International Hepatitis C in Primary Care and Drug and Alcohol Settings Education Programme

Supporting increased hepatitis C screening, linkage-to-care and treatment among people who inject drugs in the UK

Contacts:

Jason Grebely
Kirby Institute, University of New South Wales
International Network on Hepatitis in Substance Users
Email: Jgrebely@kirby.unsw.edu.au

Emma Day
Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
International Network on Hepatitis in Substance Users
Email: emma.day@ashm.org.au

Nikitah Habraken
Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
International Network on Hepatitis in Substance Users
Email: nikitah.habraken@ashm.org.au
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About

This toolkit is provided to participants of the INHSU Hepatitis C in Primary Care and Drug and Alcohol Settings Education Program. The toolkit is intended to provide participants with practical tools with which to implement HCV testing, linkage to care and treatment processes in their setting.

The toolkit is tailored in-line with local guidelines and referral pathways for each workshop location.

Although some resources will be applicable only for participants working within the local area of workshop delivery, many, such as DAA treatment regimen quick reference guides, management procedure templates and assessment checklists, will be relevant regardless of practice location.

Resources applicable across all locations within the UK are available as an enduring education program component as free downloads via the INHSU Education website www.inhsueducation.org.
Acknowledgements

UK Committee Chair:

- Prof. John Dillon
  Professor of Hepatology and Gastroenterology, Ninewells Hospital, University of Dundee

UK Committee Members:

- Dr. Ahmed Elsharkawy
  Consultant Transplant Hepatologist, QE Hospital Birmingham and Chair of British Viral Hep Group
- Ms Ann Eriksen
  Executive Lead Sexual Health & BBV, Sexual Health & BBV Managed Care Network, NHS Tayside
- Prof. Graham Foster
  Professor of Hepatology, Blizard Institute, London
- Charles Gore
  Chief Executive, The Hepatitis C Trust
- Dr. Magdalena Harris
  Associate Professor of Sociology of Health, London School of Tropical Medicine and Hygiene
- Prof. Matt Hickman
  Professor of Public Health and Epidemiology, University of Bristol and Co-Director of NIHR Health Protection Research Unit on Evaluation of Interventions
- Prof. Sharon Hutchinson
  Professor of Epidemiology and Population Health, Glasgow Caledonian University
- Dr. Sema Mandal
  Medical Consultant Epidemiologist and Viral Hepatitis Lead at PHE Colindale in the Immunisation, Hepatitis and Blood Safety Department of the National Infection Service
- Mr Danny Morris
  RCGP Expert Lead, Certificate in the Detection, Diagnosis and Management of Hepatitis B and C and Independent Consultant and Trainer
- Dr. Ewen Stewart
  General Practitioner, Edinburgh
- Ms Jan Tait
  Nurse Specialist in HCV, Ninewells Hospital, Dundee
- Dr. Jeremy Thompson
  General Practitioner, Yorkshire
- Dr. Andy Ustianowski
  Consultant in Infectious Diseases, North Manchester General Hospital

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- Ms Emma Day
  Program Manager, Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)
  Program Coordinator, International Network on Hepatitis in Substance Users (INHSU)
- Prof. Greg Dore
  Head, Viral Hepatitis Clinical Research Program, The Kirby Institute, University of New South Wales
- A. Prof. Jason Grebely
  Viral Hepatitis Clinical Research Program, The Kirby Institute, University of New South Wales
  President, International Network on Hepatitis in Substance Users (INHSU)
- Ms Nikitah Habraken
  Senior Project Officer, Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>AST-to-Platelet Ratio Index</td>
</tr>
<tr>
<td>Ascites</td>
<td>The accumulation of fluid (usually serous fluid which is a pale yellow and clear fluid) that accumulates in the abdominal cavity</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Of a condition or a person producing or showing no symptoms</td>
</tr>
<tr>
<td>Cessation</td>
<td>The fact or process of ending or being brought to an end</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>An area of necrotic tissue in the brain resulting from a blockage or narrowing in arteries supplying blood and oxygen to the brain</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>A complication of liver disease which involves loss of liver cells and irreversible scarring of the liver</td>
</tr>
<tr>
<td>Enzyme</td>
<td>Macromolecular biological catalysts. They accelerate chemical enzymes</td>
</tr>
<tr>
<td>Ethinylestradiol</td>
<td>An orally active estrogen and a synthetic derivative of estradiol, a steroid hormone and the major endogenous estrogen in humans</td>
</tr>
<tr>
<td>Etiology</td>
<td>The cause, set of causes, or manner of causation of a disease or condition</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>The formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process. This can be reactive, benign, or pathological state. In response to injury, this is called scarring, and if it arises from a single cell line this is called a fibroma.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition/Description</td>
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<tr>
<td>-------------------------------------</td>
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<tr>
<td>Genotype</td>
<td>The genetic constitution of an individual organism</td>
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<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>The most common type of primary liver cancer. It occurs predominantly in patients with underlying chronic liver disease and cirrhosis.</td>
</tr>
<tr>
<td>Jaundice</td>
<td>A medical condition with yellowing of the skin or whites of the eyes, arising from excess of the pigment bilirubin and typically caused by obstruction of the bile duct, by liver disease, or by excessive breakdown of red blood cells</td>
</tr>
<tr>
<td>Lethargy</td>
<td>A lack of energy</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Pain in a muscle or group of muscles</td>
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<tr>
<td>Opioid</td>
<td>An opium-like compound that binds to one or more of the three opioid receptors of the body</td>
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<tr>
<td>Opioid agonist treatment</td>
<td>An effective treatment for addiction to opioid drugs such as heroin and involves taking the opioid agonists methadone or buprenorphine (suboxone)</td>
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<tr>
<td>Palmar erythema</td>
<td>Reddening of the palms</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>Peripheral edema</td>
<td>An accumulation of fluid causing swelling in tissues perfused by the peripheral vascular system, usually in the lower limbs</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>An increase in the blood pressure within a system of veins called the portal venous system</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<td>--------------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
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<tr>
<td>Serology</td>
<td>The scientific study or diagnostic examination of blood serum, especially with regard to the response of the immune system to pathogens or introduced substances</td>
</tr>
<tr>
<td>Spider nevi</td>
<td>A collection of small, dilated blood vessels that are clustered close to the skin’s surface</td>
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<tr>
<td>Thrombocytopenia</td>
<td>A condition in which you have a low blood platelet count</td>
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<tr>
<td>Viremic</td>
<td>A medical condition where viruses enter the blood stream and hence have access to the rest of the body</td>
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<tr>
<td>Resource</td>
<td>Website</td>
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<tr>
<td>Child-Pugh Score calculator</td>
<td><a href="http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality">www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality</a></td>
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<td>PELD Score calculator</td>
<td><a href="http://www.mdcalc.com/peld-score-pediatric-end-stage-liver-disease-younger-12">www.mdcalc.com/peld-score-pediatric-end-stage-liver-disease-younger-12</a></td>
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<td>MELD Score calculator</td>
<td><a href="http://www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older">www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older</a></td>
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<td>Hepatitis C Trust</td>
<td><a href="http://www.hepctrust.org.uk">www.hepctrust.org.uk</a></td>
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<td>British Liver Trust</td>
<td><a href="http://www.britishlivertrust.org.uk">www.britishlivertrust.org.uk</a></td>
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<td>British Association for the Study of the Liver/ British Viral Hepatitis Group</td>
<td><a href="http://www.basl.org.uk/index.cfm/content/page/cid/3">www.basl.org.uk/index.cfm/content/page/cid/3</a></td>
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<td>Primary Care Society for Gastroenterology</td>
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<td>Harm Reduction Works</td>
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<td>Infohep</td>
<td><a href="http://www.infohep.org">www.infohep.org</a></td>
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<td>HCV Action – UK</td>
<td><a href="http://www.hcvaction.org.uk">www.hcvaction.org.uk</a></td>
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<td>Liver and Transplant Units – UK</td>
<td><a href="http://www.britishlivertrust.org.uk/liver-information/useful-links/liver-and-transplant-units">www.britishlivertrust.org.uk/liver-information/useful-links/liver-and-transplant-units</a></td>
</tr>
<tr>
<td>Public Health England campaign resources</td>
<td><a href="http://www.publichealthengland-immunisati.app.box.com/s/ipxtlzui57evyejw8zgvhimh0pjwa05">www.publichealthengland-immunisati.app.box.com/s/ipxtlzui57evyejw8zgvhimh0pjwa05</a></td>
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<tr>
<td>Find your local health protection team in England</td>
<td><a href="http://www.gov.uk/health-protection-team">www.gov.uk/health-protection-team</a></td>
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<tr>
<td>Waverly Care</td>
<td><a href="http://www.waverleycare.org/about-us/publications-and-literature/services-leaflets-forms">www.waverleycare.org/about-us/publications-and-literature/services-leaflets-forms</a></td>
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</table>
**DECISION-MAKING IN HCV**

**UNITED KINGDOM**

**Hepatitis C testing**

**STEP 1** Could it be hepatitis C?
- Patient request
- Abnormal liver function test (LFT)
- Doctor concern

**Presence of risk factors**
- Injecting drug use
- Sharing of snorting equipment
- Birth in high prevalence country
- Blood transfusion before September 1991 or a blood product (such as clotting factor) before 1986 in the UK
- Unsterile tattooing and body piercing
- Unsterile medical and dental procedures and blood transfusions in high prevalence countries
- Time in prison
- Needlestick injury
- Mother to child transmission is around 5%
- Household transmission is very rare
- Sexual transmission is rare but can occur in certain populations, such as men who have sex with men (MSM) or those who are Human Immunodeficiency Virus (HIV) positive

**Jaundice** or acute hepatitis

Get informed consent in a culturally appropriate manner.
- Reason for test
- Risk factors
- Meaning of a positive antibody test
- Availability of treatment if HCV RNA positive
- Mechanism for communicating test results

**STEP 2** Review results
- **Hep C Ab -ve**
  - LFT normal (means hepatitis C unlikely, HCV RNA not needed)
  - **Hep C Ab -ve**
  - LFT abnormal or possible acute hepatitis C

Order:
- Hep C antibody (Ab) LFT

If possible acute hepatitis, also order HCV RNA
If reflex testing done in local laboratory, request HCV RNA if anti-HCV positive

**STEP 3** Check HCV RNA
- **Hep C Ab -ve**
  - HCV RNA -ve
  - Hep C Ab -ve
  - LFT normal (means hepatitis C unlikely)

**Hep C Ab -ve**
- HCV RNA +ve
- Hep C Ab -ve
- plus repeated HCV RNA +ve
- means chronic hepatitis C (chronic if > 6 months)

**Hep C Ab +ve**
- HCV RNA -ve
- Hep C Ab +ve
- plus repeated HCV RNA -ve
- means cleared hepatitis C

Convey test result
- If positive, results should always be provided in person and explain:
  - Natural history
  - Modes of transmission and risk reduction
  - Availability of treatment
  - Need for ongoing, potentially lifelong monitoring for liver disease - for cirrhosis and cancer, if already evidence of liver damage
  - Lifestyle factors e.g. alcohol minimisation, diet
  - Availability of peer support services, information and support services

**STEP 4** Follow up and referral
- Repeat Hep C Ab if recent (possible window period) or ongoing risk
- **Option 1***
  - Further assessment and treatment in primary care
- **Option 2***
  - Refer to specialist care for further assessment and treatment
- Repeat HCV RNA if ongoing risk

* Option 1 or Option 2 depending on commissioning arrangements

www.inhsueducation.org
Confirm chronic HCV infection
- Anti-HCV +ve indicates exposure to HCV virus
- HCV RNA +ve confirms current infection

Check HCV genotype, viral load and baseline screening
- HCV genotype determines treatment choice
- Quantitative HCV RNA test - if low viral load, consider shorter duration of therapy if genotyp 1
- Full Blood Count (FBC)
- Urea, electrolytes, creatinine (UCE)
- Liver function test (LFT) and INR

Pre-treatment Assessment

Assess liver fibrosis: could they have cirrhosis?
- Cirrhotic status determines treatment regimen and length
- Detect signs of chronic liver disease: jaundice, asterixis, hepatomegaly, ascites, peripheral oedema
- Undertake non-invasive assessment of fibrosis:
  - FibroScan assessment if available (>11.5 kPa consistent with cirrhosis)
  - Serum bio markers such as APRI (if score >1.0, significant risk of cirrhosis), FIB-4, HepaScore
  - A low albumin and/or a low platelet count suggests cirrhosis
  - Liver ultrasound if cirrhosis suspected to detect portal hypertension (splenomegaly, dilated portal vein, ascites, varices) and HCC screening

Detect causes of other liver disease
- Check for viral coinfection:
  - HIV Ab
  - Hepatitis A – check hep A IgG; vaccine if -ve
  - Hepatitis B – check HbsAg, anti-HBc and anti-HBs; vaccine if all –ve
  - Heavy alcohol intake
  - Fatty liver disease
  - Further investigations (e.g. iron studies) if indicated or abnormal LFT post treatment

Detect other major co-morbidities
- Renal disease
- Drug and alcohol use
- Heart disease - may not be able to use ribavirin (causes anaemia); perform ECG if ribavirin prescribed and patient has risk factors for IHD

Review previous HCV treatment
- Choice and length of treatment is influenced by genotype and prior HCV treatment experience / response

Consider contraception, pregnancy
- DAAs are not recommended for use in pregnant or lactating women
- Dual forms of contraception are required during treatment and for 6 months post-treatment if ribavirin is prescribed

Assess adherence
- Determine likelihood of adherence with medication, readiness to have treatment and the need for adherence support
- Current injecting drug use is not a contraindication for HCV treatment

Testing and Diagnosis

Treatment, Monitoring and Follow-up

Review drug interactions
- Check for potential drug interactions with current medications including over the counter drugs at www.hep-druginteractions.org. DAA selection and dose may need to be modified or current medication may need to be reviewed prior to treatment.

Select treatment regimen
- Refer to your local clinical guidelines. Choice of treatment regimen should follow recommendations on the most cost-effective regimen for the NHS, unless there are clinical reasons to choose an alternative regimen.

Treat and monitor
- Monitoring should be individualised, see Table 1
- Side effects of DAA therapy are generally mild

Post treatment follow-up (Table 1)
- SVR (cured), normal LFT, no cirrhosis – no further follow-up needed
- SVR (cured) but persistently elevated LFTs – require evaluation for other liver diseases
- No SVR (not cured, HCV detectable 12 weeks post-treatment) need specialist referral
- Cirrhosis – lifelong monitoring and specialist care
  - 6-monthly abdominal ultrasound (hepatocellular carcinoma screening)
  - Endoscopic surveillance for oesophageal varices
  - Osteoporosis; 2-yearly DEXA scans and monitor serum vitamin D

APRI SCORE CALCULATOR

APRI = \[
\frac{\text{AST Level (IU/L)}}{\text{AST (Upper Limit of Normal) (IU/L)}} \times 100
\]

Or use an online calculator at: www.hepatitisc.uw.edu/pageclinical-calculators/apri

Table 1: Monitoring on-treatment and post-treatment

Routine monitoring for a 12-week treatment regimen

<table>
<thead>
<tr>
<th>Blood tests</th>
<th>HCV virology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>FBC, U&amp;Es, LFTs, HCV RNA (qualitative)</td>
</tr>
<tr>
<td>Week 4, 8*</td>
<td>LFTs</td>
</tr>
<tr>
<td>Week 12</td>
<td>LFTs</td>
</tr>
<tr>
<td>Week 12 after End of Treatment (SVR)</td>
<td>LFTs, HCV RNA (qualitative)</td>
</tr>
</tbody>
</table>

Note: At each visit, assess for medication adherence, treatment adverse events and drug-drug interactions. Some people will require closer monitoring.

Links to resources
STEP 1 - Could my patient have advanced liver disease?

**Advanced Liver Disease** is the term used for chronic liver disease that has progressed to near cirrhosis or cirrhosis. **Cirrhosis** is caused by severe fibrosis (scarring). In **compensated cirrhosis**, the liver is still able to keep up with its major functions. ** Decompensated cirrhosis** typically refers to the presence of ascites/ oedema, hepatic encephalopathy and other complications of portal hypertension.

**What are the causes of advanced liver disease?**
- Chronic viral hepatitis (hepatitis B and/or C)
- Hazardous alcohol consumption
- Obesity, type 2 diabetes and the metabolic syndrome
- Rarer liver diseases

**Likelihood of advanced liver disease increases with:**
- Duration of liver disease, lifetime amount alcohol consumed, comorbid liver disease (e.g. obesity related liver-injury), increasing age, male gender, co-infection with HIV.

**Why is diagnosis of advanced liver disease important?**
- To prevent progression to decompensation and hepatocellular carcinoma (HCC). Also impacts treatment choices for hepatitis C.

**How to diagnose advanced liver disease**
No single test can reliably diagnose all cases. Information from the clinical history, examination, blood tests, abdominal ultrasound and fibroscan results can provide clues.

**When to suspect advanced liver disease**
- **Physical findings:** ascites, oedema, muscle wasting, and hepatic encephalopathy
- **Laboratory abnormalities:** reversal of AST/ALT ratio (normal <1), falling albumin, rising INR and bilirubin, falling platelets (suggests portal hypertension)
- **Imaging:** irregular liver outline, enlarged portal vein, splenomegaly
- **Non invasive markers of fibrosis:** Fibroscan (Transient Elastography is a safe quick effective method to assess liver stiffness) >11.5 kpa, or blood test algorithms including APRI, ELF (Enhanced liver fibrosis) and Fibrotest

STEP 2 – Correction of underlying liver disease aetiology

**Chronic hepatitis C virus (CHC) infection**
All people with CHC infection and advanced liver disease should be encouraged to consider the benefits of HCV antiviral therapy, such as the potential to limit the progression of liver disease and assist regression of liver damage and the prevention of onward transmission.

**Chronic hepatitis B virus (CHB) infection**
All people with CHB and advanced liver disease should be on oral antiviral therapy. HBV therapy may lead to progressive recovery/regression of advanced liver disease.

It is important to manage associated causes of liver injury in advanced liver disease, including:

**Alcohol**
People with advanced liver disease should **NOT** consume any alcohol.

**Non-Alcoholic Fatty Liver Disease (NAFLD)**
- Suspect if obesity, T2DM, metabolic syndrome
- Management: lifestyle modification and weight loss by dietary, exercise and medical interventions

**Other liver diseases**
Screen for haemochromatosis (iron studies), autoimmune liver disease, alpha-1-antitrypsin deficiency, Wilson’s disease, primary biliary cirrhosis, primary sclerosing cholangitis.

**Vaccinations**
Ensure the following vaccinations are undertaken when advanced liver disease is present:
- Pneumococcus and annual influenza
- Determine Hep B (HBsAg, anti-HBc, anti-HBs) & Hep A (anti-HAV IgG) status and vaccinate if not immune.

STEP 3 – When to refer to a Specialist

- **All patients with advanced liver disease**, as recognised by methods described in Step 1, should be referred to a specialist for treatment of known aetiology or further investigation if aetiology is unknown – especially if decompensated, untreated viral hepatitis, significant co-morbidities such as HIV or diabetes, focal abnormalities detected on scanning (do not biopsy without assessment in specialist centre)

**Urgent referral to hospital if:**
- Gastrointestinal bleeding
- Confusion/drowsiness (? possible encephalopathy)
- Unexplained fever or abdominal pain (? possible spontaneous bacterial peritonitis)
- New or progressive jaundice
- Marked shortness of breath with increased abdominal distension

**Prognosis**
- Median survival for compensated and decompensated cirrhosis are 12 and 2 years respectively.
- Severity and prognosis of liver disease can be estimated using the Child-Pugh score, the MELD score or the UK Model for End-Stage Liver Disease (UKELD) score. The UKELD is used in determining priority for liver transplantation.
- Complications of cirrhosis such as hepatorenal syndrome (development of renal failure), sepsis, variceal bleed and HCC are associated with a worse prognosis.
DECISION-MAKING IN VIRAL HEPATITIS RELATED ADVANCED LIVER DISEASE

UNITED KINGDOM

STEP 4 – Management of compensated cirrhosis

**Lifelong HCC surveillance is recommended for all patients with cirrhosis – see ‘HCC’**

Develop a chronic liver disease management plan and consider ongoing chronic disease management to:

- Minimise future liver damage
- Monitor for deterioration
- Screen for the complications, including HCC, osteoporosis, oesophageal varices, malnutrition and decompensation

**Minimise future liver damage**

- Treat HBV and/or HCV infection with antiviral therapy to prevent disease progression
- Encourage abstinence from alcohol, maintain a healthy diet and develop an exercise plan, especially if obese

**Monitor for deterioration/decompensation**

- Patients with compensated disease should have 6-monthly blood tests including FBC, EUC, LFT, INR/PT in conjunction with HCC screening and a clinical review especially monitoring nutritional status
- Gastroscopy surveillance for varices – see below for guidelines
- Watch for increasing INR, low albumin and rising bilirubin

**Recommended surveillance for complications of cirrhosis**

- **HCC – 6-monthly ultrasound**
- **Osteoporosis** – 2-yearly DEXA scans and monitoring of serum Vitamin D
- **Varices** – once cirrhosis is diagnosed, all patients should have baseline endoscopic surveillance for varices
  - the intervals to next endoscopy depend on the severity of varices and liver disease

**Liver transplantation**

- Chronic viral hepatitis, particularly HCV, is on of the major indications for liver transplant in the UK
- Many patients have co-existent HCC
- A referral to the liver transplant unit from a specialist may be required

STEP 5 – Management of decompensated cirrhosis and complications of portal hypertension

**General nutritional advice**

- High protein diet; add protein supplements if albumin is low; regular exercise
- Multiple small snacks as supplements, including a night time snack
- Avoid raw seafood, unpasteurised dairy products and soft cheeses
- Vitamin D and Ca supplements if required for osteopaenia/osteoporosis

**Ascites**

- **NaCl restriction** – 80mmol or 2000mg Na+/day
- Fluid restriction is not necessary unless serum Na+ drops to <=125mmol/L
- Diuretics, if renal function allows. These are only effective with adequate Na+ restriction
  - Initially spironolactone 50-100 mg mane and titrate up every 3-5 days to combination of spironolactone and frusemide (starting at 100mg mane and 40mg mane respectively; to max 400mg mane and 80mg bd or 160mg once daily if compliance a concern)
  - Aim for 0.5kg/day weight loss (3kg per week) and monitor renal function
- In patients who do not respond to aldosterone antagonists, as defined by a reduction of body weight of less than 2 kg/week, or in patients who develop hyperkalaemia, frusemide should be added at an increasing stepwise dose from 40 mg/day to a maximum of 160 mg/day (in 40 mg steps)

**Renal function**

- Kidneys are sensitive to insults:
  - Avoid NSAIDs and other nephrotoxins
  - Any decompensation can contribute to renal impairment (Infection, bleeding)

**Hepatic Encephalopathy (HE)**

- Reversible neuropsychiatric changes: stereotypic asterixis (hepatic flap), fetor (sweet breath), dyspraxia (difficulty with 5 point star), sleep pattern reversal
- Identify precipitants such as infection, GIT bleeding, medications (esp. sedatives)
- Titrate lactulose for 2-3 loose motions per day
- Non absorbable antibiotics Rifaximin if difficult to control HE
- Patients are likely unfit to drive, particularly if there are recurrent episodes

**Hepatocellular carcinoma (HCC)**

- Therapies dictated by tumour size and location, hepatic reserve and general health
- Treatment may be curative (surgery, percutaneous ablation and liver transplant) or palliative
- Chemoembolisation, chemotherapy and support
- Management should be in a centre of excellence with a multidisciplinary team to review treatment

**Spontaneous Bacterial Peritonitis (SBP)**

- May present with fever, change in mental status or pain
- Low threshold for referral to hospital
- Ascitic fluid WCC >250 cells/mm diagnostic
- Hospitalisation for IVI antibiotics and albumin infusion required
- Secondary prophylaxis with co-trimoxazole 160/800mg ("Bactrim DS") one daily or norfloxacin 400mg daily continuously is effective

**Variceal bleeding**

- Present with hematemesis and/or melaena
- Arrange urgent admission to hospital for endoscopic evaluation and therapy
- Secondary prophylaxis with propranolol reduces further bleeding (titrate dose to achieve a 25% reduction from usual baseline pulse rate)
- After discharge, further endoscopy therapies required to obliterate varices

**Cardiopulmonary complications**

- Breathlessness may be the first sign of cardiopulmonary complication such as hepatopulmonary syndrome, porto-pulmonary hypertension or cirrhotic cardiomyopathy

This resource was originally produced in collaboration with the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, Gastroenterological Society of Australia, Australasian Society for Infectious Diseases, Australasian Hepatology Association and Hepatitis Australia. It has been adapted for the UK by the International Network on Hepatitis in Substance Users in collaboration with local partners.

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Preface

These guidelines were generated following a consensus meeting held in Birmingham on the 30\textsuperscript{th} of June 2017 of representatives from the above organisations as well as representatives from the operational delivery networks in England. They are intended to reflect best practice rather than what is currently commissioned for HCV treatment.

Headline Recommendations

1. We recommend that NHSE considers commissioning pan-genotypic regimens for use in the community for patients who are treatment naïve and do not have cirrhosis to avoid the need for genotyping and facilitate rapid access to care.

2. We recommend that ribavirin be avoided whenever possible.

3. We recommend that 8 week regimens without ribavirin are first choice for treatment naïve non-cirrhotic patients treated in community or prison settings regardless of genotype.

4. We reiterate that transplantation is not contra-indicated in patients with HCV even in the presence of ‘difficult’ drug resistant mutations.

5. Drug-drug interactions should continue to be assessed and therapy should take account of potential interactions.
Genotype Specific Recommendations

Non-cirrhotic

**G1a**
Sofosbuvir/ledipasvir 8 weeks (treatment naïve) or 12 weeks (treatment experienced)
Grazoprevir/elbasvir 12 weeks OR 16 weeks + ribavirin for patients with viral load >800,000 and resistance associated substitutions (16 weeks + ribavirin is NOT a preferred regimen)
Paritaprevir/ritonavir/ombitasvir+dasabuvir+ribavirin 12 weeks – should be discarded when Glecaprevir/pibrentasvir is available.
Sofosbuvir/velpatasvir 12 weeks
Sofosbuvir/velpatasvir/voxilaprevir - 8 weeks
Glecaprevir/pibrentasvir - 8 weeks

**G1b**
Sofosbuvir/ledipasvir 8 weeks (treatment naïve) or 12 weeks (treatment experienced)
Grazoprevir/elbasvir 12 weeks
Paritaprevir/ritonavir/ombitasvir+dasabuvir+ribavirin 12 weeks – should be discarded when Glecaprevir/pibrentasvir is available.
Sofosbuvir/velpatasvir 12 weeks
Sofosbuvir/velpatasvir/voxilaprevir 8 weeks
Glecaprevir/pibrentasvir 8 weeks

Compensated cirrhosis

**G1a**
Sofosbuvir/ledipasvir 12 weeks
Grazoprevir/elbasvir 12 weeks OR 16 weeks + ribavirin for patients with viral load >800,000 and resistance associated substitutions (16 weeks + ribavirin is NOT a preferred regimen)
Paritaprevir/ritonavir/ombitasvir+dasabuvir+ribavirin 12-24 weeks - should be discarded when Glecaprevir/pibrentasvir is available.
Sofosbuvir/velpatasvir 12 weeks
Sofosbuvir/velpatasvir/voxilaprevir 12 weeks
Glecaprevir/pibrentasvir 12 weeks

**G1b**
Sofosbuvir/ledipasvir 12 weeks
Grazoprevir/elbasvir 12 weeks
Paritaprevir/ritonavir/ombitasvir+dasabuvir 12 weeks - should be discarded when Glecaprevir/pibrentasvir is available.
Sofosbuvir/velpatasvir 12 weeks
Sofosbuvir/velpatasvir/voxilaprevir 12 weeks
Glecaprevir/pibrentasvir 12 weeks

**Decompensated cirrhosis G1a &1b**
Sofosbuvir/ledipasvir +/- ribavirin 12 weeks
Sofosbuvir/velpatasvir + ribavirin 12 weeks

**Re-treatment for DAA failures**
Requires pre-treatment virological sequencing to identify resistance associated variants whose presence/absence should be used to guide treatment decisions.

Sofosbuvir/velpatasvir/voxilaprevir 12 weeks
Glecaprevir/pibrentasvir 12 weeks (no prior NS5A) or 16 weeks (prior NS5A)

Decompensated cirrhosis – re-treatment requires Sof/vel +/- riba 24 weeks

**G2**

**Non cirrhotic**
Strongly recommend that IFN is removed and ribavirin free regimens are preferred.
Sof/Vel 12 weeks
Sof/Vel/Vox 8 weeks
Glecaprevir/pibrentasvir 8 weeks

**G2 Cirrhosis**
Sof/Vel 12 weeks
Sof/vel/vox 12 weeks
Glecaprevir/pibrentasvir 12 weeks

**Decompensated cirrhosis**
Sof/vel +/- riba 12 weeks

**Re-treatment of DAA failures**
Requires pre-treatment virological sequencing to identify resistance associated variants whose presence/absence should be used to guide treatment decisions.

Sofosbuvir/velpatasvir/voxilaprevir **12 weeks**
Glecaprevir/pibrentasvir 16 weeks
G3

Non cirrhotic
Sof/Vel 12 weeks
Sof/Vel/Vox 8 weeks
Glecaprevir/pibrentasvir 8 weeks

Cirrhotic
Sof/Vel 12 weeks
Sof/Vel/Vox 12 weeks
Glecaprevir/pibrentasvir 16 weeks

Decompensated cirrhosis
12 weeks sofosbuvir/velpatasvir +ribavirin.
Consideration should be given to the use of sof/vel for 24 weeks in patients deemed unlikely to respond or intolerant of ribavirin.

Re-treatment for DAA failures
Requires pre-treatment virological sequencing to identify resistance associated variants whose presence/absence should be used to guide treatment decisions.
Sofosbuvir/velpatasvir/voxilaprevir 12 weeks
Decompensated cirrhosis – re-treatment requires Sof/vel +/- riba 24 weeks

G4

Non Cirrhotic
Given the paucity of data and the availability of better-validated regimens we recommend that the use of sofosbuvir/ledipasvir for patients with Genotype 4 HCV should be discontinued.
Grazoprevir/elbasvir 12
Paritaprevir/ritonavir/ombitasvir 12 weeks - should be discarded when Glecaprevir/pibrentasvir is available.
Sofosbuvir/velpatasvir/voxilaprevir 8 weeks
Sofosbuvir/velpatasvir 12 weeks
Glecaprevir/pibrentasvir 8 weeks

Cirrhosis
Grazoprevir/elbasvir 12 OR 16 weeks
Sofosbuvir/velpatasvir 12 weeks
Paritaprevir/ritonavir/ombitasvir 12 weeks - should be discarded when Glecaprevir/pibrentasvir is available.
Sofosbuvir/velpatasvir/voxilaprevir 12 weeks
Glecaprevir/pibrentasvir 12 weeks

Decompensated cirrhosis
12 weeks sofosbuvir/velpatasvir +ribavirin.
**Re-treatment for DAA failures**
Requires pre-treatment virological sequencing to identify resistance associated variants whose presence/absence should be used to guide treatment decisions.

- Sofosbuvir/velpatasvir/voxilaprevir 12 weeks
- Glecaprevir/pibrentasvir 16 weeks

**G5/6**
The small number of patients G5/6 infection in trials reported to date was noted.

**Non cirrhotic**
- Sof/Vel 12 weeks
- Glecaprevir/pibrentasvir 8-12 weeks
- Sof/Vel/Vox 8 weeks

**Cirrhotic**
- Sofosbuvir/velpatasvir 12 weeks
- Glecaprevir/pibrentasvir 12 weeks
- Sof/vel/vox 8 weeks

** Decompensated cirrhosis**
- 12 weeks sofosbuvir/velpatasvir +ribavirin.

**Re-treatment for DAA failures**
Requires pre-treatment virological sequencing to identify resistance associated variants whose presence/absence should be used to guide treatment decisions.

- Sofosbuvir/velpatasvir/voxilaprevir 12 weeks
- Glecaprevir/pibrentasvir 16 weeks (note that in patients with both NS5A and NS3 resistance associated variants this regimen is likely to be inadequate)

**Special Patient Categories**

**Patients with renal impairment**
We recommend treatment as above but recommend that sofosbuvir be avoided in patients with GFR <45 ml/min.

**HIV-hepatitis C coinfection**
We recommend that patients with HIV-hepatitis C coinfection are treated for chronic hepatitis C with the same DAA-based treatment regimens as patients
with hepatitis C mono-infection, although consideration of drug-drug interactions between DAAs and antiretrovirals should be taken into account.

We recommend that where HIV therapy cannot be switched to avoid drug-drug interactions, an appropriate alternate DAA-based regimen is identified.

**Acute hepatitis C infection**

We note emerging data shows public health benefits with early DAA therapy for patients with acute HCV who are at high risk of transmission. We recognize that pegylated interferon and ribavirin (the only current treatment option) is unlikely to be acceptable to patients and we therefore recommend that DAA-based treatment is made available for the treatment of acute and early hepatitis C infection, replacing pegylated-interferon +/- ribavirin 24 to 48 weeks

**Re-infection following successful DAA-based hepatitis C treatment**

We recommend that DAA-based treatment is made available for the treatment of hepatitis C re-infection following successful DAA-based hepatitis C treatment.

**Solid Organ Transplantation**

HCV infection acquired from a donor organ can be readily treated with currently available drug regimens. We recommend that patients without HCV infection should be offered an opportunity to receive an organ infected with HCV and we recommend that such recipients are offered antiviral therapy as soon as practicable post transplantation; with usual practice being to initiate treatment within the first month.
National Clinical Guidelines for the treatment of HCV in adults

Version 4

November 2017
Sponsors and Authorship

The guidelines have been authored on behalf of the viral hepatitis clinical leads and MCN co-ordinators network; lead authors: Prof. John F Dillon, Prof P Hayes, Dr S Barclay, Dr R Fox and Dr A Fraser.

The development of the national guidance has been a collaboration between Scotland’s clinical leads in viral hepatitis, National Services Scotland and Healthcare Improvement Scotland, in response to a request from the National Sexual Health & BBV Advisory Committee of the Scottish Government.

Purpose of guidelines

To provide guidance to Health Board Area Drug and Therapeutics Committees on the recommended place in treatment of available HCV medicines taking into consideration SMC guidance, clinical effectiveness and price.

Use of these guidelines

This is a rapidly changing field and these guidelines will be updated on a regular basis and should be used to guide treatment choices. Where no contraindication exists, the most cost effective regimen amongst the recommended options should be chosen to maximise the number of patients who can be treated.

Background

HCV is a blood borne virus leading to cirrhosis of the liver and hepatocellular carcinoma, it affects up to 1% of the Scottish population. The Scottish Government under the HCV Action Plan and succeeded by the Sexual Health and Blood Borne Virus Strategic Framework have provided a world leading structure for the prevention, diagnosis, treatment and care of HCV. Rapid advances in HCV therapeutics have led to an array of anti-HCV medicines that now offer cure to more than 90% of those infected with HCV. The process of implementation of these medicines into the NHS is being guided by principles developed by the HCV Treatment & Therapies Sub-Group of the National Sexual Health & BBV Advisory Committee. The National Sexual Health & BBV Advisory Committee is chaired by the Scottish Government Minister for Public Health (and Sport), and provides advice to the minister on the Sexual Health and Blood Borne Virus Strategic Framework. To support this implementation it is necessary to evaluate the available evidence for the anti-HCV medicines, group these medicines in terms of their efficacy to allow them to be compared for cost-effectiveness and then a preferred regimen selected based on cost to NHS Scotland.

Development process

The guidelines are based on the integrated outputs from three sources of evidence. A systematic review, an expert review of recent conference abstracts and expert opinion from a national panel of expert stakeholders. The systematic review was commissioned and funded by Health Protection Scotland and performed by staff from the University of Dundee, Health Protection Scotland, and Glasgow Caledonian University. It was performed in accordance with PRISMA guidelines and adhered to Cochrane principles. The search included all phase 2b and phase 3 trials of HCV therapy published between 1st January 2009
and 31st December 2015. Subsequent to this, the guidelines have been updated to take account of newly licensed therapies and expert review of emerging data either published or presented at international liver meetings.

**Principles**

There are national pricing agreements in place for medicines covered by the guidance; NHS National Procurement will keep Health Boards and lead prescribers informed of costs.

In keeping with government policy and the preference of Health Boards only SMC approved medicines were considered for final recommendation in the guidelines.

In keeping with the principles developed by the HCV Treatment & Therapies Sub-Group of the National Sexual Health & BBV Advisory Committee, which states that patients should have an expectation that the likelihood of cure as a result of their initial treatment is at least 90% and this should be achieved with minimal possible side effects.

There is an expectation from Government and Health Boards that the most cost effective regimen will be selected for an individual patient. In each of the treatment categories below the preferred drug has been selected based on its cost to NHS Scotland from among regimens of equivalent efficacy.

**Guidance**

HCV genotype remains an important determinant of choice of regimen and chance of cure therefore the guidance is presented according to genotype. The new regimens are well tolerated with low levels of side effects and we have not differentiated between the regimens on this basis nor on duration of therapy, taking the view that they are effectively equivalent.

There is a small number of Drug-Drug Interactions (DDI) that may dictate choice of regimen and the University of Liverpool web site should be consulted for potential interactions. The issue of DDI is particularly relevant to HCV-HIV co-infection, other than the greater potential for DDI co-infected patients should be treated in the same fashion as mono-infected patients.

**Genotype 1**

The systematic reviews demonstrated that there were a number of regimens that crossed the 90% threshold for efficacy. Further the reviews show that these regimens can be regarded as equally efficacious, with overlapping confidence intervals.

The regimens are listed in the table below, the durations of some regimens have been shortened from those submitted to SMC or listed in the specific product information. This is due to emerging data from the expert review of trial data where numerical differences were not shown to be statistically different and confidence intervals overlapped on meta-analysis. This suggests that these shortened regimens with the addition of ribavirin if required are equally efficacious and likely to be much more cost effective than those of longer duration.
Where licensed, SMC approved regimens are felt to have suboptimal efficacy for a particular indication they have been removed in line with international guidelines.

For the purposes of this guideline treatment experienced is assumed to be an interferon based regimen with or without a first generation PI, or in the case of Glecaprevir/Pibrentasvir, Interferon based regimens +/- sofosbuvir, or sofosbuvir + ribavirin. For patients previously treated with Ns5a inhibitors, see the guidance below. Cirrhosis refers to compensated (Child’s A) cirrhosis. Not all regimens are recommended for patients with decompensated liver disease, advice should be sought from a liver unit before treating such patients especially with protease containing regimens.

<table>
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<tr>
<th>Genotype 1</th>
<th>Recommended regimens</th>
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| Treatment naive or experienced* non-cirrhotic | Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir +/- Ribavirin 12 weeks  
Sofosbuvir, Ledipasvir 8 (naïve) or 12 weeks (experienced)  
Sofosbuvir, Daclatasvir 12 weeks (F3 only)  
Elbasvir/Grazoprevir 12 weeks**  
**Glecaprevir/pibrentasvir - 8 weeks

Cirrhotic irrespective of previous treatment | Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir, +/- Ribavirin 12 weeks  
Sofosbuvir, Ledipasvir, Ribavirin 12 weeks  
Sofosbuvir, Daclatasvir, Ribavirin 12 weeks  
**Elbasvir /Grazoprevir, 12 weeks**  
Glecaprevir/pibrentasvir 12 weeks

*Prior exposure to Interferon containing regimens +/- first generation protease inhibitor, additionally in the case of Glecaprevir/Pibrentasvir patients exposed to Sofosbuvir with or without Interferon (but not other DAAS).

**In HCV genotype 1a elbasvir grazoprevir for 16 weeks plus ribavirin should be considered in patients with baseline HCV RNA level >800,000 IU/ml and the presence of specific NS5A polymorphisms

Genotype 2

PEG Interferon alpha with ribavirin is an effective treatment for HCV genotype 2 with SVR rates of 90%, but fails on the criteria of acceptable side effects. SMC approved alternatives are preferred.

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<th>Genotype 2</th>
<th>Recommended regimens</th>
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| Cirrhotic or non-cirrhotic | Sofosbuvir /Velpatasvir 12 weeks  
**Glecaprevir/pibrentasvir 8 weeks (non cirrhotic) or 12 weeks (cirrhotic)**
Genotype 3

The therapy of HCV genotype 3 has improved considerably. In line with international recommendations and the recognised adverse side effect profile, Interferon containing regimens are no longer recommended, even in subgroups where a greater than 90% SVR may be predicted. Both Sofobuvir/Velpatasvir and Glecaprevir/Pibrentasvir have demonstrated the ability to cure in excess of 90% of patients.

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<th>Genotype 3</th>
<th>Recommended regimens</th>
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| Non-cirrhotic | Sofosbuvir, Velpatasvir 12 weeks  
Glecaprevir/pibrentasvir 8 weeks (treatment naive) or 16 weeks (treatment experienced) 
Sofosbuvir, Daclatasvir, Ribavirin 12 weeks (F3 only) |
| Cirrhotic | Sofosbuvir, Velpatasvir, +/- ribavirin 12 weeks 
Glecaprevir/pibrentasvir 12 weeks (treatment naive) or 16 weeks (treatment experienced) |

Genotypes 4 - 6

Genotypes 4-6 are uncommon in Scotland, though effective treatments are available. The most cost-effective of the SMC available medicines should be used. These should be prescribed according to local protocols or based on expert advice.

Re-treatment of Patients not cleared by DAAs

Re-infection should be considered and if shown treatment should be based on treatment naive regimens for that genotype. In patients who adhered to therapy, who did not achieve sustained virological response and in whom re-treatment is being considered should have pre-treatment virological sequencing to identify resistance associated substitutions whose presence/absence should be used to guide treatment decisions. Treatment decisions should be made by expert clinicians or based on the advice of such clinicians. The therapeutic options are constantly being revised in light of new data and decisions should reflect this and be individualised to give the patient the best chance of cure.

Liver Transplantation

These general principles apply to other solid organ transplants in addition to liver transplantation. There may be some differences however so discussion with the parent transplant unit is important. In general, treatment before transplant is preferable as it may allow liver recovery and prevent the need for transplantation, allow patients to be aviraemic at the time of surgery and reduce the risk of fibrosing cholestatic hepatitis. However patients with significant liver decompensation may not respond as well to treatment and early
transplantation is best. Liver transplantation when patients have hepatitis C viraemia results in universal infection of the liver graft.

All patients should be considered for hepatitis C treatment post liver transplant once their steroids are stopped (or greatly reduced) usually 3 months after transplantation. An exception might include those with fibrosing cholestatic hepatitis, which is rare, where early treatment may be beneficial. Priority should be given to those with fibrosis.

Drug interactions must be considered in all patients. This is likely to be especially important early post-transplant when multiple medicines are prescribed. Pharmacy input in this setting is essential. Otherwise patients should be treated according to genotype using the drug regimens outlined in this document as appropriate. Communication between the transplant unit and the local prescriber is paramount. Annual routine biopsies to assess the fibrosis progression in post-transplant hepatitis C patients is no longer indicated.

**Drug combinations in special circumstances**

The above guidelines are recommended first line treatments, approved by SMC and should be used as the standard of care. There are special circumstances such as drug resistance where alternative approaches are needed. Where there are specific circumstances such as DAA treatment failures, co-morbid disease, especially renal failure or a clinical need for shorter duration of therapy, alternative combinations with supporting trial evidence can be considered via local agreement.
These are the risks...

Blood transfusions (prior to 1992)
Injecting drugs, even once
Unsterile tattoos/piercings
Medical/dental procedures abroad
Other blood to blood contact

Discuss with your GP whether to get tested for hepatitis C

Find out more at www.hepctrust.org.uk or call our helpline: 0845 223 4424
Introduction to hepatitis C

The word *hepatitis* comes from the Ancient Greek word for liver (*hepar*) and the Latin word for inflammation (*itis*). Chemicals, drugs, excessive alcohol consumption or blood-borne viruses can all cause inflammation to the liver.

What is hepatitis C?

Hepatitis C is an infection caused by the hepatitis C virus that causes inflammation of the liver. Infection can occur through blood-to-blood contact due to unsafe injection and other skin penetration practices, inadequate sterilisation of medical equipment, and the transfusion of unscreened blood and blood products.

Currently, there is no vaccine for hepatitis C virus, as there is for hepatitis A and hepatitis B. A person can be re-infected throughout their life and can live with more than one hepatitis virus at once.

Symptoms and diagnosis

HCV infection can range in severity from a mild illness lasting a few weeks to a serious, lifelong illness.

Common symptoms of acute infection are:

- General aches and pains
- Nausea
- Abdominal pain and discomfort
- Loss of appetite
- Rarely yellowing of the eyes and skin (jaundice)

About 25% of people infected will clear the virus naturally in the first 12 months (*acute infection*).

However, if the infection does not clear up on its own, the virus continues to damage the liver. Of those who are exposed to hepatitis C, up to 75% will go on to develop *chronic infection*.

A person living with chronic hepatitis C may not know they have it because it can take many years for symptoms to appear. Consequently, many people live undiagnosed for years. Some cannot identify how they were infected.
Impact on the liver

Over time Hepatitis C infection can seriously impair liver function, causing fibrosis or cirrhosis (scarring of the liver), and can lead to hepatocellular carcinoma (HCC).

The rate of progression to cirrhosis is variable and depends on several factors, including age of initial infection, male gender, alcohol consumption, co-infections including HIV and hepatitis B virus, and obesity. Around 10-15% of people living with chronic HCV infection will develop cirrhosis within the first 20 years after infection; those who develop cirrhosis are at increased risk of HCC.

Geographical distribution

Globally, there about 70 million people living with hepatitis C, a figure which represents roughly 1% of the population. The regions most affected are Africa and Central and East Asia.

Hepatitis C genotypes

There are six main genotypes (viral strains) of HCV worldwide, each with numerous subtypes, and their distribution varies by region. Knowing the genotype is important when making decisions about treatment.

New treatments

Unlike HIV and HBV infection, hepatitis C infection can be cured.

Testing for the virus is simple and the new generation treatments are far more effective, easier to take and have fewer side-effects than the older medications.

How hepatitis C spreads

The hepatitis C virus is a blood-borne virus, meaning it’s transmitted when the blood of an infected person enters another person’s bloodstream. It only takes a small amount of blood to transmit hepatitis C. The virus can live outside of the body for at least four days. In other conditions, it can survive for much longer (e.g. for many weeks inside a syringe).

Understanding the risks

There are many myths about exactly how hepatitis C is transmitted. It is important to know that the riskiest activities are those with the highest potential and frequency of blood-to-blood contact. Those activities that have no chance of exchanging blood are considered no risk. Based on these distinctions, high-risk, some-risk and no-risk activities are outlined below.

High-risk activities

• Unsterile medical or dental procedures and traditional medical practices where the skin is pierced.
• Re-using someone else's injecting equipment for drugs.
• Unsterile tattooing or body piercing.

Moderate-risk activities

• Needle-stick injuries to healthcare workers.
• Mother-to-child transmission may happen during pregnancy or childbirth if mother has hepatitis C.
• Received blood transfusion before September 1991 in the UK.
• Re-using someone else's personal items that may have blood on them, such as razors and toothbrushes.
• Blood-to-blood contact during sex.
No-risk activities

If there is no blood-to-blood contact, there is no risk of transmission of hepatitis C. People cannot get or transmit hepatitis C by:

- Sharing toilets, drinking glasses or eating utensils
- Hugging, kissing or touching
- Using swimming pools
- Mosquito or other insect bites
- Coughing or sneezing

Risks for people living with hepatitis C

Understanding how hepatitis C is transmitted is important for people who are living with hepatitis C so they can reduce the chance of:

- Being infected with another genotype of hepatitis C.
- Being re-infected with the same genotype of hepatitis C.
- Transmitting hepatitis C to another person.
Sometimes people who inject drugs may be part of social networks where they are unable to exercise full control over the circumstances in which they inject. For example, in some intimate or familial relationships, voicing an expectation that each person will use their own sterile equipment may be interpreted as implying a lack of trust, making a person uncomfortable or unwilling to jeopardise their relationships in this way.

In other situations, there may be a power imbalance between people who inject together which prevents the person with less power in the relationship from demanding that each person use their own, new equipment. This might be the case, for example, in a relationship between an older man with years of injecting experience and a younger woman who has injected for only a year or two and relies on her partner to purchase and prepare the drugs.

Some people may never have learnt to inject themselves, and rely on others to do it for them. In this case, they are dependent on the person injecting them to be willing to prepare the injections using new equipment, and the experienced injector may be unable or unwilling to do so. In prison, the extremely limited access to injecting equipment means that people who inject drugs in this environment inevitably do so with used equipment.
For example, Needle and Syringe Programmes may have uneven distribution. This, combined with stigma and discrimination that some drug users may experience when accessing equipment, and the potential that their confidentiality may be breached and they will be identified as someone who injects drugs, can leave people reluctant to use services.

People may also be reluctant to access NSPs if they feel their eligibility for OST may be threatened, for example if their access points for both OST and sterile equipment are co-located.

If, however, your patient is able to and comfortable accessing their local Needle and Syringe Programme, you could advise them to, where possible, stock up with more injecting equipment than they think they might need (“so there’s always some spares, for you or anyone else who might need them”). Patients may also find it useful to make contact with their local peer organisation to access advice and support from people who understand and can relate to their circumstances.
Has the person ever been exposed to HCV?

Test 1 - The Antibody (Ab) test
A positive HCV Ab result indicates that the person has been exposed to the virus at some point in their life. Note that:

- A positive HCV Ab test result does not distinguish between acute, chronic or cleared infection.
- The presence of HCV antibodies does not provide protection against HCV.

A negative result means that current HCV infection is unlikely. The HCV antibody test has low rates of false negatives or positives. However, this test may need to be repeated if the person has been exposed to risk recently (and possibly tested during the ‘window period’).

A small number (<5-10%) of immunocompromised hosts, including people living with HIV, may never develop HCV Ab, despite chronic HCV infection. In this case, HCV RNA testing should be performed to diagnose active HCV infection.

Does the person currently have HCV?

Test 2 - The RNA test
This can be determined by ordering a HCV RNA test. This is a test to detect the presence of virus in the blood, by Polymerase Chain Reaction (PCR). The HCV RNA test may be qualitative or quantitative. A positive result confirms the detection of HCV RNA and current viraemic HCV infection.
What HCV genotype do they carry?

A HCV genotype test is necessary before treatment initiation, as current treatments are genotype-specific. HCV genotyping is a routine laboratory test performed during RNA testing.

As new treatments continue to become available it is likely all genotypes will be easier to treat, with pan-genotypic therapies.

What is the HCV RNA level (HCV “viral load“)?

Quantitative HCV RNA at treatment commencement (baseline) may help predict a person’s response to therapy. A low pre-treatment HCV RNA (“viral load”) may allow for a shorter duration of therapy. The length of therapy should be discussed with your local support network at the regional MDT meeting who can advise on the most appropriate regimen and its duration.

How is their liver functioning?

Liver Function tests (LFTs) provide a baseline of current liver function and help identify damage to liver cells. The relevant component tests of a routine LFT are bilirubin, ALP, GGT, ALT and AST. Documentation of the presence or absence of cirrhosis influences treatment regimen and duration.
Consent and confidentiality

In your discussions with your patient, you need to ensure they are well informed of the testing process, and you should obtain their verbal informed consent to proceed with testing. You have an opportunity to educate your patient on how to prevent HCV transmission, and assure them of your confidentiality through the discussion.

Gaining informed consent

- Inform the patient of your confidentiality and alleviate any anxiety they have regarding this
- Enquire about their motivation for getting tested
- Provide clear, appropriate information about HCV, including natural history and modes of transmission
- Explain the process of testing, window period and possibility of indeterminate results
- Discuss benefits of early detection
- Assess their ability to cope with positive result and social supports
- Supply written material about HCV (excellent resources for patients are available from www.hepctrust.org.uk)

Conveying test results

- Always give test results in person where possible
- Explain the meaning of the result and discuss immediate implications for the patient
- Avoid overloading the person with information
- Provide emotional support
- Reinforce education about transmission prevention and harm reduction
- Allow adequate time to answer the patient’s questions
- Advise on aspects of positive status disclosure
- Arrange any further tests and offer follow-up as required
- Supply written material and contact details for relevant support services and/or peer-based drug users’ organisation.
How to test for fibrosis

Once HCV has been diagnosed, the degree of liver fibrosis needs to be determined, as accurate staging will determine appropriate treatment and monitoring.

Non-invasive assessment

Although fibrosis assessment is imperative, liver biopsy is no longer required for most patients with chronic HCV infection. Non-invasive assessment of fibrosis has eliminated the need for biopsy in the majority of patients, and histologic confirmation of clinically evident cirrhosis is not required.

Liver ultrasound

Liver imaging may be used to assess for complications of cirrhosis, including hepatocellular carcinoma and portal hypertension. An ultrasound is preferred over CT scan as the initial investigation to avoid unnecessary radiation.

- If the ultrasound shows an abnormality, such as a nodule, more accurate cross-sectional imaging, such as computed tomography scan or magnetic resonance imaging scan, with and without contrast, would be indicated.

FibroScan®

FibroScan® is most accurate in identifying patients:
- Without significant fibrosis (<7.5 kPa)
- With cirrhosis (>11.5 kPa)

It is important to note that:
- Diagnostic accuracy declines when attempting to determine intermediate stages of fibrosis.
- Liver stiffness is increased independently of the degree of fibrosis in inflammatory liver conditions (E.g. acute HCV infection, acute alcoholic hepatitis or non-alcoholic steatohepatitis).
- Hepatic steatosis may increase the liver stiffness measurement obtained by FibroScan®. Abdominal obesity may overestimate the FibroScan® score – make sure the appropriate sized probe is used for each patient.
- FibroScan® does not give a reason for fibrosis or provide info on other liver pathology.
How FibroScan® works

An ultrasonic transducer sends a vibration wave into the liver. The velocity of the wave correlates with tissue stiffness. The stiffer the liver is, the greater the degree of fibrosis.

FibroScan® examination

Ideally, a patient should have fasted for 4 hours before the procedure.

While the patient is lying down, the probe is placed on the skin over the liver area, typically in the right mid-axillary line. Generally 10 measurements are taken to exclude outliers. The patient feels a gentle ‘flick’ each time a vibration wave is generated by the probe.

The whole procedure takes 5-10 minutes to perform, causes no discomfort, and results are available immediately.

APRI score

Although serum biomarkers have a role in patient management, they should not be over-interpreted.

In general, FIB-4 or APRI is most accurate for identifying patients at both ends of the spectrum of hepatic fibrosis: those at low risk for early or minimal disease (fibrosis stage 0 to 1) and those at high risk for advanced disease (fibrosis stage 3 to 4).
FibroScan® staging – understanding a FibroScan® result

The FibroScan® provides a numerical score of liver stiffness, which indicates the severity of liver fibrosis.

The diagram below shows what FibroScan® scores mean.

<table>
<thead>
<tr>
<th>Score</th>
<th>2.5 – 7.4</th>
<th>7.5 – 9.4</th>
<th>9.5 – 11.4</th>
<th>&gt; 11.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicates</td>
<td>F0/F1</td>
<td>F2</td>
<td>F3</td>
<td>F4</td>
</tr>
<tr>
<td></td>
<td>No/Mild fibrosis</td>
<td>Moderate fibrosis</td>
<td>Severe fibrosis</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Indicates no or minimal liver fibrosis and no evidence of progressive liver disease.</td>
<td>Indicates significant liver fibrosis and evidence of progressive liver disease.</td>
<td>Indicates severe liver fibrosis and high risk progression to cirrhosis.</td>
<td>Indicates extensive liver fibrosis consistent with cirrhosis.</td>
</tr>
</tbody>
</table>
Liver disease, caused by HCV infection, can cause many signs and symptoms. As the disease evolves, signs can appear in many people – but not all, even when cirrhosis is present. Once the disease is well advanced, the features of hepatic decompensation and portal hypertension may appear, including ascites, jaundice, bleeding varices, coagulopathy, encephalopathy and renal failure.

Clinicians need to know what to look for as part of the process for staging liver disease. Cirrhosis severity can be staged by the Child-Pugh, and is based on serum bilirubin, serum albumin, INR, presence of ascites and presence of encephalopathy.

The Fib 4 (Fibrosis 4) score is a non-invasive scoring system based on several laboratory tests that help to estimate the amount of scarring in the liver. A Fib 4 calculator can be found at https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4.

An Enhanced Liver Fibrosis (ELF) score can also be used to help estimate fibrosis. The ELF score combines quantitative serum concentration measurements of three fibrosis markers. Find out more about ELF scores at www.gpnotebook.co.uk/simplepage.cfm?id=x2016072075237544321.

Physical examination findings in chronic liver disease (of any aetiology) may include hepatomegaly and splenomegaly. A wide variety of non-specific signs (e.g. leukonychia, palmer erythema and gynaecomastia) have been associated with liver disease but these signs are of limited value. It is important to determine whether there are any signs of liver decompensation and the physical examination should focus on looking for these features. If there is doubt as to the severity of the liver disease the patient should be discussed with local experts.
Physical examination findings associated with decompensated liver disease

- Signs of hepatic encephalopathy: Drowsiness, asterixis (or ‘hepatic flap’)
- Jaundice
- Ascites
- Peripheral edema
- Bruising

Complications of chronic liver disease and cirrhosis

- Portal hypertension – varices on endoscopy
- Ascites – may be detected clinically or on ultrasound examination
- Hypersplenism (with or without splenomegaly)
- Synthetic dysfunction
- Hypoalbuminaemia
- Coagulopathy
- Hepatic encephalopathy
- Hepatocellular carcinoma
- Hepatopulmonary and hepatorenal syndromes
Some of the most common extra-hepatic manifestations of HCV infection are described here.

<table>
<thead>
<tr>
<th>Immune-mediated</th>
<th>Inflammatory-related</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td><strong>Renal</strong></td>
</tr>
<tr>
<td>• Mixed cryoglobulinemia (10-25% of HCV people have cryoglobulins but this is rarely symptomatic)</td>
<td>• Glomerulonephritis</td>
</tr>
<tr>
<td>• Cryoglobulinaemic vasculitis</td>
<td>• Nephrotic syndrome</td>
</tr>
<tr>
<td>• B-cell non-Hodgkin’s lymphoma</td>
<td><strong>Endocrine</strong></td>
</tr>
<tr>
<td>• Monoclonal gammopathy</td>
<td>• Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>• Immune-mediated thrombocytopenia</td>
<td>• Insulin resistance</td>
</tr>
<tr>
<td></td>
<td><strong>Central and peripheral nervous system</strong></td>
</tr>
<tr>
<td><strong>Rheumatologic</strong></td>
<td>• Depression</td>
</tr>
<tr>
<td>• Sicca syndrome</td>
<td>• Cognitive impairment</td>
</tr>
<tr>
<td>• Arthralgia/myalgia</td>
<td>• Peripheral neuropathy</td>
</tr>
<tr>
<td>• Autoantibody production (ie, cryoglobulin, rheumatoid factor, ANA, anticardiolipin Ab, antithyroid Abs, anti-SM Ab)</td>
<td><strong>Systemic</strong></td>
</tr>
<tr>
<td>• Polyarteritis nodosa</td>
<td>• Fatigue</td>
</tr>
<tr>
<td></td>
<td><strong>Dermatologic</strong></td>
</tr>
<tr>
<td></td>
<td>• Porphyria cutanea tarda</td>
</tr>
<tr>
<td></td>
<td>• Lichen planus</td>
</tr>
<tr>
<td></td>
<td>• Cutaneous necrotising vasculitis</td>
</tr>
</tbody>
</table>
Other causes of liver damage

When determining how to treat HCV, other causes of liver disease also need to be identified, as these can influence treatment options.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-alcoholic fatty liver disease</td>
<td>Weight BMI Abdominal ultrasound</td>
<td>Very common</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>History CBC LFT</td>
<td>Raised MCV, AST&gt;ALT, raised triglycerides. History of alcohol consumption.</td>
</tr>
<tr>
<td>Hepatitis B infection HIV infection</td>
<td>Serology HBsAg anti-HBs anti-HBc HIV Ab</td>
<td>Vaccinate for hepatitis B if non-immune. Check for viral coinfection.</td>
</tr>
<tr>
<td>Haemochromatosis</td>
<td>Iron studies Genetic testing</td>
<td>Prevalence 1:400 but gene penetration is low and disease is much less common than the genotype implies.</td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
<td>Auto-antibodies</td>
<td>Uncommon, associated with other autoimmune disease</td>
</tr>
<tr>
<td>Medication-induced liver disease</td>
<td>Patient history</td>
<td></td>
</tr>
<tr>
<td>Alpha-1-antitrypsin</td>
<td>Alpha 1 antitrypsin</td>
<td>Rare</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Family history Ceruloplasmin</td>
<td>Very rare Autosomal recessive Symptoms onset usually in adolescence and early 20s.</td>
</tr>
</tbody>
</table>
Assessing severity

Assessing the severity of liver disease is not an exact science, but we can make an excellent attempt if we have:

- A good history to identify risk, likely duration, confounding factors, current symptoms
- A good physical examination to document any evidence of advancing liver disease
- An understanding of liver function tests and consistent use of these for diagnosis and monitoring
- An understanding of other investigations, which may provide insights into disease severity and/or the nature of the factors contributing to the presentation.

In the presence of cirrhosis and portal hypertension, hypersplenism develops and this leads to reduced haemoglobin, white cell count and platelet count (pancytopaenia). In many, the platelet count falls first and a count of <100 x 10^9/L is a surrogate marker of cirrhosis reflecting both the hypersplenism and a reduced production of thrombopoietin by the damaged liver.

Types of cirrhosis

In compensated cirrhosis, no complications have occurred.

 Decompensated cirrhosis shows the presence of complications of liver dysfunction and/or portal hypertension. Symptoms include:

- Jaundice
- Hepatic encephalopathy
- Ascites and peripheral oedema
- Variceal haemorrhage
Lab markers of cirrhosis

Blood tests can help identify cirrhosis. Common markers include:
- Reduced platelet count – a count of <100 often indicates cirrhosis
- Lower albumin, total protein
- Lower platelets
- Increased globulin
- Prolonged INR or PT
- Increased bilirubin
- Liver enzymes elevation AST>ALT

Low albumin and platelets <150 x 10⁹/ L are early markers of cirrhosis.

How to assess

Cirrhosis can be assessed through FibroScan® and APRI scores, described in the HCV Testing resource.

The Child-Pugh score is a scoring system that can also be used to measure the severity of chronic liver disease inclusive of cirrhosis. A higher score indicates worsening liver function. The score is calculated using several categories:

- total bilirubin, μmol/l (mg/dl)
- serum albumin, g/l
- INR
- presence of ascites
- presence of hepatic encephalopathy

Due to the complexity of managing cirrhosis, it is recommended that patients are managed in conjunction with your local liver unit.

Co-factors in the development of cirrhosis

- Heavy alcohol intake (>4 standard drinks per day)
- Co-infection with HIV or HBV
- Obesity
- Insulin resistance and/or metabolic syndrome
- Autoimmune liver disease – AICAH, PBC, PSC
- Metabolic disorders – haemochromatosis, Wilsons
- α-1 antitrypsin deficiency
- Primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia
- Chronic inflammatory conditions (e.g. sarcoidosis)
HCV treatment and pregnancy

Administration of PEG-IFN and/or ribavirin in pregnancy is contraindicated. Animal studies have demonstrated that ribavirin causes birth defects and/or foetal deaths while PEG-IFN is abortifacient.

Ribavirin

Treatment with ribavirin is not recommended during pregnancy or for women who are unable or unwilling to adhere to use of adequate contraception. This includes women who are receiving ribavirin themselves; and/or women who are sexual partners of male patients who are receiving ribavirin.

Daclatasvir

Although there is no data regarding daclatasvir for pregnant women, administration is not recommended.

In animal reproduction studies in rats and rabbits, embryo-foetal toxicity was observed in maternally toxic doses that produced exposures of 33 and 98 times the human exposure, respectively, at the recommended human dose of 60 mg.

Other treatments

Other HCV DAA drugs it is recommended that pregnancy is avoided (including sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, ombitasvir/paritaprevir/ritonavir, dasabuvir, grazoprevir/elbasvir, glecaprevir/pibrentasvir). They should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Given the lack of data, nursing mothers are advised to discontinue breastfeeding prior to commencement of HCV drug therapy.
Patients and pregnancy

Clinicians will need to advise patients who are either planning to become pregnant, or who are already pregnant, about how to manage treatment.

Planning pregnancy

Female patients who have received ribavirin, and female sexual partners of male patients who have received ribavirin should not become pregnant for at least 6 months after stopping ribavirin.

Pregnant

- Treatment with PEG-IFN and/or ribavirin is contra-indicated.
- Given lack of data, HCV DAAs should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Co-morbid conditions

When deciding on the appropriate HCV treatment, other causes of chronic liver disease (or factors which may affect the progression of liver disease) should be excluded as their presence can impact treatment.

Co-morbid conditions to consider include, but are not limited to:

- HIV
- Hepatitis B virus infection
- Alcohol misuse
- Non-alcoholic steatohepatitis (related to the metabolic syndrome, obesity, diabetes mellitus)
- Hemochromatosis
- Autoimmune hepatitis
- Drug-induced liver injury
- Right ventricular failure

Factors which impact on choice and delivery of HCV treatment include:

- Mental health issues
- Drug and alcohol use (as a marker of lifestyle stability)
- Cardiac disease
- Chronic renal disease
- Advanced decompensated liver disease

Specialist referral should be sought for the following:

- Extra-hepatic manifestations of HCV
  1. Mixed cryoglobulinemia
  2. Renal disease (i.e. membrano-proliferative glomerulonephritis)
  3. HCV-associated lymphoma (i.e. diffuse large B cell lymphoma [DLBCL]).
- Transplant recipients
- Hemoglobinopathies
- Bleeding disorders
How to address co-morbid conditions in HCV treatment

HIV

• There is no apparent impact of HIV co-infection on DAA efficacy. There is, however, lower SVR with interferon-based treatment in HIV/HCV co-infection as compared with HCV mono-infection.
• Consider referral to specialist.
• Drug-drug interactions between DAAs and cART require assessment.
• This population should be prioritised for treatment for both individual and population level benefit, given increasing liver-related morbidity and mortality in those with HIV/HCV co-infection and increasing HCV incidence in HIV-positive MSM.

HBV

• Screen all patients for evidence of current, or prior, HBV infection before starting treatment with DAAs (Hep B sAg, anti-Hep B core Ab, anti-Hep B sAb +/- HBV DNA).
• If diagnosis is chronic HBV (HepB sAg positive) or “occult” HBV infection (HepB sAg negative, anti-Hep B core Ab positive, HBV DNA detected), refer to specialist.
  1. Concurrent HBV nucleoside/nucleotide analogue therapy may be indicated.
  2. Monitor patients for HBV flare-ups or reactivation during treatment and post-treatment follow-up.
• Communicate MHRA/CHM advice that Direct-acting antiviral interferon-free regimens to treat chronic hepatitis C have a risk of hepatitis B reactivation (January 2017) to patient.
• Patients with HBV co-infection should be treated with the same DAA regimens, following the same rules as HCV mono-infected patients.

Mental health

• Discuss potential impact on adherence.
• Assess for drug-drug interactions.
• Multidisciplinary care should be considered.
• Assess social and financial situation.
Drug and alcohol use

- Integrated management of substance use, in combination with HCV care, as required.
- Multidisciplinary care should be considered.
- Discuss potential impact on adherence.
- Assess for drug-drug interactions, including illicit drugs.
- Encourage patient to moderate or abstain from alcohol use.
- Assess social and financial situation.
- Discuss harm reduction strategies.
- Advise about risk of reinfection with ongoing injecting following treatment.

Cardiac disease (patients on amiodarone)

Sofosbuvir is contra-indicated in patients receiving amiodarone. Life-threatening bradyarrhythmias have been reported.

Chronic renal disease

Mild to moderate renal impairment (CrCl 30 – 80 mL/min)

- Treat according to the general recommendations.
- No dose adjustments of HCV DAAs are needed.
- Monitor carefully.

Severe renal impairment or end-stage renal disease, including hemodialysis (CrCl <30 mL/min)

- Caution with use of ribavirin given increased risk of hemolytic anemia.
CORRELATION BETWEEN LIVER STIFFNESS (kPa) & FIBROSIS STAGE

Hepatitis B

HCV-HIV co-infection

Hepatitis C recurrence after liver transplantation

Hepatitis C

Chronic cholestatic diseases

Alcohol

NAFLD

LIVER STIFFNESS (kPa)


FibroScan®, a reliable tool in hepatology