PRACTICAL APPROACH TO HEPATITIS C INFECTION

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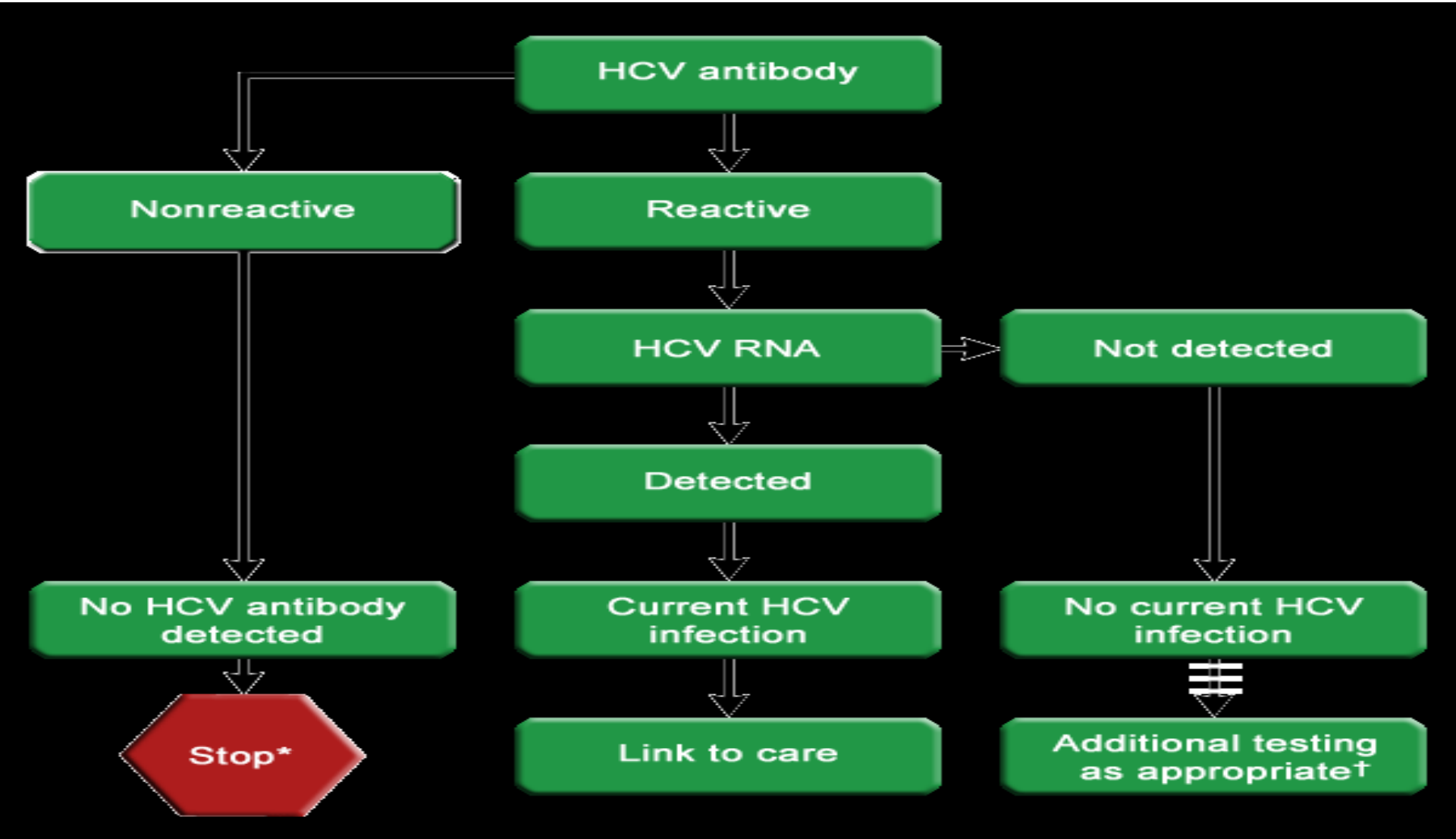
WHEN TO SUSPECT HCV INFECTION

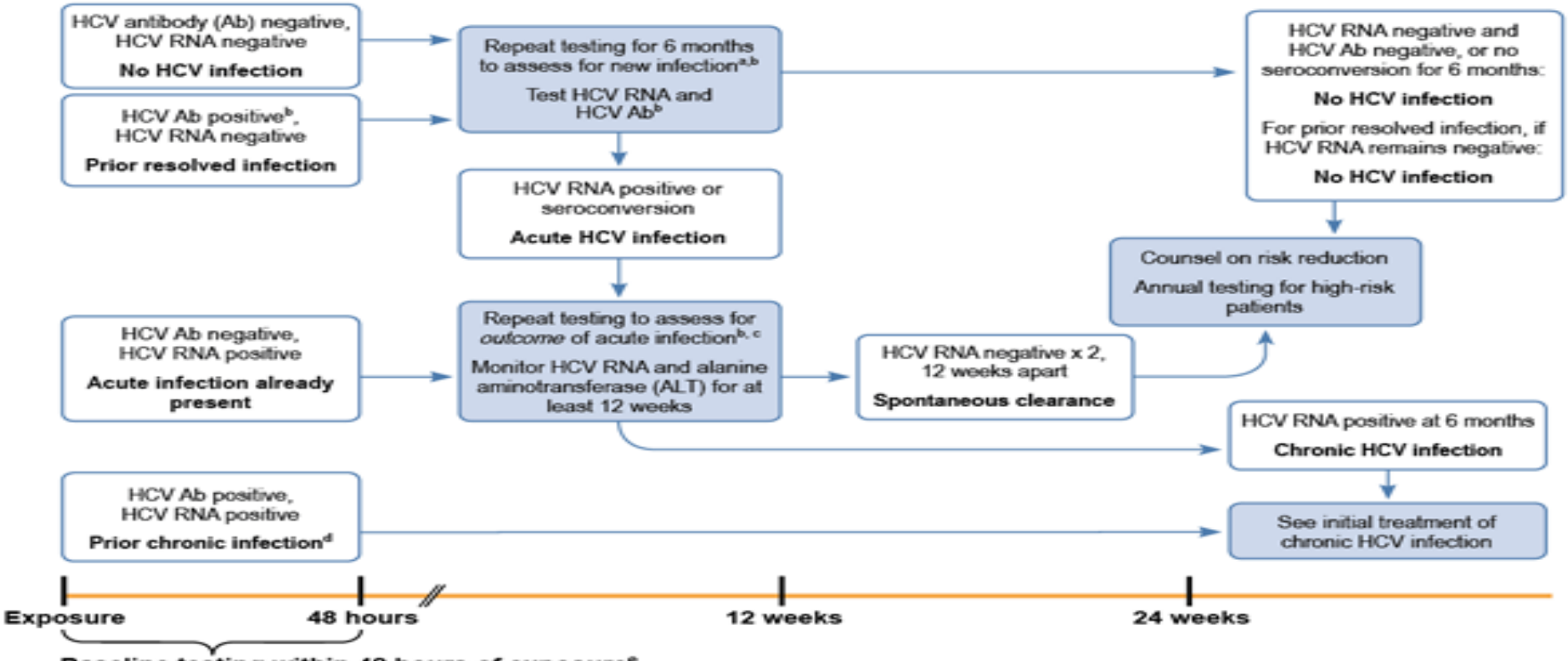
- ***Risk behavior :*** Current or former injection drug users, as well as intranasal illicit drug user.
- ***Risk exposure:***
- Chronic hemodialysis patient
- Percutaneous or parenteral exposure
- Health care ,emergency, medical and public safety workers after needle sticks, sharps or mucosal exposure involving HCV positive blood
- Recipients of blood or organs from HCV positive donors
- Patients with HIV infection
- Children born to HCV positive mothers
- Others

HOW TO PROVE THE PRESENCE OF HCV INFECTION



Is it an acute or chronic infection

Figure. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure[a]



[a] Often there is no discrete exposure or the entry to health care occurs with jaundice or elevated liver enzymes. In those instances, baseline testing cannot be done and the diagnosis of acute infection is more challenging (see text).

[b] Repeat HCV Ab is not needed if it is positive at baseline. Frequency of testing can be tailored based on management objectives (eg, monthly testing to identify and treat acute infection).

[c] Some would treat after waiting 8 weeks to 12 weeks for spontaneous clearance (see text). Benefits of HCV antiviral therapy or IFN-based (alternative) within 12 weeks of acute infection are that this may decrease transmission risk to others (eg, among injection drug users or surgeons), prevent severe complications (eg, underlying cirrhosis superinfected with acute HCV infection), and minimize chance of being lost to follow-up.

[d] If there were additional exposures in the preceding 6 months, a patient with a new diagnosis who is HCV RNA and HCV Ab positive may still be in the acute infection phase. Symptoms, high ALT level, or viral fluctuations may help distinguish acute from chronic HCV.

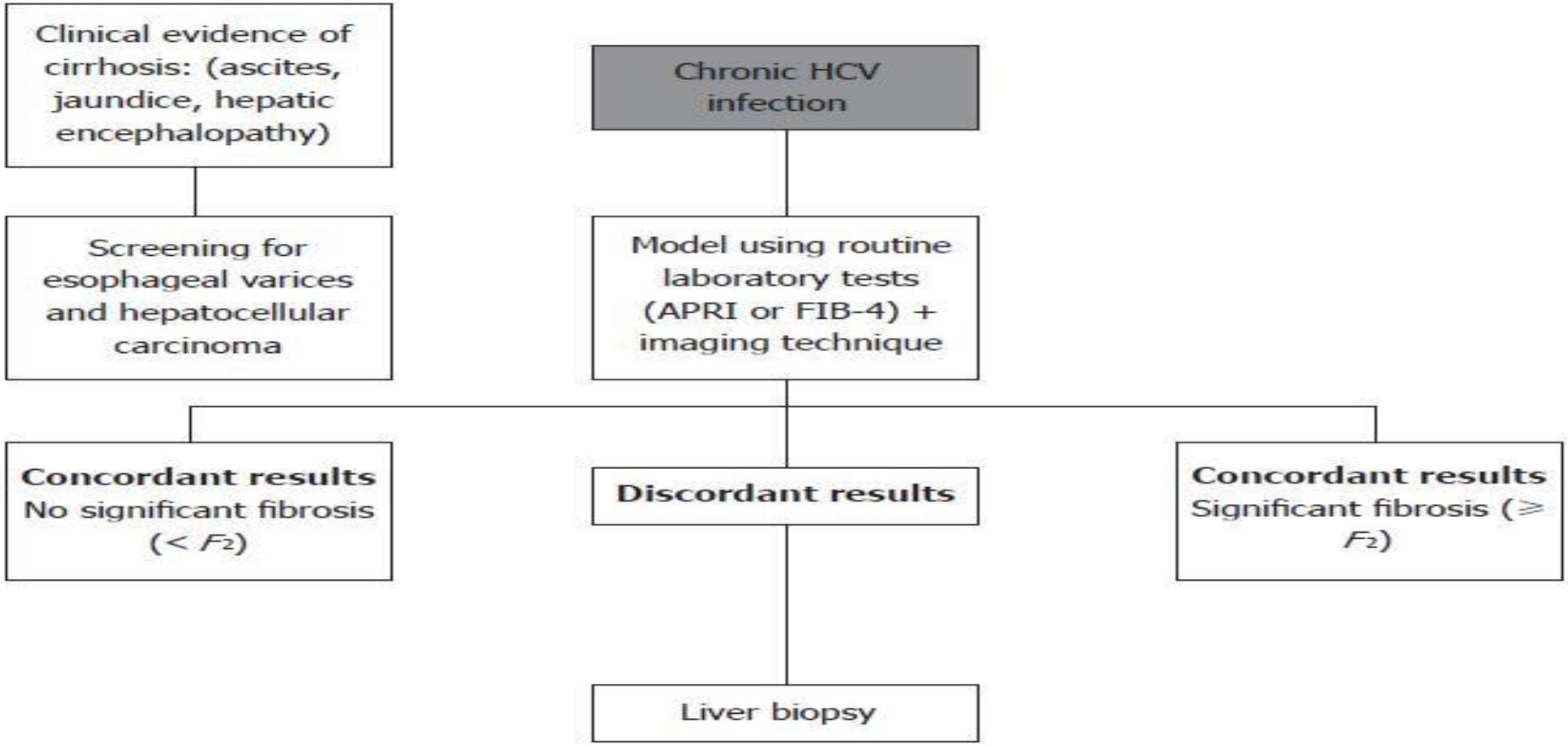
[e] Baseline testing should be done within 48 hours of exposure to determine existing infection status: HCV RNA, HCV Ab, and ALT.

WHAT IF IT IS AN ACUTE INFECTION

- Presentation may be vague or nonspecific
- Fluctuating ALT with high bilirubin and fluctuating HCV RNA (>1 log10IU/ml)
- Infection clears spontaneously in 25-50% usually within 6m rarely 12m.
- There are predictors of spontaneous clearance
- There is a choice of delayed (after 6m)or earlier(after 8-12w) therapy. Both cases receive the same DAA regimen. Why start ttt early?

IT TURNED OUT TO BE CHRONIC

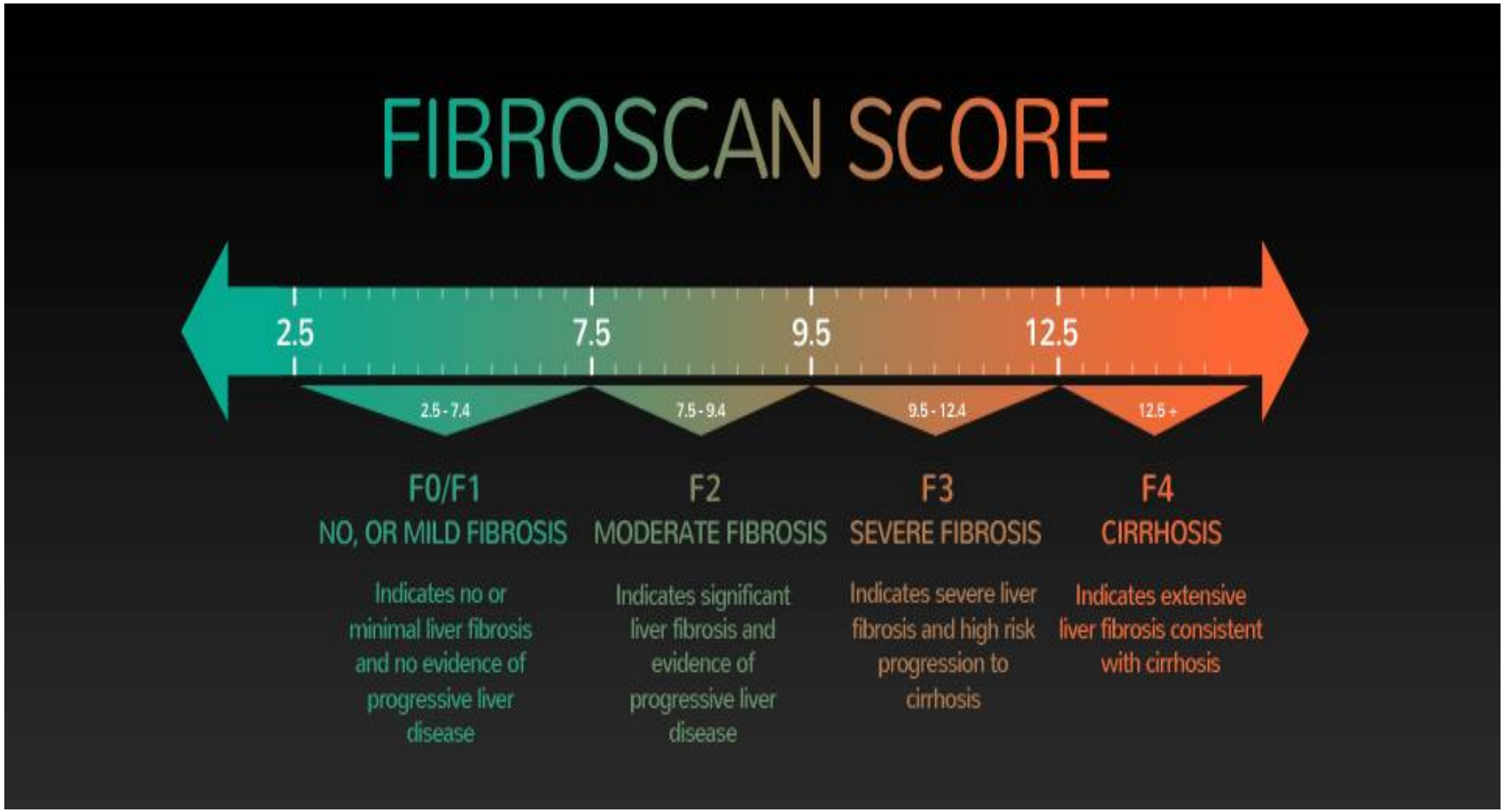
Baseline laboratory tests including HCV genotyping if needed
Assess for other causes of liver disease
Assess for liver disease severity



Score calculations

$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$


FIBROSCAN SCORE
2.5
7.5
9.5
12.5
2.5 - 7.4
7.5 - 9.4
9.5 - 12.4
12.5 +
F0/F1
NO, OR MILD FIBROSIS
Indicates no or minimal liver fibrosis and no evidence of progressive liver disease
F2
MODERATE FIBROSIS
Indicates significant liver fibrosis and evidence of progressive liver disease
F3
SEVERE FIBROSIS
Indicates severe liver fibrosis and high risk progression to cirrhosis
F4
CIRRHOSIS
Indicates extensive liver fibrosis consistent with cirrhosis

For whom is treatment recommended

- The goal of treatment is to reduce all cause mortality and liver related health adverse consequences including end stage liver disease and hepatocellular carcinoma by achieving virological cure(SVR).
- Treatment is recommended for all patients with chronic HCV infection except those with short life expectancy.

For whom is treatment prioritized?

Treatment priority	Patient group
Treatment should be prioritized	. Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis . Patients with HIV coinfection . Patients with HBV coinfection . Patients with an indication for liver transplantation . Patients with HCV recurrence after liver transplantation . Patients with clinically significant extra-hepatic manifestations . Patients with debilitating fatigue . Individuals at risk of transmitting HCV
Treatment is justified	. Patients with moderate fibrosis (F2)
Treatment can be deferred	. Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	. Patients with limited life expectancy due to non-liver related comorbidities

NS 3/4A PROTEASE INHIBITORS

- ***Simeprevir (Olysio)****:* Protease inhibitor, 2nd generation, effective in genotypes 1 and 4. In genotype 1a the presence of a baseline NS3/4A polymorphism Q80k is associated with significantly reduced SVR 12.

  It has important DDI with HIV medications.

  Not recommended in moderate or severe hepatic impairment.

  It is taken once daily 150mg with food.

- ***Asunaprevir (Sunvepra)***: a protease inhibitor used in conjunction with Daclatasvir especially in genotype 1b in patients with or without compensated cirrhosis.
- The dose is reduced to once daily in patients with creatinine clearance <30ml/min and contraindicated in moderate to severe hepatic impairment or decompensated liver disease. It is taken 100mg twice daily. It is metabolized by CYP3A.

NS5B POLYMERASE INHIBITORS

- The NS5B polymerase is highly conserved across all HCV genotypes. Inhibitors are divided into two types:

1.Nucleos(t)ide NS5B inhibitors:

Nucleotide analogs of the NS5B polymerase act as chain terminators within the catalytic site of the NS5B polymerase. These agents provide a high genetic barrier to resistance, have pangenotype activity, high potency and limited DDI and offer once daily dosing. ***Sofosbuvir*** (Sovaldi) is the only one that has reached the market to date. It can be used regardless of previous HCV treatment experience as well as with mild , moderate or severe hepatic impairment. Its safety is not established in patients with severe renal impairment. It is taken 400mg once with or without food.

2. Non-nucleotide inhibitors:

These agents bind to different allosteric site of the NS5B polymerase which result in conformational changes causing the polymerase to be ineffective. These agents only have activity against HCV genotype 1. They also have a low barrier to resistance. The only product to reach the market is ***Dasabuvir***.

NS5A INHIBITORS

- The NS5A inhibitors that have been licensed for HCV: Daclatasvir , Ledipasvir, Ombitasvir, Elbasvir and Velpatasvir.

Daclatasvir (Daklinza):

It shows safety and efficacy when combined with Sofosbuvir including patients with decompensated cirrhosis, post transplantation HCV infection or HIV/HCV co-infection and can be used without dose adjustment in renal insufficiency. It has very few DDI and can be used safely with opioid substitution therapy. Some adjustment is needed in persons on Anti-Retroviral Therapy for HIV

Daclatasvir has broader genotype activity and is the only NS5A inhibitor licensed for HCV-3. It is taken once daily 60mg with or without meals.

Daclatasvir dose should be modified with CYP3A inhibitors and inducers. With strong inhibitors, the dose should be reduced to 30mg once daily. With moderate inducers, the dose of Daclatasvir should be increased to 90mg daily. With strong CYP3A inducers, Daclatasvir is contraindicated.

FIXED DRUG COMBINATIONS

- ***Harvoni*** :

Ledipasvir 90mg/***Sofosbuvir*** 400mg: NS5A inhibitor administered with an NS5B nucleotide inhibitor, shows efficacy when used in patients infected with genotypes 1 and 4,5,6 and in the setting of decompensated liver disease. It has few DDI but it requires low gastric PH for Ledipasvir's absorption. It should be used with caution with certain ART drugs especially Tenofovir. Food does not affect its absorption.

FIXED DRUG COMBINATION

- ***Viekera Pak:***

Paritaprevir/ritonavir/Ombitasvir. Paritaprevir(150mg) is an NS3/4A protease inhibitor boosted by ritonavir(100mg), Ombitasvir(25mg) is an NS5A inhibitor and are taken as two tablets once in the morning with food. They are effective in genotype 4. The addition of Dasabuvir, an NS5B non-nucleotide inhibitor (250mg) taken twice daily is necessary for genotype1. It is administered with or without weight based Ribavirin. It is contraindicated in advanced liver disease(CP B or C) but NO dosage adjustment is necessary in renal impairment.

FIXED DRUG COMBINATION

- ***Epclusa :***

Velpatasvir 100mg/Sofosbuvir 400mg an NS5A inhibitor with an NS5B polymerase nucleotide inhibitor. This combination shows signs of being a strong pangenotypic regimen. It is indicated for patients with or without compensated cirrhosis as well as decompensated cirrhosis. It is taken once daily with or without food. It is not recommended for patients with severe renal impairment.

FIXED DRUG COMBINATION

- ***Zepatier :***

Grazoprevir100mg/Elbasvir50mg a protease inhibitor and an NS5A inhibitor. This fixed combination is effective against a broader array of HCV genotypes (1,4,6) as well as some of the major resistance associated variants. It demonstrated efficacy in HIV coinfection, stage 4-5 chronic kidney disease including dialysis. It has similar efficacy with or without cirrhosis but should not be used in advanced liver disease. Patients with genotype 1a should undergo HCV RNA NS5A resistance(detected in 12% of the population) testing prior to therapy.

GUIDELINES FOR TREATMENT NAÏVE G4 NO CIRRHOSIS/COMPENSATED CIRRHOSIS

- Paritaprevir/ritonavir/Ombitasvir PLUS weight based Ribavirin FOR 12 weeks (1A)
- Sofosbuvir/Velpatasvir FOR 12 weeks (1A)
- Elbasvir/Grazoprevir FOR 12 weeks (2a B)
- Ledipasvir/Sofosbuvir FOR 12 weeks (2a B)

GUIDELINES FOR TREATMENT EXPERIENCED G4 NONCIRRHOTIC

- Paritaprevir/ritonavir/Ombitasvir PLUS weight based Ribavirin FOR 12 weeks (1 A)
- Sofosbuvir/ Velpatasvir FOR 12 weeks (1A)
- Elbasvir/Grazoprevir in relapsers FOR 12 weeks BUT in patients with on treatment failure ADD weight based Ribavirin FOR 16 weeks (2a B)
- Ledipasvir/Sofosbuvir FOR 12 weeks (2a B)

GUIDELINES FOR TREATMENT EXPERIENCED G4 COMPENSATED CIRRHOSIS

- Paritaprevir/ritonavir/Ombitasvir PLUS weight based Ribavirin FOR 12 weeks (1A)
- Sofosbuvir/Velpatasvir FOR 12 weeks (1 A)
- Elbasvir/Grazoprevir in relapsers FOR 12 weeks BUT in patients with on treatment failure ADD wt. based Ribavirin FOR 16 weeks (2a B)
- Ledipasvir/Sofosbuvir PLUS weight based Ribavirin FOR 12 weeks (2a B)
- Ledipasvir/Sofosbuvir FOR 24 weeks (2a B)

GUIDELINES FOR DECOMPENSATED CIRRHOSIS G4

With/without HCC who are/aren't candidates for liver transplantation:

1. Ledipasvir/Sofosbuvir PLUS a low initial Ribavirin (600 mg increased as tolerated) FOR 12 weeks (1A)
2. Daily Sofosbuvir/Velpatasvir PLUS weight based Ribavirin FOR 12 weeks (1 A)
3. Sofosbuvir/Daclatasvir PLUS low initial dose of Ribavirin FOR 12 weeks (1 B)
4. Sofosbuvir/ Velpatasvir FOR 24 weeks (1 A)
5. Sofosbuvir/ Daclatasvir FOR 24 weeks (2 C)
6. Ledipasvir/Sofosbuvir FOR 24 weeks (2 C)

GUIDELINES FOR DECOMPENSATED CIRRHOSIS G4

Decompensated cirrhosis who failed prior Sofosbuvir based treatment

1. Ledipasvir/Sofosbuvir PLUS Ribavirin (low initial dose: 600mg and increased as tolerated) FOR 24 weeks (2 C)
2. Velpatasvir/Sofosbuvir PLUS weight based Ribavirin FOR 24 weeks (2 C)

GUIDELINES FOR LIVER CIRRHOSIS AND RENAL IMPAIRMENT G4

- For patients with mild to moderate renal impairment (Creatinine Clearance 30 ml/min.-80 ml/min) : No dosage adjustment is required to treat or retreat HCV infection (1 A)
- Patients with Creatinine Clearance <30 ml/min or End Stage Renal Disease:

  Elbasvir/Grazoprevir FOR 12 weeks (2a B)

- As for patients on dialysis anti HCV treatment depends on the comorbidities of the patient. Therapy should be considered for transplant candidates as liver damage may be accelerated by immunosuppression.

RECOMMENDED MONITORING DURING THERAPY

- Regular clinical visits to monitor for adverse events and potential drug-drug interactions.
- Complete blood picture, creatinine level, calculated GFR and hepatic function panel are recommended after 4w.
- Ten fold increase in ALT at week 4, or any increase in ALT of less than 10 folds with weakness, nausea, vomiting, jaundice, increased INR should prompt discontinuation.
- Quantitative HCV RNA at week 4 then at week 12 post therapy. Then at week 24 or longer.
- HBsAG+ patients should be monitored by HBV DNA during and immediately after therapy.

RECOMMENDATION FOR DISCONTINUATION OF THERAPY

- If HCV RNA is detected at 4weeks repeat 2 weeks later.
- If viral load is increased 10 folds, stop therapy.
- If viral load is less than that there are no specific recommendations.

EASL RECOMMENDATION: TREATMENT FAILURE

Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Sofosbuvir and daclatasvir or Sofosbuvir and ledipasvir	Genotype 1	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 2 or 3	No	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 4	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Genotype 1	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir and ombitasvir	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis