



Scottish Guidelines on assessment and treatment of Hepatitis C

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Guideline process:

This guideline has been produced using expert opinion to distil evidence and recommendations from international guidelines, to give a pragmatic guide for local implementation. Where there are areas of contention between guidelines, updated evidence used to arrive at recommendations has been referenced.

Guidelines on baseline assessment and monitoring for HCV direct acting antivirals (DAAs)

1. Baseline assessment:

The minimum information required to treat hepatitis C is confirmation of active infection, with a positive HCV PCR result, along with knowledge of concomitant medications. Ideally, HIV and HBV status should be determined prior to commencing therapy whenever feasible, and all reasonable efforts should be made to obtain this information. Furthermore, assessment of fibrosis should be offered to all patients.

As the goal of treatment is to prevent liver related morbidity and mortality, then more extensive work up may be appropriate depending on the individual patient.

Obtaining such an assessment or waiting on results over and above the minimum required, should not jeopardise or delay treatment. In circumstances where, after explanation of the benefits, an individual is not willing to undergo assessment of fibrosis (e.g. Fibroscan, shear wave elastography or blood for FIB-4 score), then treatment may still be considered if it is felt the patient is otherwise able to comply with treatment.

All patients should have alcohol consumption recorded, with appropriate advice and signposting to alcohol services as appropriate.

A BMI should be calculated, if feasible, and the adverse effects of obesity on liver and general health discussed.

1.1 Confirmation of HCV status:

The majority of patients with positive HCV Antibody and PCR tests (indicating active infection) will have chronic hepatitis C and should be worked up and proceed to treatment on this basis.

The exception is the minority of patients with either a clearly defined recent time of acquisition (e.g. needlestick injury or symptomatic acute hepatitis C infection), or for whom testing has revealed a positive HCV PCR in the absence of Hepatitis C Antibody. Such patients may choose to wait until 6 months have elapsed (to satisfy the traditional definition of chronic hepatitis C and give the maximal chance for spontaneous clearance to occur). Alternatively, treatment may be initiated if still positive at 3 months, at which time point the majority of patients who spontaneously clear will have done so. Such a decision should be taken in the context of the risk of such a patient being lost to follow up. Where onward transmission or retention in care is a concern then it may be appropriate to treat without delay.

If HCV RNA is detected by dried blood spot testing, it is recommended the diagnosis should be confirmed by a plasma/serum sample. This is particularly relevant for those with low-level RNA results on dried blood testing, which may represent either a false positive, or low level viraemia.

1.2 Blood Borne Virus (BBV) screen:

A BBV screen should be done within the past 12 months, or ideally within 3 months for those with ongoing risk:

- HIV antigen/antibody screen
- HBsAg test (Surface Antigen)
- Anti-HBc Antibody (Anti core antibody, need not repeat if previously positive)

In addition to the above, vaccination for Influenza and Pneumococcus is advised for all patients with chronic liver disease. Anti-HBsAg antibody titres should be checked, and Hepatitis B vaccination should be recommended to the primary care provider if HBsAb is negative or if titre <100. Patients at risk of hepatitis A e.g. travel risk or MSM should have Hep A IgG serology checked and vaccination advised if this is negative. Please refer to The Green Book for details.

<https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-greenbook#the-green-book>

1.2.1 Hepatitis B co-infection/resolved infection:

Patients with HBV co-infection (HBsAg positive) are at risk of reactivation/flares of hepatitis B subsequent to DAA therapy. Such patients should be treated with a prophylactic nucleos(t)ide analogue (Tenofovir or Entecavir) during treatment and for 12 weeks afterwards. They should be referred on for follow up and management of hepatitis B after SVR achieved.

Patients with resolved infection (anti-HBc positive, HBsAg negative) have a very low risk of reactivation. They should have LFTs checked at the end of treatment with HBsAg/HBV DNA if new or persistently elevated ALT, and a repeat HBsAg at time of SVR.

1.2.2 HIV co-infection

Patients with HIV/HCV co-infection have excellent SVR rates that do not differ from patients with HCV mono-infection, provided appropriate specialist assessment and adequate treatment of HIV has been undertaken. Drug-drug interactions with anti-retroviral therapy may require management, with input from the BBV specialist pharmacist.

1.3 HCV Genotyping/resistance testing.

Genotyping in Scotland is nationally provided by two BBV Specialist Scottish Testing Centres. The availability of pan-genotypic treatment means that genotypic testing is not a requirement for commencement of therapy and treatment should not be delayed if a genotype result is unavailable. However, genotype can be a valuable tool in the event of treatment failure and reinfection. A reflex genotype agreement may be in place with some health boards, if this is the case a genotype test will automatically be added by the laboratory on all new HCV. Clinicians should discuss with their local laboratory if such an agreement is in place. This will determine whether a pre-treatment sample is required to be sent for genotype. In the event of treatment failure, a sample should be sent for genotype testing.

NS5A resistance testing should be requested for the small number of patients who have presumed virological failure following a DAA regimen. Decisions on retreatment should be made following MDT/expert discussion.

1.4 Co-morbidities and concomitant medication:

A list of comorbid conditions should be obtained along with a list of the patients regular and as required medications. They should also be asked about over the counter medications, herbal medications, and recreational drugs. All identified medications should be screened against the www.hep-druginteractions.org website and any potential interactions appropriately managed, with input from specialist pharmacists if required. The importance of not starting new medication without confirming safety with the CNS should be reinforced to the patient and the patient's GP.

1.5 Pre-treatment discussion

Pre-treatment discussion should include the importance of adherence on achieving SVR12, and reinforcement of any specific dosing requirements (e.g., dosing with food). The importance of not discontinuing medication prematurely, due to the risk of resistance, should be stressed to the patient. The importance of the SVR12 blood test in determining treatment success should be made at the initial assessment and reinforced at all subsequent visits.

To date, there is no universal screening of hepatitis C in pregnancy in Scotland. Therefore, when assessing female patients with children, discuss the potential risk of vertical transmission (depending on the likelihood of hepatitis C infection during the pregnancy) and refer children for HCV testing if appropriate.

1.6 Assessment of fibrosis

Fibrosis may be assessed non-invasively by Fibroscan or non-invasive scores using routine lab results, such as the FIB-4 score.

Fibroscan

The following cut offs may be used to define different stages of liver disease:

- F4 \geq 12.5 kPa
- F3 9.5 - 12.4 kPa
- F2 7.1 - 9.4 kPa
- F0-1 \leq 7.0 kPa

FIB-4

The FIB-4 score is calculated:
$$\frac{\text{Age (years)} \times \text{AST}}{\text{Platelets} \times \sqrt{\text{ALT}}}$$

This can be most easily calculated by using an online calculator (e.g. <https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis>) or app (e.g. Calculate by QxMD, available for iOS and Android).

A FIB-4 <1.45 is sufficient to rule out advanced fibrosis.

Note: alcohol excess increases AST and lowers the platelet count, making false positives more likely in those drinking to excess. False positives are also more likely in those with HIV co-infection. Those patients with a score >1.45 should be considered for Fibroscan.

Patients with a liver stiffness measurement (LSM) in the F3 range should have careful consideration as to their disease stage taking into account LFTs, platelet count, stigmata of chronic liver disease, and ultrasound findings. Some patients with LSM within the F3 range will have cirrhosis and a consultant decision (taking into account the above factors) should be made about the probable disease stage.

Identifying patients with cirrhosis allows for appropriate discussion of prognosis, as well as consideration of post SVR follow up, including HCC surveillance. However, for any patient with advanced fibrosis/cirrhosis, the benefits of successful HCV treatment outweigh the benefits of post SVR follow up. Accurate assessment of fibrosis, attendance for ultrasound or consultant clinic, should therefore not be a barrier to treatment of HCV in circumstances where such assessment is not achievable in an individual patient, but overall, the patient is felt able to comply with treatment.

1.7 Review pre-treatment

Patients with F0-2 fibrosis (or FIB-4 < 1.45) may be initiated directly onto treatment by nurse specialists or specialist pharmacists according to local protocol arrangements or discussed at an MDT. Those with evidence of advanced fibrosis (F3-F4) should have consultant review, which may initially be via MDT or discussion with named consultant to facilitate a treatment decision. Those with Child's A cirrhosis should be offered a consultant appointment, as should those with F3 fibrosis for whom review is felt appropriate to guide post-treatment care (see below). Treatment may proceed pending review, and review should not be a barrier to care in those who are otherwise judged suitable for treatment.

Those with decompensated (Child's B/C) cirrhosis require urgent consultant review.

Patients may undergo either a comprehensive liver assessment, or a standard assessment. The latter may be more applicable in community settings.

1.7.1 Standard Assessment and follow up:

Required within 12 months*:

HIV Screen

Hepatitis B screen (HBsAg)

- this may be either via dried blood spot test or serum sample

Full Blood count

Liver Function Tests

Ideal

UEs

*ideally updated at assessment, results within 12 months acceptable

For some patients who decline blood tests (e.g. severe needle phobia) or attempts to obtain blood are unsuccessful, it may be appropriate to proceed with treatment on the basis of either a BBV screen and Fibroscan or a BBV screen alone (with a suitable regimen that would be appropriate regardless of liver disease stage). Such a decision should be made by consultant/MDT discussion.

For patients with normal liver function tests, no further monitoring is required on treatment. An end of treatment HCV PCR may be helpful in assessing causes of treatment failure but is not mandatory. A SVR12 should be obtained.

For patients with abnormal LFTs in keeping with HCV (raised ALT/AST < 250/200), patients should be aware of the need for repeat bloods, at end of treatment or SVR, to ensure normalisation. Those failing to normalise should have a non-invasive full liver screen checked (see 1.7.2), and their case discussed with a consultant/MDT regarding the need for further investigation or follow up.

Those patients with abnormal LFTs not typical of HCV related liver disease (e.g. elevated Alkaline Phosphatase, more significant elevations of AST/ALT) should be discussed with a consultant/at MDT. Typically, such patients may proceed with treatment in parallel with any required investigation or follow up.

UEs rarely preclude treatment, however significant impairment (eGFR <30) may increase the risk of side effects with sofosbuvir based regimens, and alternative regimens may be preferred. New renal impairment may require further assessment but should not preclude treatment.

1.7.2 Comprehensive assessment:

A more comprehensive liver assessment may be preferred in patients with good venous access, and those attending clinics with phlebotomy services.

In addition to those tests performed as part of a standard assessment, a coagulation screen and a liver screen may be obtained at baseline (ferritin, transferrin saturation, immunoglobulins, antinuclear antibody, liver autoantibodies (AMA/SMA), alpha-fetoprotein. This may prevent the need for recall if baseline bloods are abnormal and fail to normalise with treatment.

1.8 Work up of patients with advanced fibrosis

Patients with a Fibroscan in the F3/F4 range should ideally have an ultrasound prior to commencing treatment, to exclude HCC. Patients with F0/2 disease typically do not need an ultrasound, unless there are other concerns.

Patients with cirrhosis should have their Child-Pugh Score calculated.

(<https://www.mdcalc.com/child-pugh-score-cirrhosis-mortality>)

Patients should be counselled of the reasons for ultrasound and encouraged to attend. Most patients with compensated (Child-Pugh A) cirrhosis will be able to have treatment initiated in parallel with requesting a scan and consultant review. Most patients in this group will not have a cancer at the time of initiating treatment and the balance of risks to the patient is likely to favour proceeding with treatment if the patient does not attend for the ultrasound.

Patients with cirrhosis require an upper GI endoscopy to exclude the presence of varices unless they meet the Baveno criteria for non-invasive exclusion of varices (LSM <20kPa and platelet count >150/mm³ (both performed within one year)) or are already established on carvedilol.

1.9 Pregnancy/contraception

There is limited data on the safety and efficacy of direct-acting antivirals (DAAs) in pregnancy and currently no large-scale clinical trials have been published. There is also no data on the use of DAAs to prevent mother-to-child transmission of HCV. As a result, HCV treatment during pregnancy is not recommended. In exceptional circumstances, treatment may be considered during pregnancy or continued in the case of accidental conception during treatment, only in discussion with specialist services after a thorough consideration of the potential risks/benefits of treatment.

Contraception

Female patients who are not post-menopausal and have not undergone sterilisation require counselling around contraception as below:

Non ribavirin containing regimens:

None of the DAAs are licensed for use in pregnancy, and patients should be counselled around the unknown risk to a child conceived during treatment. Pregnancy is not recommended. It should be documented that contraception has been discussed, and the method of contraception the patient is planning to use during treatment be documented. If pregnancy is possible/suspected, a pregnancy test should be performed prior to starting treatment.

Ribavirin containing regimens:

Ribavirin is highly teratogenic and effective contraception is mandatory. A negative pregnancy test should be obtained before commencing therapy. Couples, with one partner receiving treatment, should use two forms of contraception (as listed below) during treatment and for six months after treatment has ended. This conversation should be clearly documented and patients reminded of this at the end of treatment visit and the SVR12 visit.

Acceptable contraception includes:

- oral contraceptive pills (taking into account potential drug-drug interactions)
- contraceptive implant
- male or female condoms
- cap plus spermicide
- intrauterine device (IUD)/intrauterine system (IUS) with hormone
- abstinence during treatment.

1.10 Regimen specific considerations:

With regards to specific regimens, prescribers are expected to familiarise themselves with the summary of product characteristics (SPC) for regimens they prescribe, including any contraindications.

Patients with advanced chronic liver disease (Child's B/C) should not be treated with an NS3/4a protease inhibitor-containing regimen (e.g. grazoprevir/glecaprevir/voxilaprevir), due to the substantially higher concentrations seen in these patients.

2. On treatment monitoring

On treatment monitoring is not generally required for patients except in the circumstances below:

Advanced (Child-Pugh B/C) cirrhosis, or those taking a ribavirin-containing regimen:

- UEs/LFTs/FBC/Coag screen should be taken at week 2, week 4 and every 4 weeks until the end of treatment, along with 4 weeks post treatment and at SVR12

3. Sustained Viral Response

Sustained viral response should be checked 12 weeks following completion of treatment (SVR12). HIV and HBsAg status should be updated at this time.

SVR should where possible be checked by serum sample, as DBS is less sensitive to low level viraemia. However, where a patient was positive on DBS pre-treatment, or their pre-treatment viral load was > 3,000 iu/ml, a DBS is acceptable.

3.1 Post SVR management

All patients should be counselled that they should have at least annual BBV testing if they are engaging in activities with an ongoing risk of transmission. The risk of re-infection and the need for safe injecting practices (if relevant) should be discussed. Patients with F0-2 disease should be counselled about any identified ongoing risk factors for liver disease (obesity and alcohol excess) and may be discharged once any issues around abnormal LFTs have been satisfactorily resolved (see 1.7.1.)

Patients with cirrhosis have a significant risk of hepatocellular carcinoma (HCC) that should in most cases lead to an offer of HCC surveillance with biannual ultrasound and serum AFP. The exception would be patients with decompensated disease otherwise ineligible for transplant, and those with significant co-morbidities or frailty, such that early detection of HCC would not lead to a beneficial treatment outcome. Any offer of HCC surveillance should include discussion of the limitations of surveillance. Whilst surveillance improves outcomes, it remains the case that the minority of patients with surveillance detected HCC are eligible for treatment with curative intent (Haq et al. 2021). In addition, patients should be made aware that false positives are common, leading to a burden of additional investigations that is highest amongst those patients with lowest risk of HCC (Curran et al. 2021).

The balance of risks versus harms is particularly relevant amongst those with F3 fibrosis at the time of SVR, for whom there is variation between various international guidelines. Whilst EASL recommends surveillance (European Association for the Study of the Liver et al. 2020), this is not supported by BSG guidelines on HCC surveillance (Suddle et al. 2024) or AASLD guidelines (Singal et al. 2023).

For patients with F3 fibrosis by Fibroscan, we recommend an individualised approach to decisions on HCC surveillance. This should consider other indicators of cirrhosis, such as ultrasound appearances, platelet count, and liver function tests. In addition, risk factors for fibrosis progression, including co-factors for liver disease such as alcohol excess and metabolic syndrome, as well as patient factors such as age and gender should be considered along with patient preference. Whilst increasing age is a risk factor for HCC, there is evidence to suggest that the risk of HCC diminishes over time following SVR (Kim et al. 2023). One way of quantifying risk is the use of a risk score such as the aMAP score, which utilises age, sex, albumin and platelets to stratify risk of HCC following SVR (Fan et al. 2020),

and for which online calculators are available. A low-risk score gives reassurance of a very low risk (0.0-0.2% per year) of HCC, and may be used to further define risk in those patients where there is uncertainty around the benefits of surveillance.

3.2 Patients not attending for SVR12

All best efforts should be made to capture an SVR result.

These should include attempts to phone the patient, followed up by a letter reinforcing the importance of SVR12. A letter to the patient's GP (and/or ADRS worker) asking them to check an HCV PCR should be sent. In addition, a note should be entered on the front page of the patient's electronic patient record, noting that "This patient has completed treatment for hepatitis C but not attended for bloods to ensure this has been successful. If they attend secondary care for any reason, please offer an HCV PCR blood test noting "post treatment" on the request."

3.3 Patients not achieving SVR

Failure to achieve SVR may be due to non-adherence, virological treatment failure, or re-infection. A repeat sample should be obtained to confirm relapse, along with a sample for genotype and NS5A resistance.

The following should be discussed and documented:

- Risk factors for re-infection
- Adherence with treatment
- Any new medication started during treatment

If acute re-infection is likely, then the patient should be monitored for at least 3 months to see if they achieve a spontaneous cure. Alternatively, if there are concerns regarding retention in care, it may be appropriate to proceed directly to treatment. Attempts should be made to offer risk contacts testing and treatment.

Patients with likely virological failure/proven resistance require MDT discussion to decide on optimal re-treatment strategies.

Standard Assessment:

Exclude HIV/HBV by DBS or serum sample
(specialist assessment if present)

†Fibrosis Assessment
LFTs check

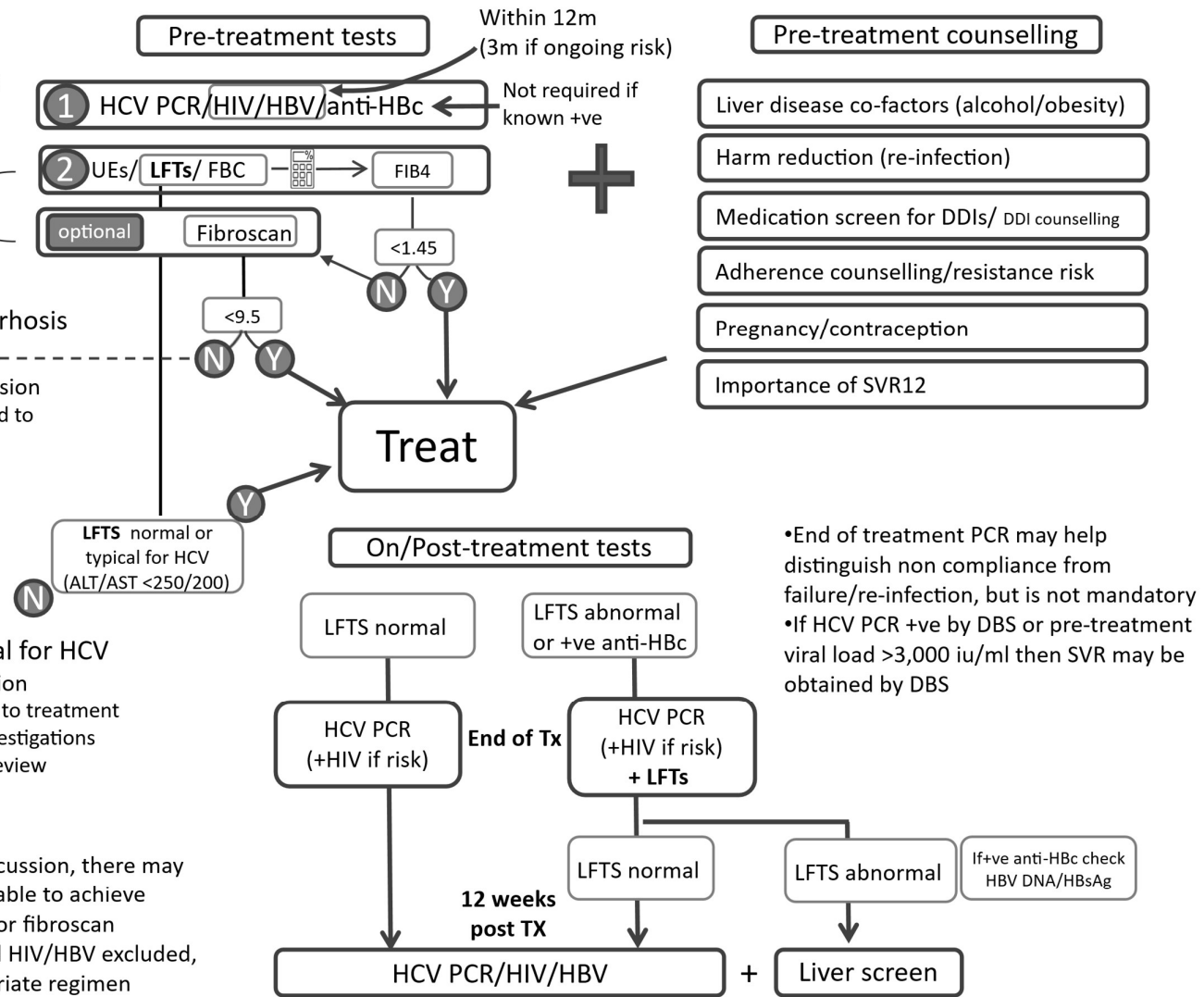
Advanced fibrosis/cirrhosis

- Request US
 - Consultant/MDT discussion
- Most patients may proceed to treatment in parallel with specialist review

Abnormal LFTs atypical for HCV

- Consultant/MDT discussion
- Most patients may proceed to treatment in parallel with required investigations (eg US/liver screen)/clinic review

†Following consultant/MDT discussion, there may be cases where patients are unable to achieve bloods (access/needle phobia) or fibroscan (patient attendance) – provided HIV/HBV excluded, then treatment with an appropriate regimen should be considered.



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