2] 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 facilities involved in the New Zealand needle exchange programme, see: **www.nznep.org.nz/outlets**

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.[1,3] 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.[1,3] 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.[4]

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.[5] The symptoms of acute HCV infection are nonspecific and include:[6]

- 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.[7] These levels typically spontaneously decrease to within normal limits within three to six months.[8] Acute HCV infection is a Notifiable disease.

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] Patients of Polynesian and Asian ethnicity are also more likely to achieve clearance due to genetic differences associated with higher rates of spontaneous viral clearance.[9, 10]

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. Liver function tests may be persistently normal in more than one-quarter of people with chronic HCV infection.[11] 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, 3]

Opportunistic testing for patients at high risk of HCV infection

Identify patients who are most likely to have been infected with HCV through their personal and maternal history. The majority of people with chronic HCV infection in New Zealand have used injectable drugs.[12]

Risk factors for HCV infection include:[1, 3, 13]

- Injectable drug use
- Receiving a blood transfusion 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, which was not performed in a licenced premises within New Zealand, i.e. either 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 infant transmission occurs in approximately 5% of infected mothers[14]

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.


For further information on strategies for identifying patients at risk and discussing HCV testing, see: **www.bpac.org.nz/2017/hepc.aspx**

The HCV testing process

Diagnosing HCV infection typically involves two tests; some laboratories may perform these as reflex tests:

1. Screening test for HCV exposure: anti-HCV antibodies
2. Confirmatory test for active HCV infection. Either*:
   a. HCV RNA assay
   OR
   b. HCV core antigen assay

* Some laboratories may perform these as reflex tests
Additional tests for other forms of hepatitis and HIV are generally requested at the same time.


For further information on the diagnosis and management of hepatitis B, see: **www.bpac.org.nz/2018/hepb.aspx**

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.[15] Discuss the limitations 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 or HCV core antigen 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.[16] 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.[16] **If a patient has a positive serology and a negative HCV RNA or HCV core antigen 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 or HCV core antigen will test positive for anti-HCV antibodies.[17]

A positive HCV RNA assay or HCV core antigen assay confirms current infection

HCV RNA detected through a polymerase chain reaction 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.[7]

It is anticipated that an alternative test for current infection, the HCV core antigen assay, will replace HCV RNA assays at some stage during 2019. These will be performed as reflex tests in patients who test positive for anti-HCV antibodies. The HCV core antigen assay detects viral antigens produced during HCV replication.[18] It is less sensitive than an HCV RNA assay and may not detect very early HCV infection.[19] However, a positive HCV core antigen test can reliably confirm established chronic infection, with a sensitivity of 93.4% and specificity of 98.8% compared to an HCV RNA assay.[20] As is the case with the HCV RNA assay, a negative HCV core antigen assay at 12 weeks after completion of antiviral therapy confirms successful HCV eradication.[20, 21]

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.nznep.org.nz/outlets**

A positive HCV RNA or HCV core antigen result indicates current infection, either acute or long-term (see: "Conservative management is generally appropriate for acute 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").

A negative HCV RNA or HCV core antigen assay indicates the patient does not have current infection and does not require treatment. For patients diagnosed during the acute stage of infection, repeat testing after three months is recommended to confirm the negative result.[15]

HCV genotyping is no longer required

Previously, HCV genotyping was required to determine eligibility for treatment, as Viekira Pak regimens are only effective against HCV genotypes 1 and 4. From 1 February, 2019, genotype testing is no longer required as glecaprevir + pibrentasvir (Maviret) is effective against all HCV genotypes.[6]

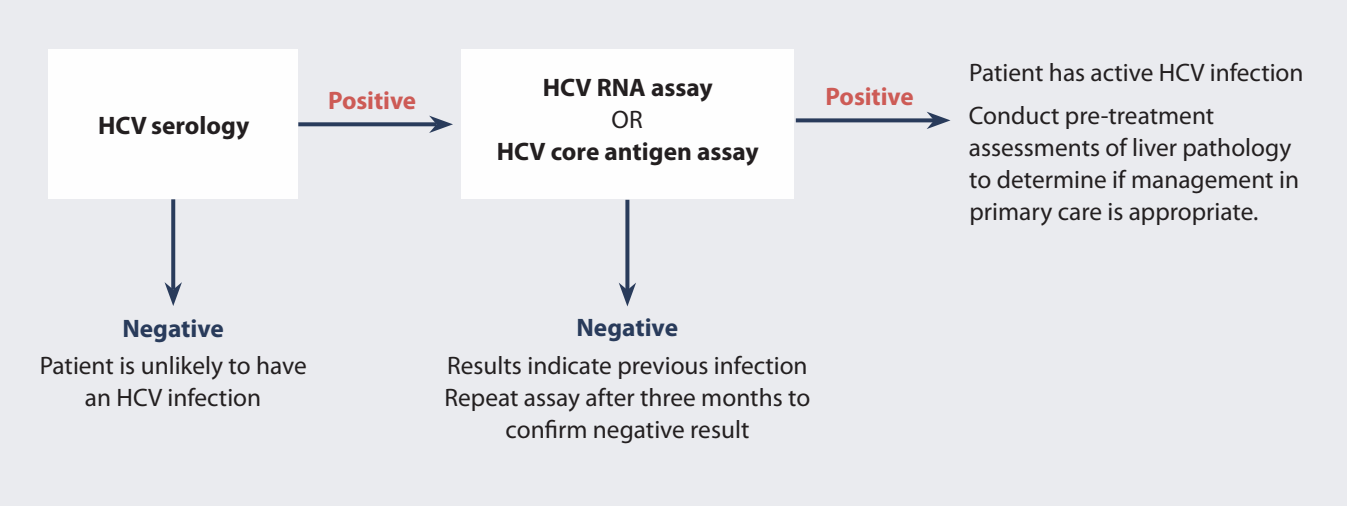

Figure 1: Testing patients for HCV infection.[22, 23]

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 or HCV core antigen 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.[7]

In the first few months of infection, viral RNA and core antigen 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 or HCV core antigen 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.[1,6]

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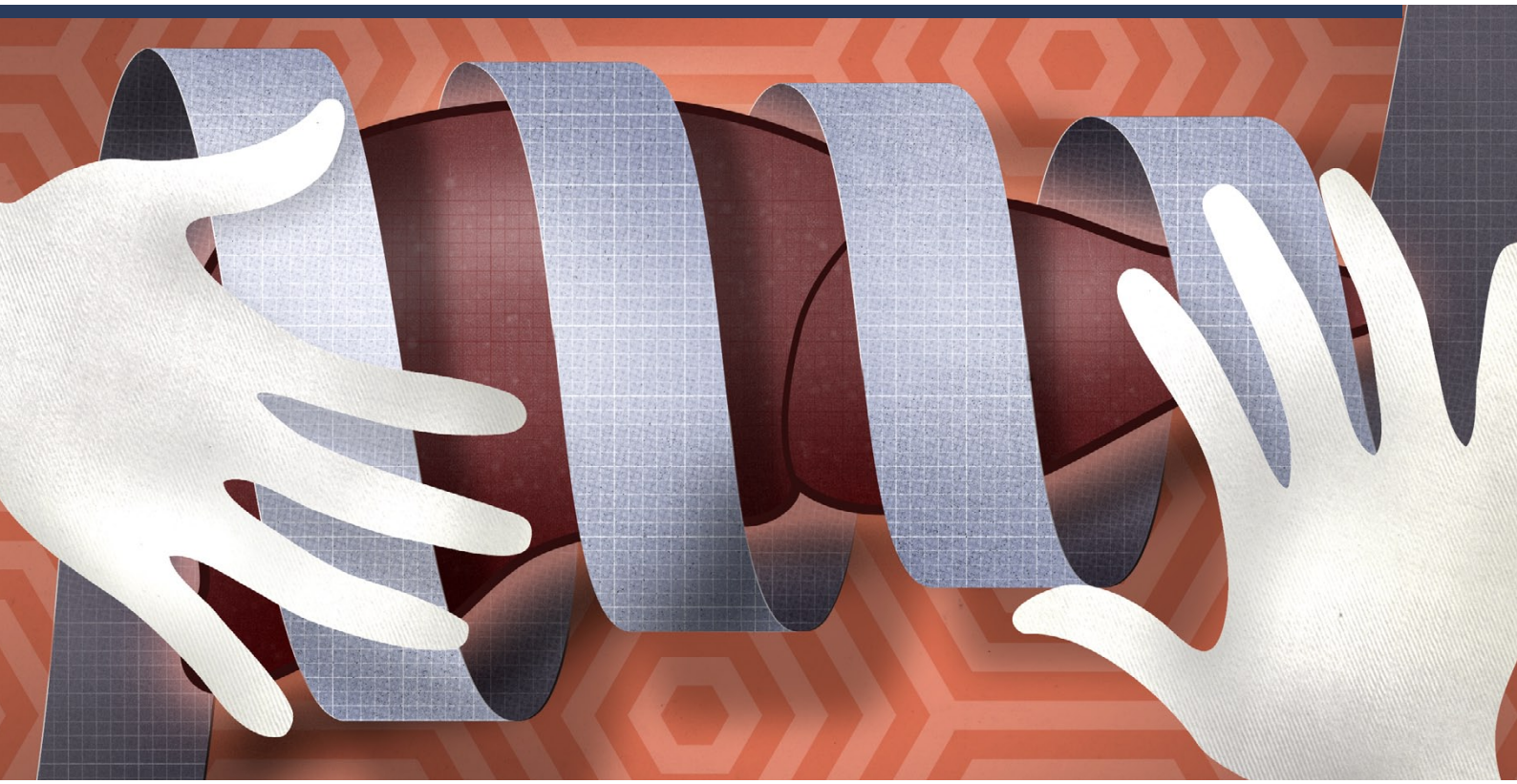

Pre-treatment assessment for patients with chronic HCV infection

KEY PRACTICE POINTS:

- Prior to treatment patients should be assessed for cirrhosis using clinical examination, laboratory tests and a non-invasive assessment of liver pathology (see below); treatment can be initiated in primary care for patients without evidence of cirrhosis
- Liver elastography is the gold-standard method to determine cirrhosis status. However, access to liver elastography is limited therefore the ratio of aspartate aminotransferase (AST) levels to platelet concentration (APRI) is a pragmatic alternative method of assessment for cirrhosis.
- Test patients for HIV and chronic hepatitis B infection
- Assess potential medicine interactions before prescribing glecaprevir + pibrentasvir. Medicines frequently prescribed in primary care which are contraindicated in combination with glecaprevir + pibrentasvir include statins, some antiepileptic medicines, dabigatran, rivaroxaban and combined oral contraceptives.
- Warn patients not to take St John's wort while taking glecaprevir + pibrentasvir as it may decrease the effectiveness of treatment

Discuss with a gastroenterologist or refer to secondary care patients:

- Who have previously been unsuccessfully treated with other hepatitis C medicines; longer treatment courses may be necessary
- With evidence of cirrhosis, which can include:
  - Clinical signs or symptoms, i.e. jaundice, abdominal pain and ascites, peripheral oedema
  - Laboratory findings, e.g. decreased serum albumin, elevated serum bilirubin, high INR (> 1.3), low platelet count
  - Liver elastography results suggestive of severe fibrosis or cirrhosis (see below)
  - An APRI score ≥ 1.0
- With uncertain results from investigations for liver pathology
- With eGFR < 30 mL/min/1.73 m^2
- With hepatitis B or HIV co-infection

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 glecaprevir + pibrentasvir, similar to the pre-treatment assessment previously recommended for patients initiating Viekira Pak regimens. Pre-treatment assessment is necessary to identify patients with cirrhosis, as these patients will need long-term follow-up for complications including hepatocellular carcinoma (liver cancer) and oesophageal varices.[1] Patients with cirrhosis should be referred to secondary care for further assessment in order to exclude the presence of hepatic decompensation. Patients with decompensated cirrhosis cannot be treated with glecaprevir + pibrentasvir because of the risk of toxicity. They can, however, receive treatment with ledipasvir + sofosbuvir (Harvoni) + ribavirin in secondary care.

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

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

For further information on the diagnosis and management of hepatitis B, see: **wwwbpac.org.nz/2018/hepb.aspx**

* For patients with an existing long-term infection, an HCV RNA assay or HCV core antigen assay should also be performed if one has not been done in the last five years to confirm ongoing infection.[2] Spontaneous clearance of HCV can occur during the acute stage of infection but is rare during chronic infection.[1]

Assess patients for the presence of cirrhosis

Excluding the presence of cirrhosis is required prior to prescribing glecaprevir + pibrentasvir in primary care, as this medicine is contraindicated in patients with severe, i.e. decompensated, cirrhosis.[4, 5] In addition, patients with cirrhosis will require long-term monitoring for the development of hepatocellular carcinoma after treatment with glecaprevir + pibrentasvir has finished, and this assessment must take place prior to initiating HCV medicines as treatment affects the reliability of non-invasive assessments.[6] Referral to secondary care or discussion with a gastroenterologist is recommended for patients with cirrhosis.

Table 1: Risk factors for cirrhosis based on clinical examination and patient history.[1, 8–13]

Risk factors for cirrhosis include:	Clinical features consistent with cirrhosis include:	Clinical features consistent with 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 ■ HIV or HBV coinfection	■ Signs of portal hypertension: splenomegaly or caput medusae (dilated superficial abdominal veins) ■ Spider naevi ■ Leukonychia (white spots on nails) ■ Palmar erythema	■ Jaundice ■ Ascites ■ Peripheral oedema ■ 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 ■ Increased INR (> 1.3) ■ Decreased platelet count (< 150 × 10^9/L) ■ Elevated serum bilirubin, e.g. >20 micromol/L ■ A liver stiffness measurement of > 12.5 KPa on liver elastography (Fibroscan) ■ If a liver elastography scan is not possible, assess the possibility of cirrhosis with: – An APRI ≥ 1.0 (cirrhosis cannot be excluded and referral to secondary care is recommended) – A score of F3–F4 on Fibrotest or Fibrosure tests (see below)

A combination of clinical examination, laboratory tests and liver imaging (Table 1) is used to determine the presence and severity of any liver disease.[2, 8]

Assessing liver disease stage with an APRI score

Patients with HCV infection can be assessed for the likelihood of cirrhosis by calculating an AST to platelet ratio index (APRI) score.

An APRI score of < 1.0 has a negative predictive value of approximately 94% to exclude cirrhosis in patients with hepatitis C.[17] A recent clinical trial investigated the safety of using an APRI score of ≤ 1.0 to rule out cirrhosis in over 200 patients prior to prescribing glecaprevir + pibrentasvir and reported that <1% of patients discontinued treatment due to adverse effects.[18]

An APRI score of:[8, 19]

- < 1.0 indicates that the patient is unlikely to have cirrhosis and clinicians in primary care can be confident that treatment can be initiated in the community
- ≥ 1.0 indicates that the patient **may** have cirrhosis and should be referred for liver elastography to confirm cirrhosis status prior to starting treatment. If the liver elastography result is < 12.5 kPa then the patient can still be treated in primary care.

For example, a female patient with a low platelet count of 120 × 10^9/L and a mildly elevated AST value of 50 U/L (reference range 10–35 U/L)[13], 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 freely 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, can also 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.

Liver elastography

Liver elastography performed by Fibroscan or shear wave ultrasound can be used to detect fibrosis or cirrhosis in patients with HCV infection. It is strongly recommended that this investigation be conducted in all patients with hepatitis C, wherever possible, before treatment with glecaprevir + pibrentasvir is initiated. However, access to liver elastography is variable, therefore it is accepted that calculating an APRI score is a pragmatic alternative. Both liver elastography measurements and APRI scores will give falsely low results after successful treatment; even patients with cirrhosis may have normal liver stiffness measurements following successful treatment, due to rapid resolution of liver inflammation associated with HCV infection.[6, 7]

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.[14]

Either a Fibroscan machine or an ultrasound machine capable of "shear wave" assessments is used to perform liver elastography.[2, 15] Elastography testing takes approximately ten minutes, with results available immediately. The availability of liver elastography varies throughout the country; clinicians are advised to contact a local radiology service to determine if this type of imaging is available in their DHB and how patients can be referred for assessment.

Elastography measures the velocity of a low-frequency wave which correlates with the degree of liver stiffness which is increased in patients with fibrosis.[8] Liver biopsy is typically reserved for patients where either elastography is unsuccessful (see below) or there is uncertainty regarding the cause of cirrhosis detected with imaging.[8, 12] A standard liver ultrasound is inappropriate for liver assessment in patients with HCV infection.

Liver elastography results will report a liver stiffness measurement (LSM) in kilopascals (kPa). A cut-off of 12.5 kPa is recommended to detect cirrhosis; patients with liver elastography measurements of:[16]

- **< 12.5 kPa are unlikely to have cirrhosis and can be treated in primary care** with glecaprevir + pibrentasvir (Table 2)
- **≥ 12.5 kPa are likely to have cirrhosis and the patient should be referred to secondary care or discussed with a gastroenterologist** prior to prescribing glecaprevir + pibrentasvir

The reliability of elastography is decreased or the scan may be unsuccessful if performed immediately after a meal or in patients with:[12]

- Obesity
- Ascites/peritoneal dialysis
- Heart failure
- A narrow intercostal space (where a smaller paediatric probe may be indicated)

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.[2]

Table 2: Treating or referring on the basis of liver assessments[2, 14]

Treatment in primary care is appropriate for patients with ALL of the following:	Referral to or discussion with a gastroenterologist is appropriate for patients with ANY of the following:
■ Clinical examination does not suggest cirrhosis ■ No evidence of cirrhosis on non-invasive liver assessments: – APRI <1.0 OR – Liver stiffness measurement < 12.5 kPa on liver elastography ■ Laboratory results, e.g. bilirubin, platelet count, INR and albumin, do not suggest cirrhosis	■ Clinical examination consistent with cirrhosis ■ APRI ≥ 1.0 ■ Liver stiffness measurement ≥ 12.5 kPa on liver elastography ■ Laboratory results consistent with cirrhosis

Non-hepatic assessment prior to initiating treatment in primary care

Patients with cryoglobulinaemia can now be treated in primary 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.[20] 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]

Previously, patients with hepatitis C and cryoglobulinaemia in New Zealand were recommended to undergo treatment with Harvoni in secondary care.[2] These patients can now be treated in primary care with glecaprevir + pibrentasvir.

Patients with severe renal impairment should be referred to secondary care or discussed with a gastroenterologist

Glecaprevir + pibrentasvir is the preferred treatment for patients with severe renal impairment (< 30 mL/min/1.73m^2).[8] In clinical trials, no accumulation of either glecaprevir or pibrentasvir was observed in patients with chronic kidney disease (CKD) stage 4 or 5 (an eGFR < 30 mL/min/1.73 m^2); hence, the same dosing is recommended in these patients. Most patients with CKD stage 4 or 5 will already be managed in secondary care. If not, then discussion with a gastroenterologist is recommended prior to commencing glecaprevir + pibrentasvir as patients with CKD have higher rates of adverse effects than patients without renal impairment.[8, 21]

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. In patients with HCV-HBV co-infection, treatment for HCV may cause reactivation of hepatitis B viral activity and careful monitoring is required.[8, 12] In patients with HIV-HCV co-infection, serious drug-drug interactions may occur between glecaprevir + pibrentasvir and several of the commonly prescribed antiretroviral medicines.

Ensure that patients' vaccinations against hepatitis A and B are up to date to reduce the progression of any liver disease.[22] Hepatitis B vaccination is funded for patients with chronic HCV infection. Hepatitis A vaccination is recommended but not funded. Pneumococcal vaccination is recommended but not funded for individuals with chronic liver disease.[23]


For further information on the diagnosis and management of patients with hepatitis B, see: **www.bpac.org.nz/2018/hepb.aspx**

Defer treatment in patients who are pregnant or breastfeeding

The safety of glecaprevir + pibrentasvir in pregnancy or breastfeeding has not been studied. Deferring treatment until after pregnancy is recommended.[24] Mothers can be reassured that the risk of transmission of HCV to their child is low, as approximately only 6% of infants born to mothers with HCV become infected.[25]

For women who are breastfeeding, clinicians can discuss with them the benefits and risks of deferring treatment with glecaprevir + pibrentasvir until breastfeeding has ceased, or stopping breastfeeding early to initiate treatment.

Defer treatment in children aged under 18 years

Glecaprevir + pibrentasvir is not currently approved for use in children aged under 18 years. A clinical trial has been

undertaken evaluating the safety and efficacy of glecaprevir + pibrentasvir in patients of this age, with the results presented at a conference in late 2018.[26] On the basis of these clinical trial results, glecaprevir + pibrentasvir may be approved for use in children in the future.

Check potential medicine interactions prior to prescription

A number of significant interactions are possible between glecaprevir + pibrentasvir and other commonly prescribed medicines, including statins, some antiepileptic medicines, and anticoagulants (Table 3).

Contraceptives containing ethinylestradiol or oestrogen are contraindicated during treatment with glecaprevir + pibrentasvir, as studies have found some patients experience increased ALT levels when these medicines are taken with glecaprevir + pibrentasvir.[27] Female patients using combined oral contraceptives or the combined hormonal contraceptive ring should be prescribed an alternative form of contraception during treatment.

St John's wort can reduce antiviral efficacy so should be avoided.[27]

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**
- The NZF interactions checker: **www.nzf.org.nz**

In patients where a potential interaction with glecaprevir + pibrentasvir has been identified, consider if the current regimen can be temporarily withdrawn, replaced with another medicine or the dose reduced. For example, patients using statins could withdraw from these medicines while taking glecaprevir + pibrentasvir and reinitiate the statin after treatment has

Table 3: Examples of medicines which are contraindicated or should be used with caution in patients taking glecaprevir + pibrentasvir*:[5, 27]

Examples of medicines which are contraindicated	Examples of medicines that should be used with caution
■ Simvastatin, atorvastatin ■ Antiepileptic medicines, including phenytoin, primidone, phenobarbital, carbamazepine ■ Combined oral contraceptives and ethinylestradiol + etonogestrel contraceptive ring ■ Dabigatran ■ Rifabutin and rifampicin ■ Many medicines for the treatment of HIV ■ Other medicines for the treatment of HCV	■ Amiodarone ■ Aripiprazole ■ Carvedilol ■ Cyclosporine ■ Clozapine ■ Colchicine ■ Digoxin ■ Domperidone ■ Enalapril ■ Erythromycin ■ Ezetimibe ■ Gemfibrozil ■ Glibenclamide ■ Ketoconazole ■ Methotrexate ■ Modafinil ■ Opioid medicines: fentanyl, oxycodone ■ Pravastatin ■ Quetiapine ■ Rivaroxaban ■ Sulfasalazine ■ Tacrolimus ■ Theophylline ■ Ticagrelor ■ Verapamil ■ Warfarin

* This table is not a complete list of medicine interactions; further information is available from: **www.hep-druginteractions.org/checker and medicine data sheets**

finished. Subsidised anticoagulant medicines are either contraindicated (dabigatran) or should be used with caution (warfarin and rivaroxaban) in patients taking glecaprevir + pirbentasvir. Increased monitoring of INR or increased attention to the possibility of bleeding are recommended in patients taking warfarin or rivaroxaban; consider discussion with a gastroenterologist or cardiologist.[27] Discussion with a gastroenterologist is recommended if patients have medicine interactions which cannot be avoided.

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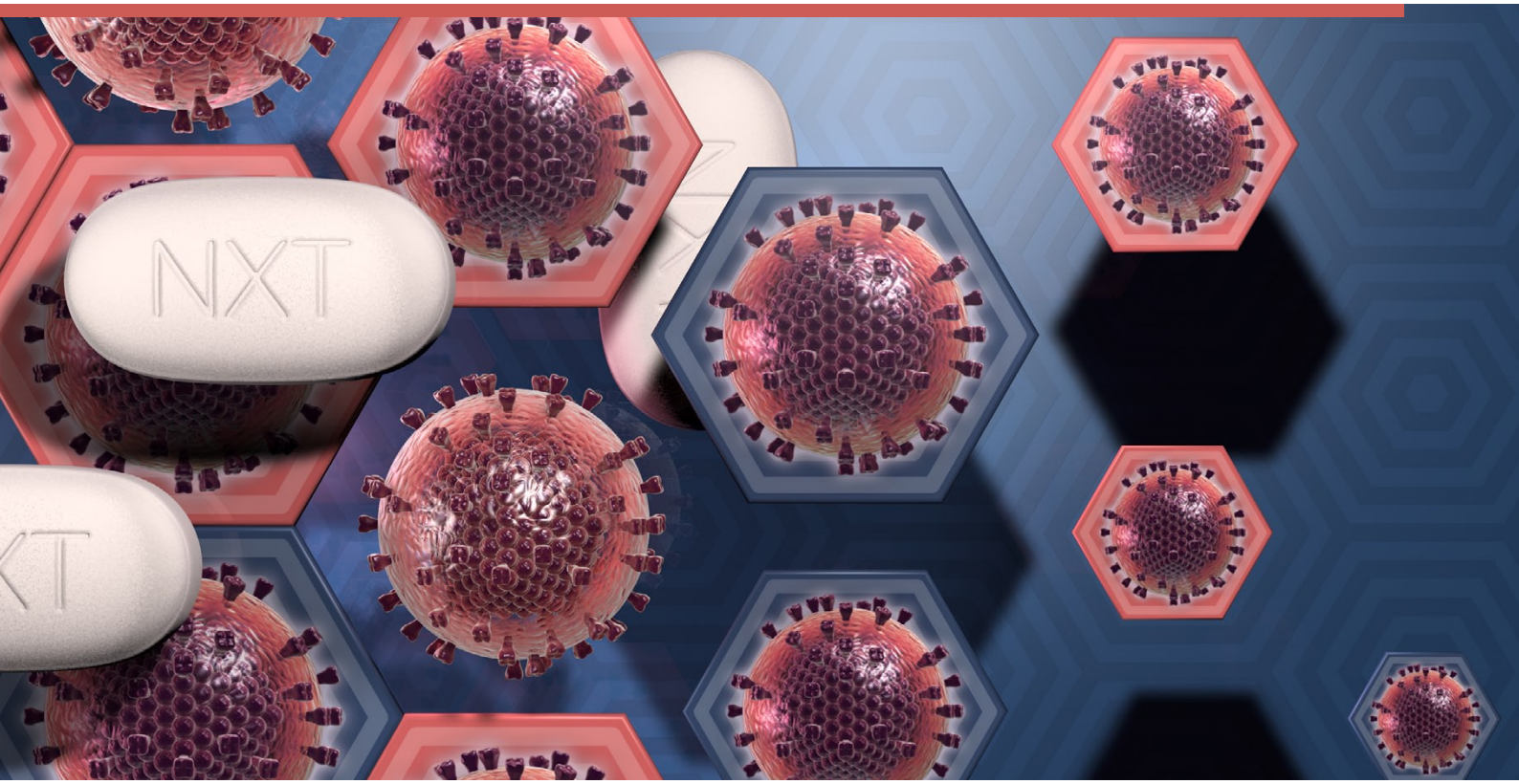


Management and follow-up of patients prescribed glecaprevir + pibrentasvir

KEY PRACTICE POINTS:

- Patients should take three tablets of glecaprevir + pibrentasvir in the morning with food, for eight weeks
- Dose reductions are not required for patients with an eGFR between 30 to 50 mL/min/1.73 m^2; referral to or discussion with a gastroenterologist is recommended for patients with an eGFR < 30 mL/min/1.73 m^2
- Headache and fatigue are the most common adverse effects
- Measure HCV RNA levels or HCV core antigen 12 weeks after treatment has finished to determine if treatment has been successful; ≥ 97% of patients treated with glecaprevir + pibrentasvir can be expected to have undetectable HCV RNA at this point
- 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

Initiating treatment in primary care

How to prescribe glecaprevir + pibrentasvir

Treatment with glecaprevir + pibrentasvir is once daily; patients should be instructed to take three tablets in the morning with food.[1] Glecaprevir + pibrentasvir is mainly excreted in faeces and dose reductions based on renal function are not necessary.[1]

Provide patients with a prescription; distribution forms a no longer required

Treatment with Viekira Pak regimens required clinicians to submit a distribution form directly to PHARMAC. However, this is not the case for prescriptions of glecaprevir + pibrentasvir and patients can be provided with a prescription to present at an approved pharmacy.

Dispensing of glecaprevir + pibrentasvir occurs at enrolled pharmacies

Only enrolled pharmacies can dispense subsidised glecaprevir + pibrentasvir, similar to the previous arrangements which were in place for Viekira Pak regimens.

From 1 February, 2019, a list and map of enrolled pharmacies will be available at: **www.maviret.co.nz**

Instructions for pharmacies that wish to become enrolled to dispense glecaprevir + pibrentasvir and further information on distribution arrangements is available from PHARMAC; see: **www.pharmac.govt.nz/news/notification-2018-12-18-hep-c-and-psoriasis-treatments/**

Alternatives are available for patients unable to access an enrolled pharmacy

For patients who are unable to access an enrolled 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/**

During treatment

If patients miss a dose

They should:[1]

- Take the missed dose if less than 18 hours have passed since the previous dose
- Skip the dose if more than 18 hours have passed since the previous dose

In either case, patients should take the subsequent dose at the normal time.

Mild adverse effects occur in some patients but treatment can be continued

The most common adverse effects experienced by patients taking glecaprevir + pibrentasvir are:[2]

- Headache, occurring in 17% of patients
- Fatigue, occurring in 14% of patients
- Diarrhoea in 6% of patients

In a placebo-controlled clinical trial, adverse effects typically occurred at the same rate in participants taking placebo tablets or glecaprevir + pibrentasvir, with the exception of nausea, which was reported by 7% of participants taking glecaprevir + pibrentasvir, compared to 3% of participants taking placebo tablets.[3] Less than 1% of patients discontinue treatment due to adverse effects.[2]

Treatment with glecaprevir + pibrentasvir is better tolerated than treatment with the previously subsidised Viekira Pak regimens, which resulted in fatigue, headache or nausea in 24–46% of patients.[4–6]

Patients may drink up to two standard alcoholic drinks per day while taking glecaprevir + pibrentasvir, however, those with evidence of severe fibrosis or cirrhosis should be advised to avoid alcohol before, during and after treatment.[7]

Monitoring patient safety

A follow-up visit after four weeks of treatment is recommended to discuss whether patients are experiencing any adverse effects.[8]

In patients without cirrhosis treated in primary care, no blood tests are needed for monitoring safety or efficacy during glecaprevir + pibrentasvir treatment.[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.[8]

Patients treated with the previously subsidised HCV medicine Viekira Pak-RBV required full blood count tests during treatment, in order to detect reductions in haemoglobin levels caused by ribavirin. Full blood count tests during treatment are not required for patients taking glecaprevir + pibrentasvir treatment as ribavirin is not included in the treatment regimen.

Follow-up after treatment is completed

Evaluating the success of treatment

The effectiveness of treatment in eradicating HCV infection is determined by conducting an HCV RNA assay or HCV core antigen assay 12 weeks after treatment has finished. Liver function tests can be ordered at the same time in order to assess whether additional follow-up is required (see: "Follow-up testing of liver disease after treatment of HCV infection").

A negative HCV RNA assay (undetectable HCV RNA levels) or negative HCV core antigen assay 12 weeks after treatment has finished indicates cure. Over 97% of patients treated with glecaprevir + pibrentasvir can be expected to test negative 12 weeks after treatment.[2] If the HCV RNA assay or HCV core antigen test at 12 weeks after treatment is positive, patients should be discussed with a gastroenterologist.

Treatment improves quality of life, eliminates the risk of transmission and reduces the risk of HCV complications

Successful treatment of HCV infection results in patients experiencing improvements in their quality of life, general wellbeing and improved physical health, with resolution of fatigue and low mood. Patients may begin to experience these benefits during treatment.[9] Treatment also eliminates the risk of transmitting HCV to others.

Following treatment, patients are likely to have improved liver function and a reduced risk of hepatic and non-hepatic

complications. 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.[8, 10, 11] Treatment may also resolve or improve non-hepatic complications, such as cryoglobulinaemia, porphyria cutanea tarda and non-Hodgkin lymphoma.[8]

Follow-up of patients who relapse after treatment

Approximately 3% of patients relapse after treatment with Viekira Pak regimens, and 1% after treatment with glecaprevir + pibrentasvir, due to viral resistance to these medicines.[12, 13] Patients who remain infected after treatment with Viekira Pak or glecaprevir + pibrentasvir should be referred to or discussed with a gastroenterologist. Further treatment options are available, however, these are not currently subsidised.

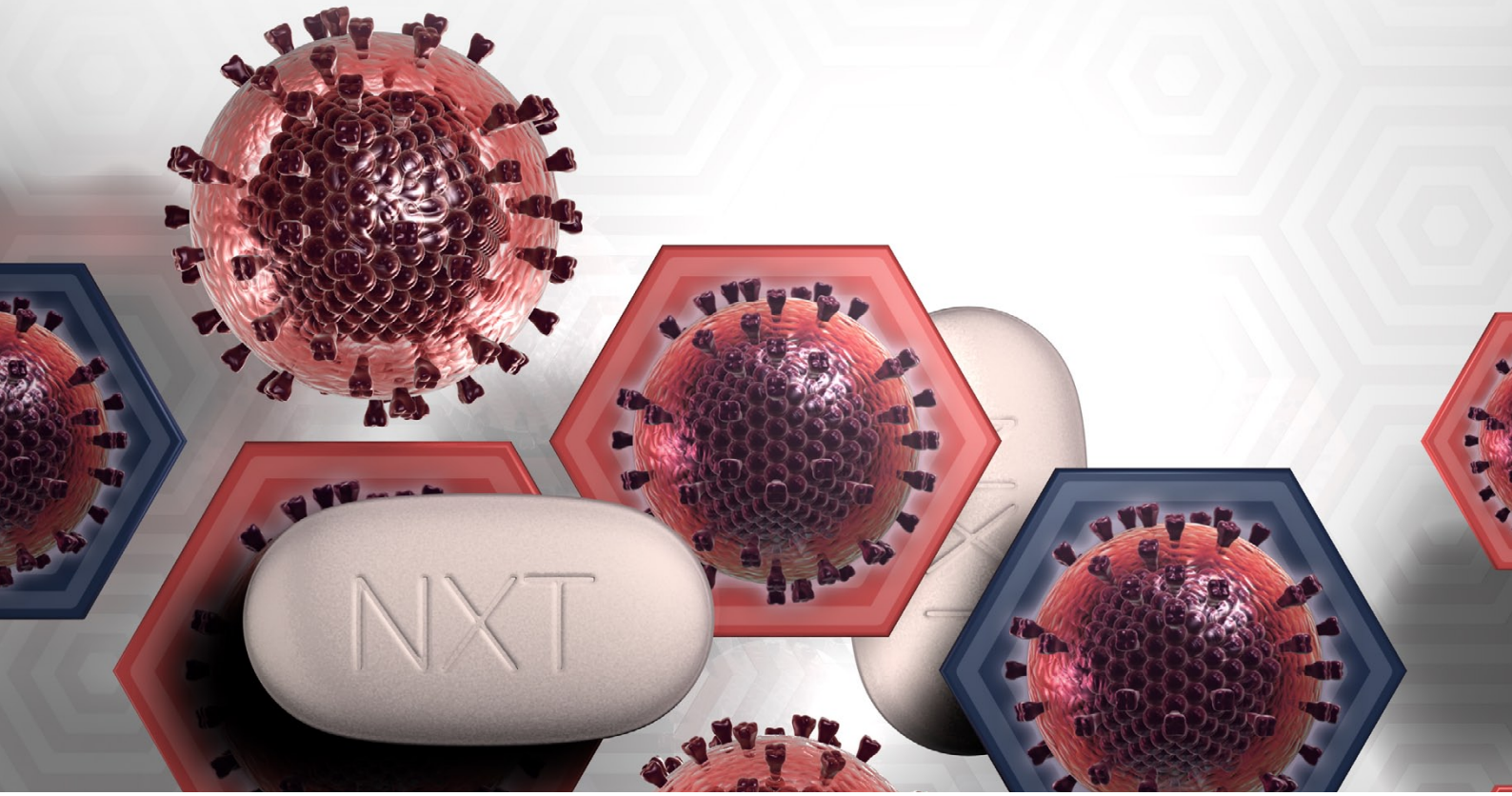
Follow-up testing of liver disease after treatment of HCV infection

After successful treatment, patients with normal liver function tests and without cirrhosis do not require additional follow-up.[7] 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.[7]

Successful treatment of HCV infection in people with cirrhosis reduces, but does not abolish, the risk of hepatocellular carcinoma.[14] Therefore, following successful treatment long-term monitoring for the development of hepatocellular carcinoma is recommended in all patients with cirrhosis, with six monthly with measurement of serum alpha fetoprotein (AFP) levels and liver ultrasounds.[15] If an ultrasound result is unreliable, e.g. due to liver nodularity, discuss the use of a CT or MRI scan for surveillance with a gastroenterologist.[16] Patients with cirrhosis with low platelet counts or evidence of portal hypertension on ultrasound should also have a baseline endoscopy to assess for oesophageal varices.[17] If no varices are present and the patient has no other underlying risk factors for disease progression such as heavy alcohol intake or obesity, then no further endoscopic surveillance is required.[18]

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 or HCV core antigen assays.[7] 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.[19] 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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