NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Adult Hepatitis C Treatment

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

NHS Greater Glasgow & Clyde Viral Hepatitis Managed Care Network

Guidelines on baseline assessment and treatment monitoring of patients receiving direct acting antiviral treatment for Hepatitis C

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

1. Baseline assessment:

The minimum information required to treat hepatitis C is an assessment of fibrosis and screening for HIV/HBV co-infection.

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.

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 a single positive result (HCV Antigen or PCR) 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). 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.

1.2 BBV screen:

All patients should have an up to date (within 6 months):

• 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, which are required for treatment, 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 if HBsAb is negative, or titre <100. If HBsAb result not available and no clear history of a completed vaccination course then a full vaccination course is recommended. Primary care or secondary care can support vaccination via vaccination Hub referral if a GGC resident. Adult Non Routine Vaccinations

Patients at risk of hepatitis A e.g. travel risk or MSM should have Hep A serology checked and vaccination advised if this is negative. Please refer to The Green Book for details.

Immunisation against infectious disease - GOV.UK

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. Drug-drug interactions with anti-retroviral therapy may require management, with input from the blood borne virus specialist pharmacist.

1.3 HCV Genotyping/resistance testing.

Genotyping is funded nationally and provides useful information on epidemiology. It may also be helpful in distinguishing treatment failure from re-infection. It is therefore optimal to obtain a sample pre-treatment, even when pan-genotypic regimens are available. However, the absence of a genotype, either due to a sample not being obtained or unable to be analysed, should not prevent or delay treatment.

Ns5A resistance testing should be requested for the small number of patients who fail treatment with 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 Liverpool HEP Interactions website and any interactions identified appropriately managed, with input from the BBV 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.

Discussion about transmission risk should include advice around any known contacts and signposting them to testing.

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 ≥12.5 kPa (11.9 HIV co-infected)
- F3 ≥ 9.5 <12.5 kPa (8.8 HIV co-infected)
- F2 >6.9 <9.5 kPa (6.5 HIV co-infected)
- F0-1 ≤ 6.9 kPa (<6.5 HIV co-infected).

FIB-4

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

This can be most easily calculated by using an online calculator (e.g. Fibrosis-4 (FIB-4) Index for 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 may be initiated directly onto treatment by nurse specialists or specialist pharmacists according to local protocol arrangements or discussed at an MDT. Some patients may require a consultant discussion or review for the reasons outlined above (1.6), but this is not mandatory. Patients outside the agreed local protocols can proceed to treatment under nurse/pharmacist care following MDT discussion, and patients diagnosed with compensated (Child-Pugh A) cirrhosis, should typically proceed with treatment whilst awaiting 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:

Mandatory*:
HIV Screen
Hepatitis B screen (HBsAg)
- this may be either via dried blood spot test or serum sample

*ideally updated at assessment, results within 6 months acceptable (3 months if ongoing risk)

Required*
Full Blood count
Liver Function Tests

Ideal
UEs

*ideally within 12 months. 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 is preferred, but not mandatory. A SVR12 should be obtained (see below).

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 full liver screen may be obtained at baseline (ferritin, transferrin saturation, immunoglobulins, antinuclear antibody, liver autoantibodies (AMA/SMA), alpha-1-antitrypsin, alpha-fetoprotein and (< 50 years only) caeruloplasmin). This may prevent the need for recall in the event that 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 do not, unless there are other concerns about their liver.

Patients with cirrhosis should have their Child-Pugh Score calculated.
Child-Pugh Score for 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 in the event that 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)).

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:

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 in to 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.

1.11 Missed doses
If a patient **misses ≤ 7 days of consecutive doses**, treatment should be continued and missed doses added onto the end of the course to ensure the planned treatment duration is completed where possible. If a patient **misses ≥ 8 days of consecutive doses**, please discuss with the HCV pharmacy team and/or MDT: treatment may be continued on an individual basis. Frequent periods of missed doses (even if ≤ 7 days) should also be highlighted, and additional adherence support attempted.

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 ideally 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. It can be inferred that 2 or more DBS PCR negative >12 weeks post treatment indicates an SVR

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), as well as other BBV harm reduction interventions such as smoking rather than injecting drugs, condom use 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.)

The need for F3 patients to be followed up should be made by a consultant, taking into account co-factors for liver disease and certainty as to absence of cirrhosis. Most patients with cirrhosis will receive ongoing follow up, unless other co-morbidities/frailty make this unlikely to be beneficial.

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 clinical 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."

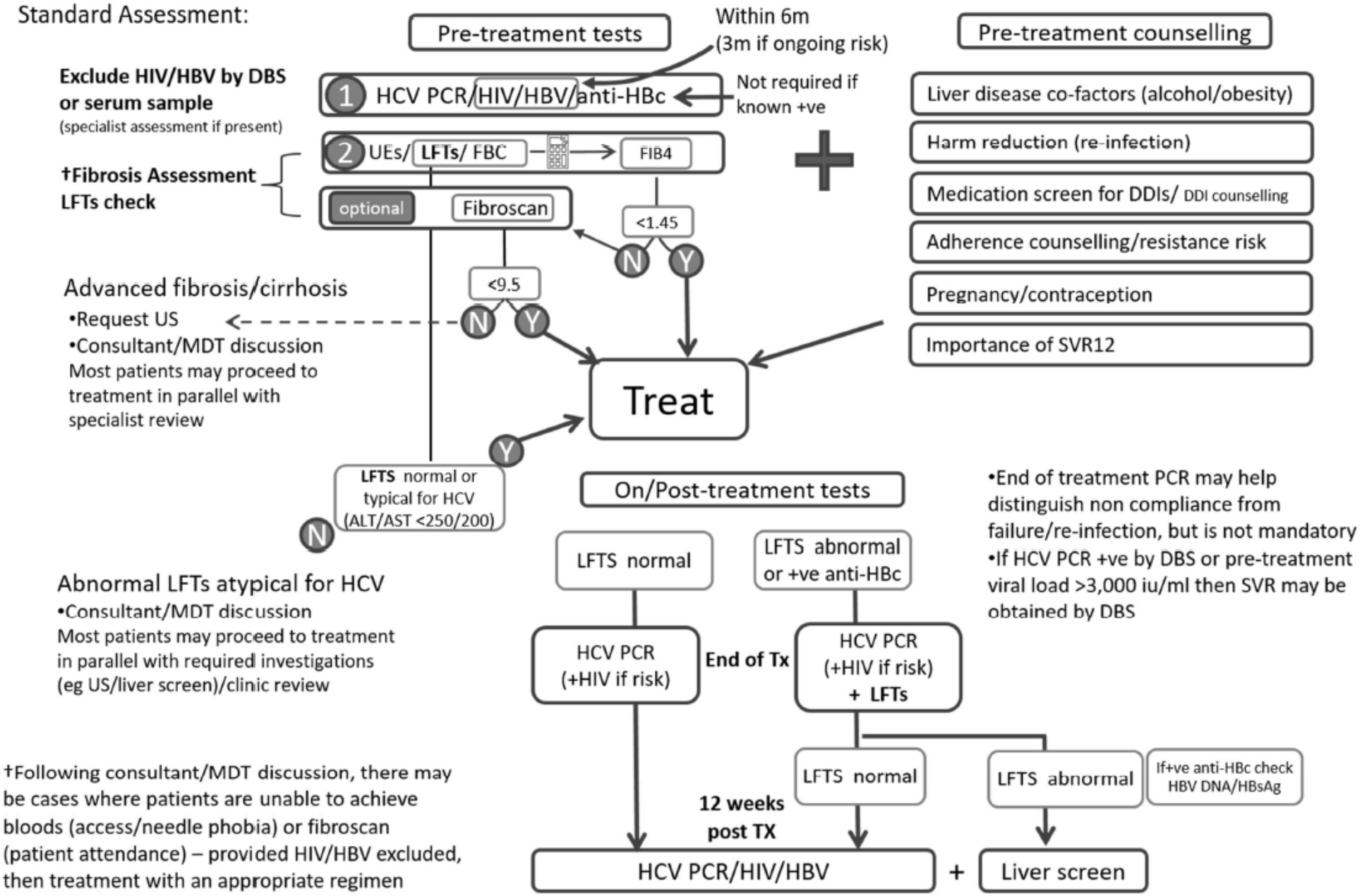
3.3 Patients not achieving SVR

Failure to achieve SVR may be due to non-adherence, treatment failure/relapse or re-infection.
A repeat sample should be obtained to confirm relapse, along with a sample for genotype and Ns5A resistance unless the GT has changed which would indicate re-infection.
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 treatment failure/proven resistance require MDT discussion to decide on optimal re-treatment strategies.


Standard Assessment:
Pre-treatment tests
Within 6m
(3m if ongoing risk)
Pre-treatment counselling
Exclude HIV/HBV by DBS or serum sample
(specialist assessment if present)
1 HCV PCR/HIV/HBV/anti-HBc
Not required if known +ve
Liver disease co-factors (alcohol/obesity)
Harm reduction (re-infection)
2 UEs/ LFTs/ FBC
FIB4
†Fibrosis Assessment LFTs check
optional
Fibroscan
Medication screen for DDIs/ DDI counselling
<1.45
N
Y
Adherence counselling/resistance risk
Advanced fibrosis/cirrhosis
•Request US
•Consultant/MDT discussion
Most patients may proceed to treatment in parallel with specialist review
<9.5
N
Y
Pregnancy/contraception
Importance of SVR12
Treat
Y
LFTS normal or typical for HCV (ALT/AST <250/200)
N
On/Post-treatment tests
•End of treatment PCR may help distinguish non compliance from failure/re-infection, but is not mandatory
•If HCV PCR +ve by DBS or pre-treatment viral load >3,000 iu/ml then SVR may be obtained by DBS
LFTS normal
LFTS abnormal or +ve anti-HBc
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
HCV PCR (+HIV if risk)
End of Tx
HCV PCR (+HIV if risk) + LFTs
LFTS normal
LFTS abnormal
If+ve anti-HBc check HBV DNA/HBsAg
12 weeks post TX
HCV PCR/HIV/HBV
+
Liver screen
†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.