CAPACITY STRENGTHENING TOOLKIT

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

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

INHSU

Contents

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 United Kingdom are available as an enduring education program component as free downloads via the INHSU website https://www.inhsu.org/what-we-do/education/united-kingdom/

Acknowledgements

This program has been developed in collaboration with:

- British Association for the Study of the Liver
- British Viral Hepatitis Group
- British Liver Trust
- Change Grow Live
- The Hepatitis C Trust
- UK Health Security Agency
- The Kirby Institute, UNSW Sydney
- Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)

UK Steering Committee:

- Prof. John Dillon
  Professor of Hepatology and Gastroenterology, Ninewells Hospital, University of Dundee
- Dr. Ahmed Elsharkawy
  Consultant Transplant Hepatologist, QE Hospital Birmingham
- 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
  Executive Director, Medicines Patent Pool; formerly 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
  Midlands & West Regional Manager, The Hepatitis C Trust

- 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

- Ms Tracey Kemp
  National Hepatitis C Strategy Lead, Change Grow Live

- Mr Arran Ludlow-Rhodes
  Regional BBV Delivery Nurse Manager | HCV Action Ambassador, Midlands, Thames Valley, South Central and South

- Dr. Monica Desai
  Consultant Epidemiologist and Head of Hepatitis C, UK Health Security Agency

Project Staff

Olivia Dawson
Program Manager
International Network on Health and Hepatitis in Substance Users
Email: Olivia.Dawson@inhsu.org

Michelle Kwok
Project Officer
Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
Email: Michelle.Kwok@ashm.org.au

INHSU HCV in Primary Care and Drug and Alcohol Settings

Glossary

Term	Definition
APRI	AST-to-Platelet Ratio Index
Ascites	The accumulation of fluid (usually serous fluid which is a pale yellow and clear fluid) that accumulates in the abdominal cavity
Asymptomatic	Of a condition or a person producing or showing no symptoms
Cessation	The fact or process of ending or being brought to an end
Cerebral infarction	An area of necrotic tissue in the brain resulting from a blockage or narrowing in arteries supplying blood and oxygen to the brain
Cirrhosis	A complication of liver disease which involves loss of liver cells and irreversible scarring of the liver
Enzyme	Macromolecular biological catalysts. They accelerate chemical enzymes
Ethinylestradiol	An orally active estrogen and a synthetic derivative of estradiol, a steroid hormone and the major endogenous estrogen in humans
Etiology	The cause, set of causes, or manner of causation of a disease or condition
Fibrosis	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.
Genotype	The genetic constitution of an individual organism
Hepatocellular carcinoma (HCC)	The most common type of primary liver cancer. It occurs predominantly in patients with underlying chronic liver disease and cirrhosis.
Jaundice	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
Lethargy	A lack of energy
Myalgia	Pain in a muscle or group of muscles
Opioid	An opium-like compound that binds to one or more of the three opioid receptors of the body
Opioid agonist treatment	An effective treatment for addiction to opioid drugs such as heroin and involves taking the opioid agonists methadone or buprenorphine (suboxone)
Palmar erythema	Reddening of the palms
PCR	Polymerase Chain Reaction
Peripheral edema	An accumulation of fluid causing swelling in tissues perfused by the peripheral vascular system, usually in the lower limbs

Portal hypertension	An increase in the blood pressure within a system of veins called the portal venous system
RNA	Ribonucleic acid
Serology	The scientific study or diagnostic examination of blood serum, especially with regard to the response of the immune system to pathogens or introduced substances
Spider nevi	A collection of small, dilated blood vessels that are clustered close to the skin's surface
Thrombocytopenia	A condition in which you have a low blood platelet count
Viremic	A medical condition where viruses enter the blood stream and hence have access to the rest of the body

INHSU

Online Resources – UK

Child-Pugh Score calculator	www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality
PELD Score calculator	www.mdcalc.com/peld-score-pediatric-end-stage-liver-disease-younger-12
MELD Score calculator	www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older
APRI calculator	https://www.hepatitisc.uw.edu/page/clinical-calculators/apri
Hepatitis C Trust	www.hepctrust.org.uk
British Liver Trust	www.britishlivertrust.org.uk
British Association for the Study of the Liver/ British Viral Hepatitis Group	www.basl.org.uk/index.cfm/content/page/cid/3
Primary Care Society for Gastroenterology	www.pcsg.org.uk
British Society of Gastroenterology	www.bsg.org.uk
Harm Reduction Works	www.harmreductionworks.org.uk
Infohep	www.infohep.org
HCV Action – UK	www.hcvaction.org.uk
Liver and Transplant Units – UK	www.britishlivertrust.org.uk/liver-information/useful-links/liver-and-transplant-units
RCGP Toolkit	www.rcgp.org.uk/clinical-and-research/resources/toolkits/liver-disease-toolkit.aspx
Find your local health protection team in England	www.gov.uk/health-protection-team
How to report notifiable diseases	www.gov.uk/guidance/notifiable-diseases-and-causative-organisms-how-to-report
Waverly Care	https://www.waverleycare.org/index.php
Clinical recommendations for pre-treatment assessment of people preparing to initiate therapy for chronic hepatitis C infection	Link to document

DECISION MAKING IN HEPATITIS C

ashm

HCV

1 When To Test

Clinical Indicators

- Abnormal liver function tests (LFTs) (males, ALT ≥ 30 U/L; females, ALT ≥ 19 U/L)
- Jaundice

Presence of Risk Factors

- Injecting drug use (current/ever)
- Sharing of snorting equipment
- Born in high prevalence region^
- Blood transfusion before September 1991 or a blood product (such as clotting factor) before 1986 in the UK
- Recipient of organ or tissue transplants before 1992 in the UK
- Unsterile tattooing/body piercing
- Unsterile medical/dental procedures/blood transfusions in high prevalence countries
- Time in prison
- Needlestick injury
- Mother to child transmission
- Sexual transmission in men who have sex with men (MSM)
- Sexual transmission in those who are HIV positive

^Africa, the Middle East (in particular Egypt), the Mediterranean, Eastern Europe, and South Asia

Other

- Initiating PrEP
- When someone requests a test

When gaining informed consent before testing, discuss:

- Reason for test
- Availability of curative treatment

2 Test/s, Results and Actions

Order HCV Antibody (Ab)*

HCV Ab negative

HCV Ab positive

HCV RNA (qualitative) **+ LFTs**

HCV RNA negative

HCV RNA positive

Does NOT have HCV

NO action
However, if possible recent infection re-test (HCV Ab) or if ongoing risk factors repeat screening (HCV Ab) annually

Has CLEARED HCV

RE-TEST if:
Ongoing risk factors
(repeat RNA test annually)

Has CHRONIC HCV
(chronic = > 6 months)

Further ASSESSMENT and TREATMENT
(see next page)

When conveying a negative result, discuss:

- Modes of transmission and risk reduction

When conveying a positive result, discuss:

- Modes of transmission and risk reduction
- Availability of curative treatment
- Lifestyle factors e.g. alcohol minimisation, diet
- Availability of peer support services, information and support services

***If high level suspicion also consider requesting reflexive HCV RNA + LFTs**

INHSU

This resource was created by the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine and has been adapted for the UK by the International Network on Health and Hepatitis in Substance Users in collaboration with local partners

ashm

DECISION MAKING IN HEPATITIS C

HCV

3 Pre-Treatment Assessment

Baseline screening after positive HCV PCR

- ☐ Full Blood Count
- ☐ Urea, electrolytes, creatinine
- ☐ LFTs (including AST) and INR

Assess liver fibrosis: cirrhotic status

- ☐ Signs of chronic liver disease (spider naevi, palmar erythema, jaundice, encephalopathy, hepatomegaly, splenomegaly, ascites, peripheral oedema)
- ☐ Non-invasive assessment of fibrosis:
  - Serum biomarkers such as APRI (<1.0 means cirrhosis unlikely). Calculator available www.hepatitisc.uw.edu/page/clinical-calculators/apri
  - Elastography assessment e.g. Fibroscan® (>12.5 kPa consistent with cirrhosis)

Check for other causes of liver disease

- ☐ Check for viral coinfection:
  - HIV Ab
  - Hepatitis A – check hep A IgG; vaccinate if negative
  - Hepatitis B – check HBsAg, anti-HBc and anti-HBs; vaccinate if all negative
- ☐ Heavy alcohol intake
- ☐ Fatty liver disease - check weight, BMI

Check for other major co-morbidities

- ☐ Renal impairment (eGFR < 50)

Review previous HCV treatment

- Choice/length of treatment may be influenced by prior HCV treatment experience/response

Consider pregnancy and contraception

- HCV treatment not recommended for use in pregnant or lactating women

4 Treatment

Is your patient likely to have cirrhosis?
(APRI ≥ 1.0 or Fibroscan > 12.5 kPa

- ☐ Yes → Discuss with or refer to a specialist#
- ☐ No

Has your patient received previous treatment for HCV?

- ☐ Yes → Discuss with or refer to a specialist#
- ☐ No →
  - Click HERE to view treatment recommendations for **England**
  - Click HERE to view treatment recommendations for **Scotland**
  - Click HERE to view treatment recommendations for **Wales**
  - Click HERE to view treatment recommendations for **Northern Ireland** (NHS Scotland)

- ☐ Check for drug-drug interactions at www.hep-druginteractions.org.

Additional information can be found at:

- Hepatitis C in the UK 2020
- Northern Ireland Hepatitis C Elimination Plan: phase 1 2021-2025

#All patients with cirrhosis or prior HCV treatment experience should be reviewed by someone experienced in hepatitis C treatment. If cirrhosis is suspected (APRI ≥ 1.0 or elastography > 12.5 kPa), further evaluation is required before commencing treatment.

5 Monitoring

Monitoring while on treatment

- Generally not required but approach should be individualised
- Side effects of HCV treatment are generally minimal

12 weeks post treatment

- ☐ HCV RNA to confirm cure (sustained virological response SVR12 = cure)
- ☐ LFTs

6 Follow Up

If your patient has no cirrhosis and normal LFT results (males, ALT< 30 U/L; females, ALT < 19 U/L) ALT = alanine aminotransferase

No clinical follow-up for HCV required

If your patient has ongoing risk factors

Annual HCV RNA test. If re-infected offer re-treatment and harm reduction strategies

If your patient has abnormal LFT results

(males, ALT ≥ 30 U/L; females, ALT ≥ 19 U/L)Evaluate for other causes of liver disease and refer to specialist for review

If your patient has cirrhosis

Refer to specialist. Patients with cirrhosis require long-term monitoring:

- 6-monthly abdominal ultrasound (hepatocellular carcinoma screening)
- Consideration of screening for oesophageal varices
- Osteoporosis: 2-yearly DEXA scans and monitor serum vitamin D

CONSULT WITH A SPECIALIST IF:

Pre-treatment

- Prior treatment failure of HCV treatment
- Cirrhosis is present or likely – APRI ≥1 and elastography score not available; elastography >12.5kPa
- Coinfected with HIV or HBV
- Renal impairment (eGFR < 50)
- Complex drug interactions
- Complex co-morbidities
- Not comfortable prescribing HCV treatment

During treatment

- Major medication side effects

Post treatment

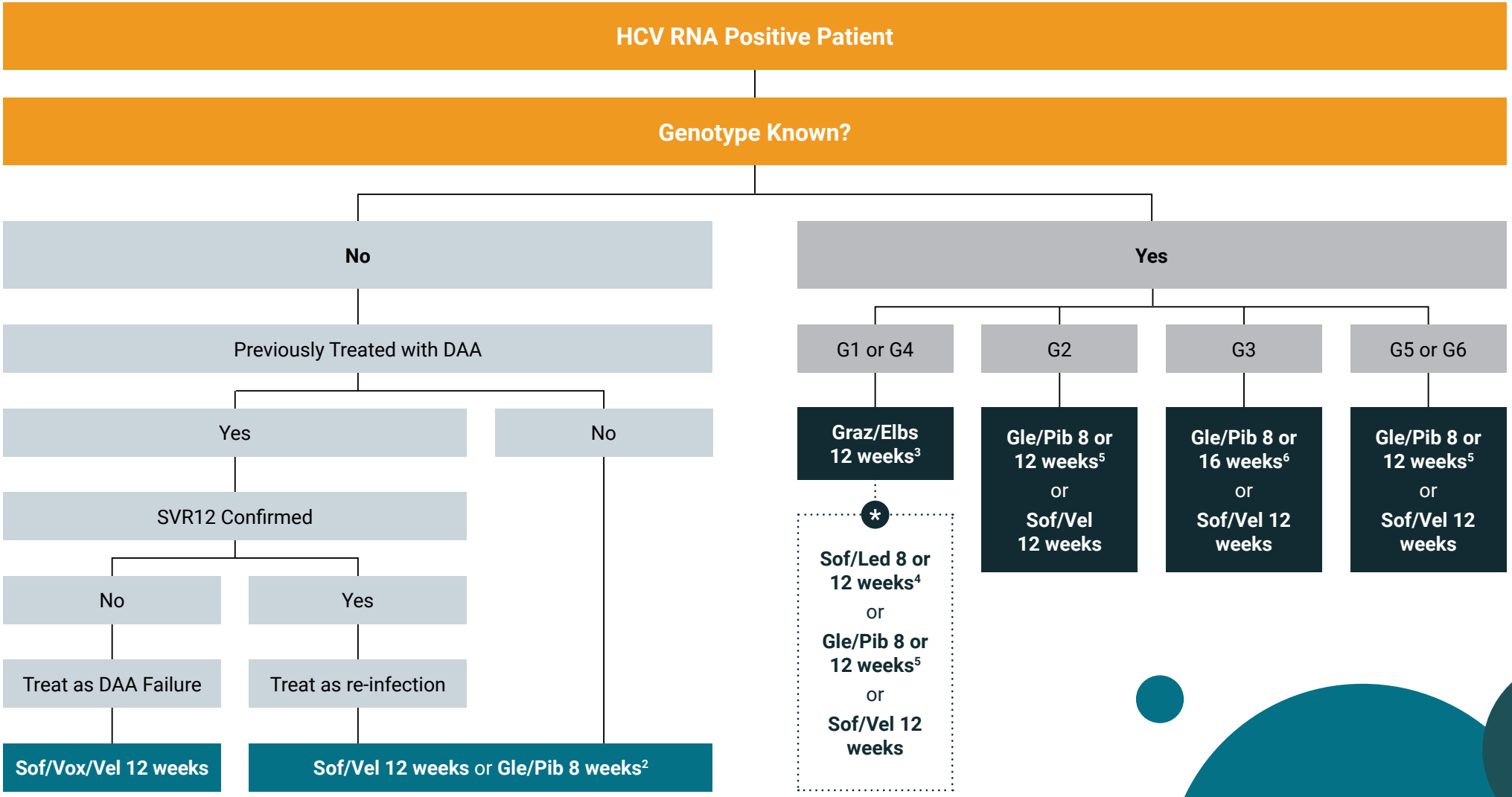
- RNA positive 12 weeks post treatment
- Abnormal LFTs at SVR12

Disclaimer: Guidance provided on this resource is based on guidelines and best-practices at the time of publication. This quick-reference guide is not intended to be a comprehensive list of all available options.

 ISBN: 978-1-921850-47-9

Summary of HCV Treatment Decisions in England[1]

INHSU ashm



Local arrangements are in place in England- contact your local operational delivery network for advice

[1]This flow pathway does not apply to those with decompensated cirrhosis. In these patients, those with G1 can be treated with Sof/Led and ribavirin or Sof/Vel and ribavirin, both for 12 weeks. Patients with other genotypes should be treated with Sof/Vel and ribavirin for 12 weeks.

[2]Gle/Pib therapy can be extended to 12 weeks in those with cirrhosis. Consider 16 weeks in patients with G3 HCV pre-treated with interferon or G3 cirrhotics.

[3]Application for exceptional use of the options in the box marked with a * may be made if there are clear clinical indications not to use Graz/Elbs, e.g. drug to drug interactions.

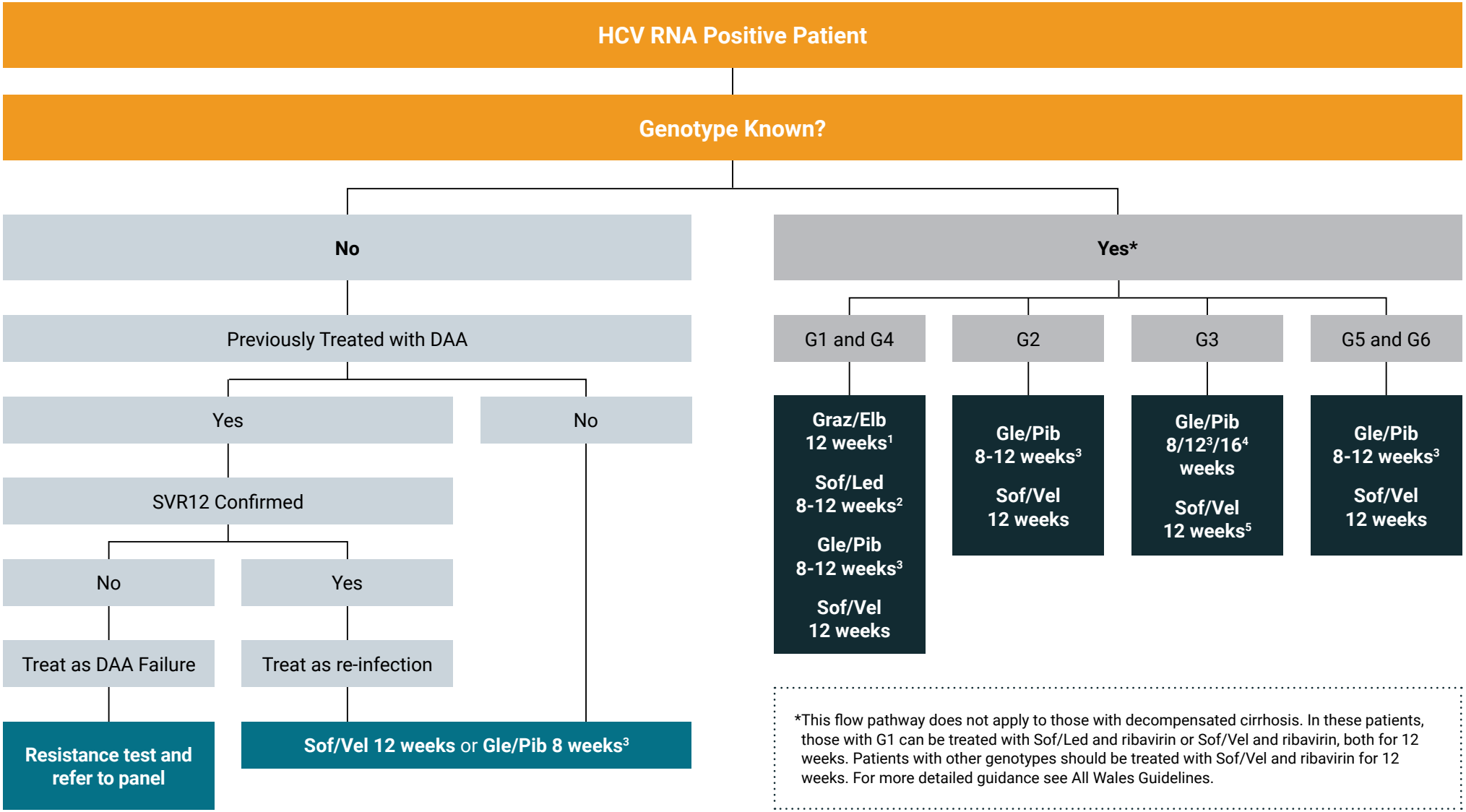
[4]12 weeks should be used in any patients previously treated with PEG-IFN and those with cirrhosis (in whom ribavirin should also be considered).

[5]12 weeks is recommended for patients pre-treated with PI ± Sofosbuvir ± ribavirin

[6]16 weeks is recommended for G3 patients pre-treated with PI ± Sofosbuvir ± ribavirin

Summary of HCV Treatment Decisions in Wales

INHSU ashm



*This flow pathway does not apply to those with decompensated cirrhosis. In these patients, those with G1 can be treated with Sof/Led and ribavirin or Sof/Vel and ribavirin, both for 12 weeks. Patients with other genotypes should be treated with Sof/Vel and ribavirin for 12 weeks. For more detailed guidance see All Wales Guidelines.

[1]Only if viral load <800,000 iu/ml or no NS5A RAS.

[2]Consider 8 weeks only in those with F0-F2 disease and viral load <6million iu/ml. 12 weeks in those with CPA cirrhosis.

[3]Consider increase to 12 weeks in those with CPA cirrhosis and treatment experienced.

[4]Increase to 16 weeks in those who are treatment experienced (defined as peg IFN ± Sofosbuvir ± ribavirin).

[5]Resistance testing in those with cirrhosis. Refer to panel for advice once resistance test back.

Guidelines for England

BVHG/BASL/BSG/BHIVA/BIA/CVN Guidelines for management of chronic HCV infection

Preface

These guidelines were generated following a consensus meeting held in Birmingham on the 30th 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 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 – retreatment 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 – retreatment 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 8-12weeks
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.

Guidelines for Scotland

Healthcare Improvement Scotland

NHS National Services Scotland

National Clinical Guidelines for the treatment of HCV in adults

Version 5

June 2018

Sponsors and Authorship

The guidelines have been authored on behalf of the viral hepatitis clinical leads and MCN co-ordinators network; lead authors: Prof. J F Dillon, Prof P Hayes, Dr S Barclay, 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. For the first iteration a systematic review was undertaken, augmented by 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, together with published international guidelines

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. 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 relevant to the choice of some regimens and the guidance is presented according to genotype. However pan-genotypic regimens are available and in some circumstances where delay in initiation is detrimental to patient care, these may be preferred. 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 are 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 in line with emerging data. SMC approved regimens that are felt to have suboptimal efficacy for a particular indication 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.

Genotype 1	Recommended regimens
Treatment naive or experienced* non-cirrhotic	• **Elbasvir/Grazoprevir 12 weeks** or 8 weeks (GT1b F0-2)** • **Glecaprevir/pibrentasvir - 8 weeks** • Sofosbuvir, Ledipasvir 8 (naïve) or 12 weeks (experienced) • Sofosbuvir/velpatasvir 12 weeks • Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir +/- Ribavirin 12 weeks
Cirrhotic irrespective of previous treatment	• **Elbasvir /Grazoprevir, 12 weeks**** • **Glecaprevir/pibrentasvir 12 weeks** • Sofosbuvir, Ledipasvir, +/- Ribavirin 12 weeks • Sofosbuvir/velpatasvir 12 weeks • Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir, +/-Ribavirin 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 Intereferon (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 approaching 90%, but has an unacceptable side effect profile so is not eligible for inclusion.

Genotype 2	Recommended regimens
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. Phase 2 and real world data demonstrate 8 weeks of Sofosbuvir/velpatasvir is highly effective against GT3 infection in treatment naive, non cirrhotic patients.

Genotype 3	Recommended regimens
Non-cirrhotic	• **Sofosbuvir, Velpatasvir 8 weeks (treatment naive), 12 weeks +RBV (treatment experienced)** • **Glecaprevir/pibrentasvir 8 weeks (treatment naïve) or 16 weeks (treatment experienced)** • Sofosbuvir/Velpatasvir/Voxilaprevir 8 weeks • Sofosbuvir, Daclatasvir, Ribavirin 12 weeks (F3 only)
Cirrhotic	• **Sofosbuvir, Velpatasvir, +/- ribavirin 12 weeks** • **Glecaprevir/pibrentasvir 12 weeks (16 weeks if treatment experienced)** • Sofosbuvir/Velpatasvir/Voxilaprevir 8weeks

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-treatment should be considered in all patients. Patients who adhered to therapy, who did not achieve sustained virological response, 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. In patients who did not clear virus due to poor adherence to therapy, re-treatment should be consider if adherence is likely to be improved on the next attempt.

Sofosbuvir/Velpatasvir/Voxilaprevir for 12 weeks has SMC approval for treatment of Ns5A treatment failures.

Combinations of other licensed regimens, notably Sofosbuvir/Glecaprevir/Pibrentasvir are supported by post licensing data and European guidelines and may be considered according to patient and virological factors following MDT discussion.

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**

THE HEPATITIS C TRUST

The Hepatitis C Trust is patient-led and is the national UK charity.
All calls are confidential and are charged at the national rate
(but may be more from a mobile).
We are a member of the Helplines Association.

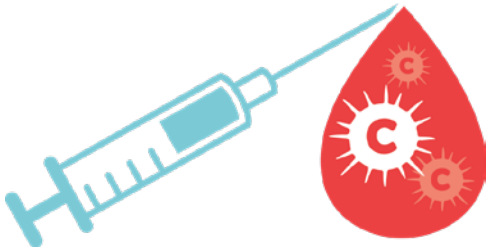
Charity Registration Numbers: England and Wales 1104279, Scotland SCO39914

INHSU

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.

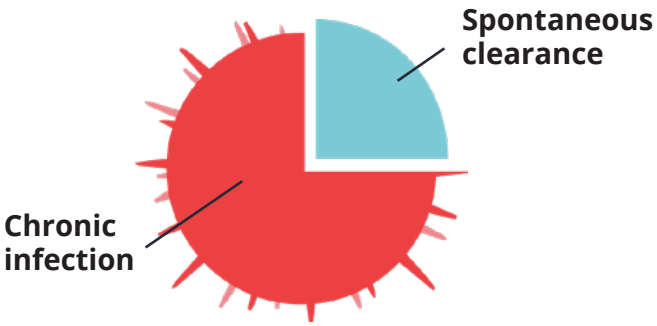
Symptoms and diagnosis

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[1] . The regions most affected are Africa and Central and East Asia.

1%

70 million people

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.

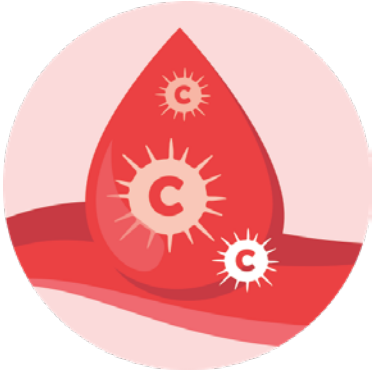
[1] The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterology and Hepatology 2016 Dec 15. http://dx.doi.org/10.1016/S2468-1253(16)30181-9

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.

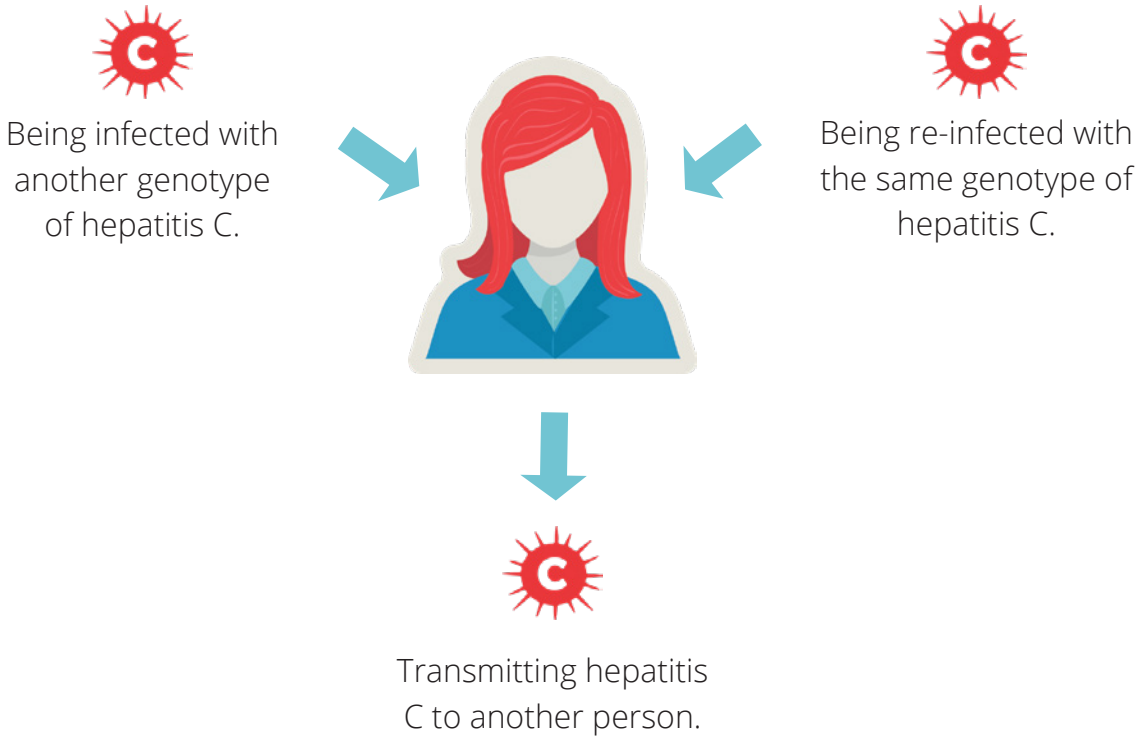
No-risk activities

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

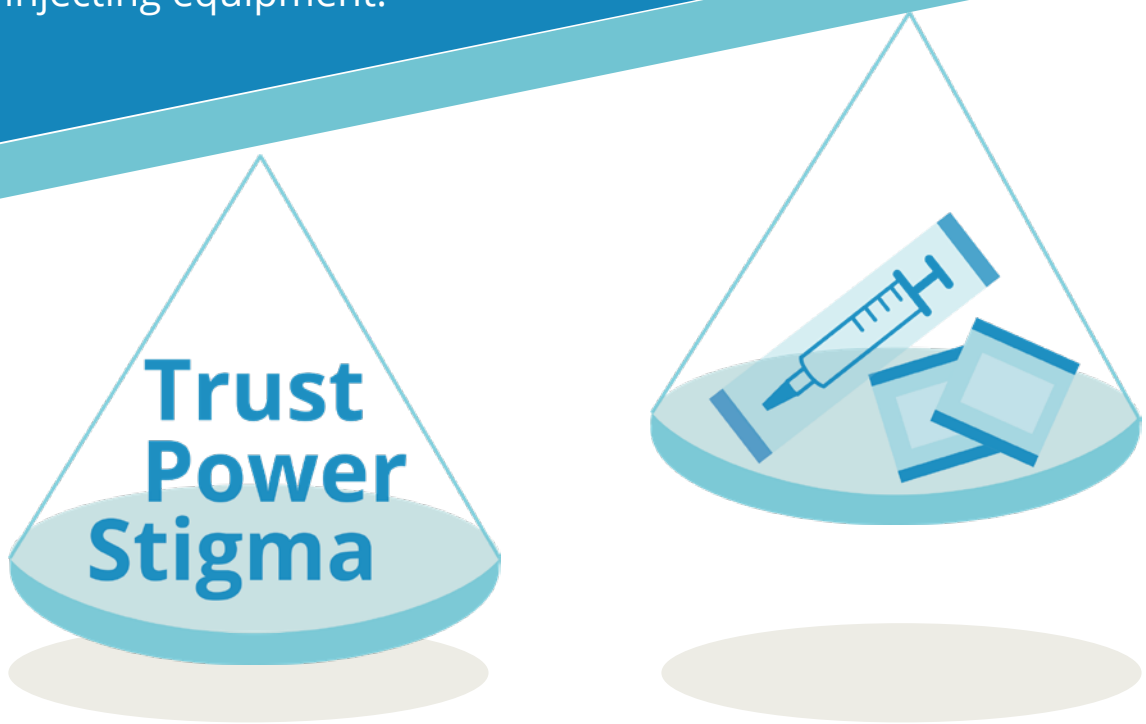
Understanding how hepatitis C is transmitted is important for people who are living with hepatitis C so they can reduce the chance of:



INHSU

Something to think about: **injecting in the real world**

There are multiple reasons why someone who injects drugs may not feel able to access new, sterile injecting equipment.



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.

It is helpful if you acknowledge patients' best intentions while recognising the reality of their lived constraints.

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.

INHSU

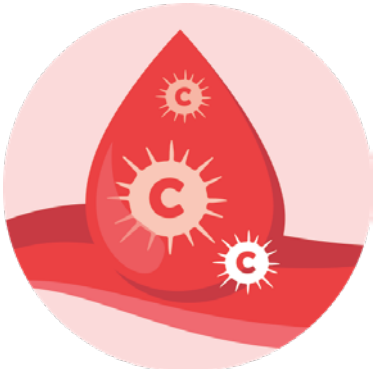
Hepatitis C virus testing and baselining

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.



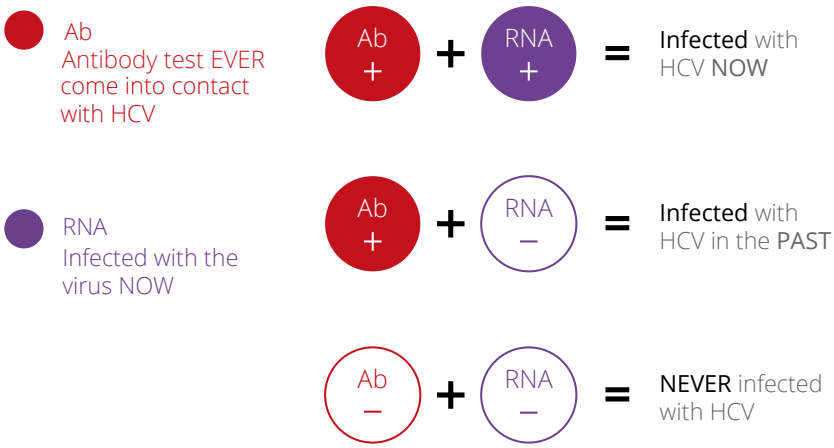
A negative result means that current HCV infection is unlikely. The HCV antibody test has low rates of false negatives or positives. However, this test may need to be repeated if the person has been exposed to risk recently (and possibly tested during the 'window period').

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?

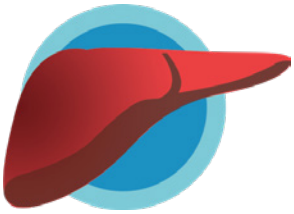
A HCV genotype test is necessary before treatment initiation, as current treatments are genotype-specific. HCV genotyping is a routine laboratory test performed during RNA testing.

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.

INHSU

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.

INHSU

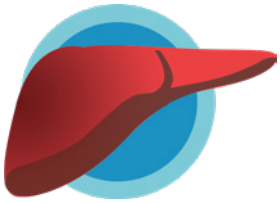
How to test for fibrosis

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.

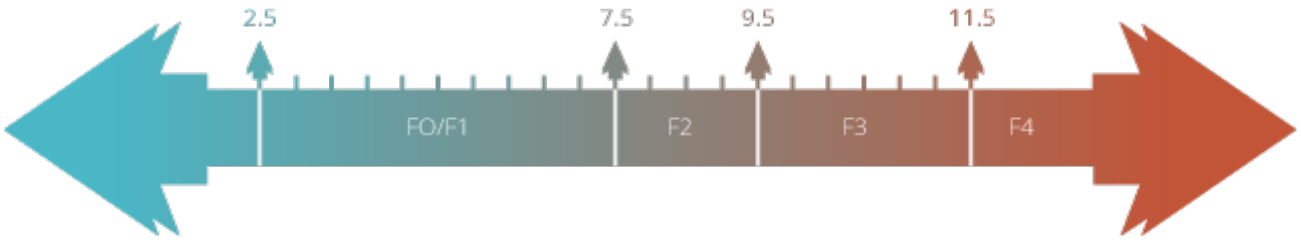
In general, FIB-4 or APRI is most accurate for identifying patients at both ends of the spectrum of hepatic fibrosis: those at low risk for early or minimal disease (fibrosis stage 0 to 1) and those at high risk for advanced disease (fibrosis stage 3 to 4).

INHSU

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 show what FibroScan® scores mean.



Score	2.5 – 7.4	7.5 – 9.4	9.5 – 11.4	> 11.5
Indicates	F0/F1	F2	F3	F4
	No/Mild fibrosis	Moderate fibrosis	Severe fibrosis	Cirrhosis
	Indicates no or minimal liver fibrosis and no evidence of progressive liver disease.	Indicates significant liver fibrosis and evidence of progressive liver disease.	Indicates severe liver fibrosis and high risk progression to cirrhosis.	Indicates extensive liver fibrosis consistent with cirrhosis.

INHSU

Signs of advanced liver disease

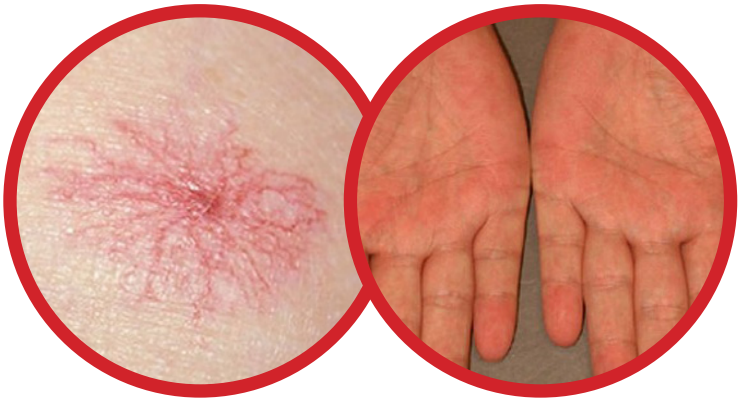
Liver disease, caused by HCV infection, can cause many signs and symptoms. As the disease evolves, signs can appear in many people – but not all, even when cirrhosis is present. Once the disease is well advanced, the features of hepatic decompensation and portal hypertension may appear, including ascites, 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.

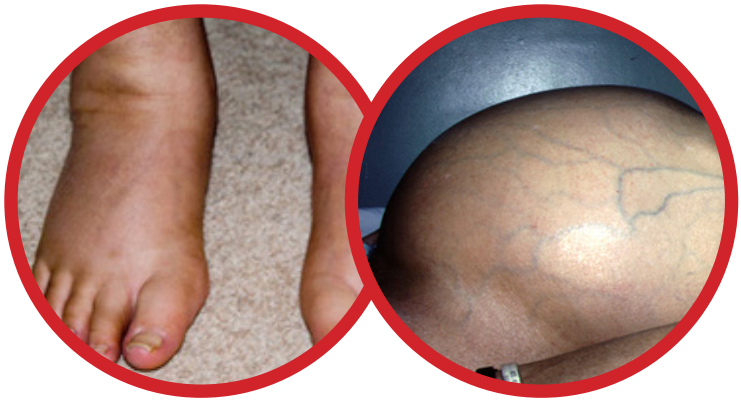
An Enhanced Liver Fibrosis (ELF) score can also be used to help estimate fibrosis. The ELF score combines quantitative serum concentration measurements of three fibrosis markers. Find out more about ELF scores at www.gpnotebook.co.uk/simplepage.cfm?ID=x2016072075237544321

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.

Immune-mediated

Hematologic

- Mixed cryoglobulinemia (10-25% of HCV people have cryoglobulins but this is rarely symptomatic)
- Cryoglobulinaemic vasculitis
- B-cell non-Hodgkins's lymphoma
- Monoclonal gammopathy
- Immune-mediated thrombocytopenia

Rheumatologic

- Sicca syndrome
- Arthralgia/myalgia
- Autoantibody production (ie, cryoglobulin, rheumatoid factor, ANA, anticardiolipin Ab, antithyroid Abs, anti-SM Ab)
- Polyarteritis nodosa

Inflammatory-related

Renal

- Glomerulonephritis
- Nephrotic syndrome

Endocrine

- Type 2 diabetes mellitus
- Insulin resistance

Central and peripheral nervous system

- Depression
- Cognitive impairment
- Peripheral neuropathy

Systemic

- Fatigue

Dermatologic

- Porphyria cutanea tarda
- Lichen planus
- Cutaneous necrotising vasculitis

INHSU

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.

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

INHSU

Understanding cirrhosis

Assessing liver fibrosis helps determine whether the patient could have cirrhosis. Cirrhosis is a histological diagnosis indicating liver disease with necrosis, collapse of architecture, regeneration, and fibrosis surrounding nodules of liver tissue. Cirrhotic status determines treatment regimen and length of treatment, and determines whether the patient needs specialist care.

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.

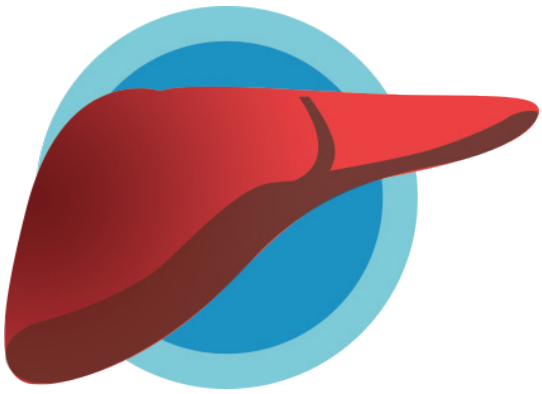
In the presence of cirrhosis and portal hypertension, hypersplenism develops and this leads to reduced haemoglobin, white cell count and platelet count (pancytopaenia). In many, the platelet count falls first and a count of < 100,000 is a surrogate marker of cirrhosis reflecting both the hypersplenism 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 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
- a-1 antitrypsin deficiency
- Primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia
- Chronic inflammatory conditions (e.g. sarcoidosis)

INHSU

HCV treatment and pregnancy

Administration of PEG-IFN and/or ribavirin in pregnancy is contra-indicated. 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.

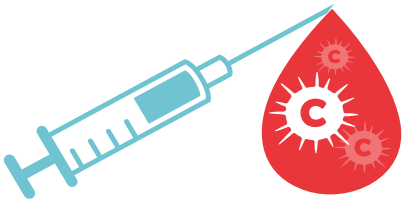
Daclatasvir

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.

INHSU

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.

Refer to specialist

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.

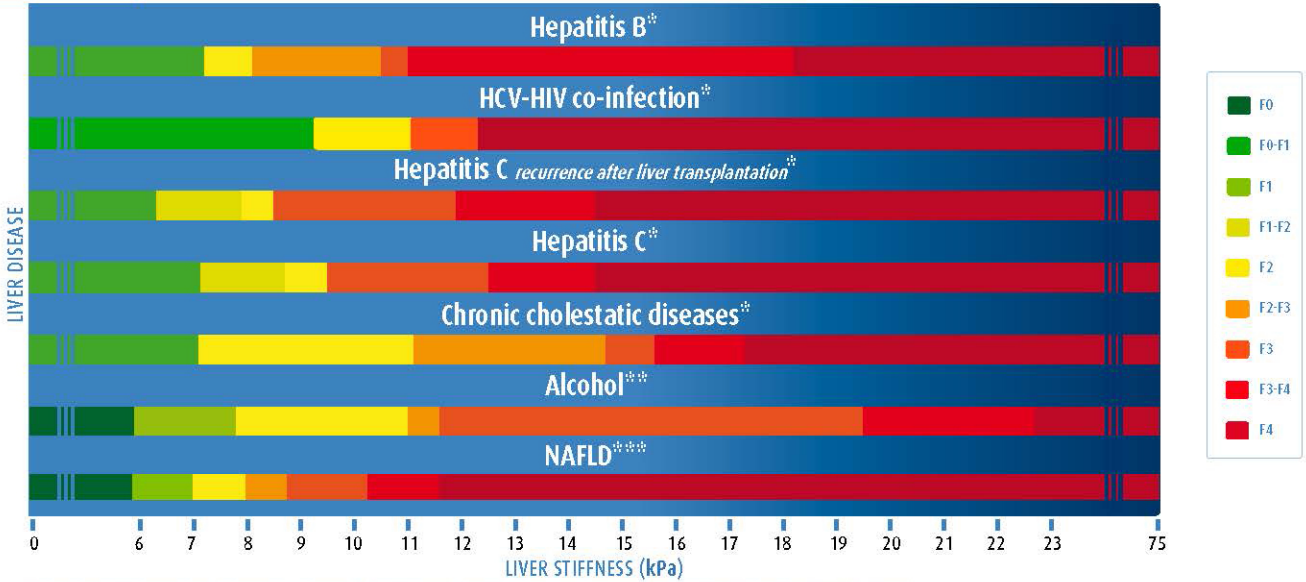
Severe renal impairment or end-stage renal disease, including hemodialysis (CrCl <30 mL/min)

Refer to specialist

- Caution with use of ribavirin given increased risk of hemolytic anemia.

SCORING CARD

CORRELATION BETWEEN LIVER STIFFNESS (kPa) & FIBROSIS STAGE



*According to Metavir score: Transient elastography (FibroScan): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67
**According to Brunt score: Nahon et al. J Hepatol (2009) 49, 1062-68, Nguyen-Khac et al. , Aliment Pharmacol Ther (2008), 28, 1188-98
***According to Brunt score: Wong et al. Hepatology (2010) 51, 454-62Transient elastography (FibroScan®): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67