Clinical guidelines for the treatment of hepatitis C in Iceland

For the **Treatment as Prevention for Hepatitis C in Iceland (TraP Hep C)**

A nationwide campaign for reducing disease burden using combination antiviral treatment

Whom to treat

All patients infected with the hepatitis C virus should be considered for treatment. An eligible case of chronic hepatitis C infection is defined by two separate positive HCV PCR tests obtained at least 3 months apart. Patients who actively inject drugs and have high risk of transmitting disease and have one positive PCR will be considered for treatment as well.
Children age 16-18 may be considered for treatment.

Highest priority for treatment

A. Highest risk for progression to cirrhosis or severe complications
Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4/transient elastography>12.5 kPa)
Organ transplant: pre- or post liver transplantation
Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)
HIV-1 coinfection and moderate fibrosis (Metavir 2)
Hepatitis B virus (HBV) coinfection and moderate fibrosis (Metavir 2)

B. Persons at Elevated risk of HCV transmission* and in whom HCV treatment may yield transmission reduction benefits
Active injection drug users
Incarcerated persons

Absolute contraindications for treatment

Imminent risk of death (within 6 months) due to serious comorbid diseases as judged by the treating physicians
Pregnancy, breastfeeding or plans to become pregnant

Treatment regimens

First choice - Ledipasvir/Sofosbuvir (LDV/ SOF)

The first choice of treatment regimen for all genotypes is a fixed dose combination with sofosbuvir and ledipasvir, with or without ribavirin.

Sofosbuvir (SOF) is a nucleotide NS5B inhibitor that was approved in the EU in November 2013 and in the USA in December 2013. Ledipasvir (LDV) is a NS5A inhibitor of HCV and is only available in a fixed dose combination with SOF (SOF 400mg/LDV 90 mg) in a product named Harvoni® which was approved in the EU in 2014. Harvoni® is given as a single pill once daily. Patients will need 8-24 weeks of treatment, depending on fibrosis stage, HCV genotype, treatment history, and viral load. Patients with genotype 3 as well as treatment-experienced patients with genotype 1 who have cirrhosis and treatment naive cirrhotics with advanced disease will need ribavirin (RBV) along with LDV/SOF. When used in combination with ribavirin, refer to the Summary of Product Characteristics of ribavirin. In patients without decompensated cirrhosis, RBV is given twice daily with food with dosing according to body weight. (< 75 kg = 1.000 mg and ≥ 75 kg = 1.200 mg). In patients with decompensated cirrhosis, ribavirin should be administered at a starting dose of 600 mg given in a divided daily dose. If the starting dose is well-tolerated, the dose can be titrated up to a maximum of 1,000-1,200 mg daily (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg). If the starting dose is not well-tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels.

Efficacy, side effects and duration of treatment with LDV/ SOF.

Studies show that with the treatment regimen LDV/SOF with or without RBV, 90-99% of patients with genotype 1 clear the virus[1]. In the SIRIUS study it was demonstrated that LDV/SOF plus RBV for 12 weeks and LDV/SOF for 24 weeks provided similarly high SVR12 rates in previous non-responders with HCV genotype 1 and compensated cirrhosis[2]. In a recent study (SOLAR-1) LDV/SOF plus RBV for 12 weeks produced high rates of SVR in patients with genotype 1 and advanced disease and response rates were similar for 12 and 24 weeks of treatment[3]. The response rate among cirrhotic and treatment experienced patients with GT3 may be lower[4]. For most patients, expected treatment duration is 8 -12 weeks. Side effects from LDV/SOF are mild. 13% experience fatigue, 14% headache, 7% nausea, 3% diarrhea and 5% insomnia. Laboratory abnormalities can be encountered as bilirubin elevation above 1.5 x ULN was seen in 1%, and lipase was elevated more than 3x ULN in less than 3% of patients treated with LDV/SOF for 12 weeks. RBV, which will be used in patients with genotype 3,

[1] Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 (GT1) infection. N Engl J Med. 2014a;370(20):1889-1898

[2] Bourlière M, Jean-Pierre Bronowicki JP, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patientBs with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis. 2015 Apr;15(4):397-404.

[3] Af Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology. 2015 Sep;149(3):649-59.

[4] Gane EJ, Hyland RH, An D, et al. Efficacy of Ledipasvir and Sofosbuvir, With or Without Ribavirin, for 12 Weeks in Patients With HCV Genotype 3 or 6 Infection. Gastroenterology. 2015 Aug 7. pii: S0016-5085(15)01096-3. doi: 10.1053/j.gastro.2015.07.063. [Epub ahead of print].

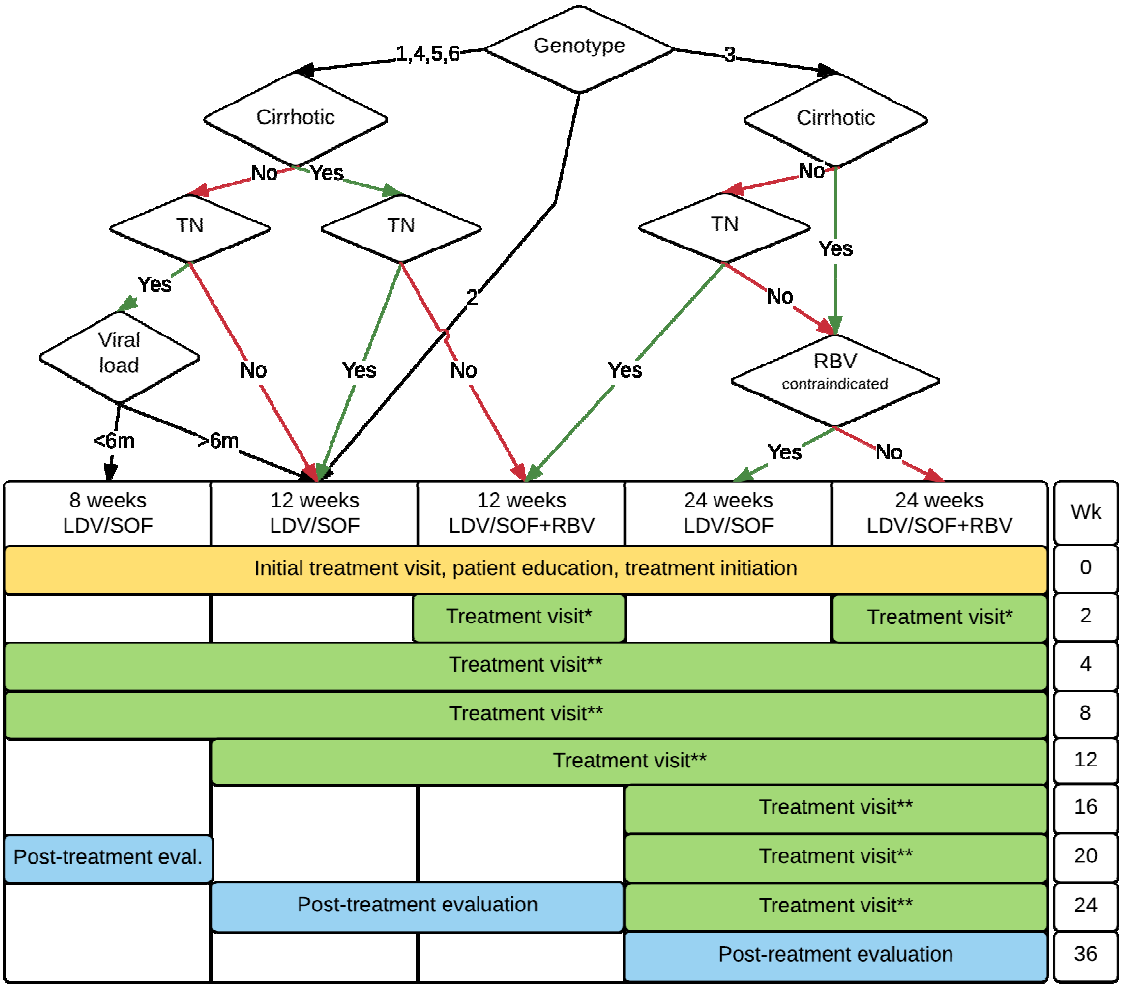
treatment experienced patients with cirrhosis, or patients with decompensated cirrhosis, along with LDV/SOF , causes anemia that is usually treated with dose reduction. RBV also has teratogenic effects and female study participants who receive RBV should not conceive for the duration of the study and for six months after the treatment has stopped. Male patients who receive RBV should not father a child for the treatment period and the following six months. The current package insert should be consulted prior to initiation of therapy.

Initial treatment regimens:

GT1,4,5,6		
TN, non-cirrhotic	LDV/SOF	Viral load<6 million IU/mL, 8 weeks (GT 1 only)
TN, non-cirrhotic	LDV/SOF	Viral load>6 million IU/mL, or non-GT-1, 12 weeks
TN, cirrhotic	LDV/SOF	12 weeks
TE, non-cirrhotic	LDV/SOF	12 weeks
TE, cirrhotic	LDV/SOF+RBV	12 weeks (24 weeks if no RBV)
Decompensated/post-transpl	LDV/SOF+RBV	12 weeks (24 weeks if no RBV)
GT 3		
TE or cirrhosis	LDV/SOF+RBV	24 weeks (24 if no RBV)
TN	LDV/SOF+RBV	12 weeks (24 if no RBV)
GT 2		
TN/TE	LDV/SOF	12 weeks

Table 1. Initial treatment regimens for chronic HCV in Iceland.
Legends: TN: treatment-naïve; TE: treatment-experienced.

Figure 1 shows an overview of the treatment assignment or SOF/LDV and treatment visit plan



*Only patients treated with ribavirin come for a treatment visit at week two. At this visit only a CBC is performed.
**At all other treatment visits the following lab tests are performed: CBC, Crea, ALT, Bilirubin. PCR is performed at the baseline visit (not shown in this figure), at the last treatment visit (week 8, 12, or 24 depending on treatment length), and at the post-treatment evaluation. At each visit following the initial treatment visit the patient answers questions regarding compliance and substance abuse.

Figure 1. Flow-chart of the treatment assignment and visit schedule (TN=Treatment Naïve).

Relative contraindication for treatment/contraindication for LDV/SOF.

For contraindications, precautions and drug interactions guidance should be sought by the European Medicines Agency SmPC most current recommendations.

LDV/SOF is contraindicated in patients receiving rosuvastatin or St John´s Wort. The safety of LDV/SOF has not been assessed inpatients with severe renal impairment [eGFR] < 30 ml/mín./1,73 m2 or end stage renal disease requiring hemodialysis.
Patients receiving certain medications such as amiodarone, tipranavir boosted with ritonavir, the anti-seizure medications carbamazepine, phenytoin, phenobarbital, or oxcarbazepine; or undergoing TB treatment using rifampicin will be informed of potential drug interactions and offered treatment modifications or deferral of HCV treatment until it becomes feasible as determined by the patient´s physician.

Second choice - Alternative treatment regimens to consider for patients who have contraindications for SOF/LDV +/-RBV.

GT 1a/1b
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) (Viekirax®) plus twice-daily dosed dasabuvir (250 mg) (Exviera®)for 12 or 24 weeks plus or minus weight-based RBV depending on the presence or absence of cirrhosis, viral subtype and previous treatment history.

or
Daily daclatasvir (60 mg*) (Daklinza®)and sofosbuvir (400 mg) (Sovaldi®)for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) (cirrhosis).

GT 2
Daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks.

GT 3
Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (cirrhosis).Depending on the presence or absence of cirrhosis and previous treatment history.
or
Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks.

GT 4
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (compensated cirrhosis).

GT 5 or 6
There are no cases of these genotypes in Iceland, if encountered they should be treated following consultation with the coordinators of the nationwide campaign.

Recommended screening and monitoring strategy for patients who are starting hepatitis C treatment, are on treatment, or have completed therapy**.**

At an initial, baseline visit the following blood tests will be performed: CBC, , creatinine, ALAT, ASAT, bilirubin, albumin, INR, HCV RNA by PCR (quantitative, "viral load"), HCV genotyping (unless already genotyped since 2009), HBsAg, anti-HBc, HIV ab. For female patients of childbearing age, pregnancy test should be performed. Hepatic elastography will be performed unless an elastography or a liver biopsy has been performed within the preceding 6 months. An interview should be performed where the patients risk for transmitting the hepatitis C virus is assessed and recorded. The results of these laboratory tests, elastography, and interview are used to assess the need for therapy.

If a subject qualifies for treatment they will start the indicated treatment program as per these guidelines within 4 weeks. Following a treatment initiation visit at week 0, clinic visits will be at week 2 (for patients receiving ribavirin), 4, 8, 12, 16, 20, 24, and 36 depending on the length of treatment. Patients deemed at high risk of transmitting disease may have their treatment initiation visit on the same day as their screening visit.

At clinic visit week 2 (patients receiving ribavirin) CBC will be measured. At all other clinic visit the following tests will be performed: CBC, creatinine, ALAT and bilirubin. For female patients of childbearing age receiving RBV, pregnancy test should be performed at each visit. Quantitative HCV RNA by PCR will be performed at the end of treatment and at 12 weeks post treatment (at 8, 12, 20, 24, and 36 weeks depending on length of treatment). SVR is defined as negative HCV RNA PCR 12 weeks post treatment (SVR12). These recommendations represent the minimum amount of monitoring, but if more close monitoring is deemed necessary (such as for patients with cirrhosis) by the treating physician, additional visits should be planned. For patients who are at risk for poor compliance such as active drug users, special measures, such as more frequent clinic visits will be implemented.
Patients with who do not acheive SVR will need continued follow up with office visits every 6 months.
Patients with cirrhosis will need continued monitoring every 6 months regardless of response to therapy to evaluate for development of HCC and/ or decomensation.
Patients with significant fibrosis (Metavir F3 or transient elastography >11.0 kPa) who achieve SVR should be followed with yearly clinic visits for 5 years.

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