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EASL Recommendations on Treatment of Hepatitis C 2015
SUMMARY

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Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. The long-term impact of HCV infection is highly variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). The number of chronically infected persons worldwide is estimated to be about 160 million, but most are unaware of their infection. The implementation of extended criteria for screening for HCV is a subject of major debate among different stakeholders. Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, thanks to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention.

These EASL Recommendations on Treatment of Hepatitis C are intended to assist physicians and other healthcare providers, as well as patients and other interested individuals, in the clinical decision-making process by describing the optimal management of patients with acute and chronic HCV infections. These recommendations apply to therapies that have been approved in the European Union at the time of their publication.

1. Diagnosis of acute and chronic hepatitis C

- Anti-HCV antibodies are the first-line diagnostic test for HCV infection **(A1)**
- In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation **(A1)**
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method **(A1)**
- Anti-HCV-positive, HCV RNA negative individuals should be retested for HCV RNA three months later to confirm true convalescence **(A1)**

2. Screening for chronic hepatitis C

- Screening for HCV infection must be recommended in targeted populations defined according to the local epidemiology of HCV infection, ideally within the framework of national plans **(A1)**
- Screening for HCV infection must be based on the detection of anti-HCV antibodies **(A1)**
- Rapid diagnostic tests can be used instead of classical enzyme immunoassays to facilitate anti-HCV antibody screening and improve access to care **(B1)**
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method to identify patients with on-going infection **(A1)**

3. Goals and endpoints of HCV therapy

- The goal of therapy is to cure HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, severe extra-hepatic manifestations and death **(A1)**
- The endpoint of therapy is undetectable HCV RNA in a sensitive assay (≤15 IU/ml) 12 weeks (SVR12) and 24 weeks (SVR24) after the end of treatment **(A1)**
- In patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, albeit not abolish, the risk of HCC. In these patients surveillance for HCC should be continued **(A1)**
- In patients with decompensated cirrhosis, HCV eradication reduces the need for liver transplantation. Whether HCV eradication impacts mid-to long-term survival in these patients is unknown **(B2)**

4. Pre-therapeutic assessment

- The causal relationship between HCV infection and liver disease should be established **(A1)**
- The contribution of comorbid conditions to the progression of liver disease must be evaluated and appropriate corrective measures implemented **(A1)**
- Liver disease severity should be assessed prior to therapy. Identifying patients with cirrhosis is of particular importance, as their prognosis is altered and their treatment regimen may be adapted **(A1)**
- Fibrosis stage can be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional aetiologies **(A1)**
- HCV RNA detection and quantification should be made by a sensitive assay with a lower limit of detection of ≤15 IU/ml **(A1)**
- The HCV genotype and genotype 1 subtype (1a/1b) must be assessed prior to treatment initiation and will determine the choice of therapy **(A1)**
- *IL28B* genotyping has no role in the indication for treating hepatitis C with the new DAAs **(A1)**
- HCV resistance testing should not be performed prior to therapy, because the SVR rates are very high both in patients without and with detectable amounts of resistance-associated variants by means of population sequencing at baseline (with the exception of patients infected with subtype 1a who receive the combination of PegIFN-α, ribavirin and simeprevir) **(A1)**

5. Indications for treatment: who should be treated?

- All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy **(A1)**
- Treatment should be prioritized for patients with significant fibrosis or cirrhosis (METAVIR score F3 to F4) **(A1)**
- Patients with decompensated cirrhosis (Child-Pugh B and C) should be urgently treated with an IFN-free regimen **(A1)**
- Treatment should be prioritized regardless of the fibrosis stage in patients with HIV or HBV coinfection, patients in the pre- or post-liver transplant setting, patients with clinically significant extra-hepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma), and patients with debilitating fatigue **(A1)**
- Treatment should be prioritized regardless of the fibrosis stage for individuals at risk of transmitting HCV, including active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, and incarcerated individuals **(B1)**
- Treatment is justified in patients with moderate fibrosis (METAVIR score F2) **(A2)**
- In patients with no or mild disease (METAVIR score F0-F1) and none of the above-mentioned extra-hepatic manifestations, the indication for and timing of therapy can be individualized **(B1)**
- Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities **(B1)**

6. Drug-drug interactions

- Numerous and complex drug-drug interactions are possible with the HCV DAAs, especially when they are used in IFN-free combinations. Strict rules should thus be applied. As the data accumulate, guidance for contra-indications and dose adjustments can be found in Tables 4A to 4F of these Recommendations and at *www.hep-druginteractions.org* where they are regularly updated **(B1)**
- The use of cobicistat-based regimens, efavirenz, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir **(A1)**
- The daily daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz **(B2)**
- No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs **(A2).**
- The fixed-dose combination of sofosbuvir and ledipasvir can be used with all antiretrovirals. However, this regimen should not be used with the combination of tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir or elvitegravir/cobicistat when possible, or used with caution with frequent renal monitoring **(B1)**
- The combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir should not be used with efavirenz, etravirine or nevirapine, and rilpivirine should be used cautiously with repeat ECG monitoring. Atazanavir and darunavir should be taken without ritonavir and other protease inhibitors are contra-indicated with this combination. Elvitegravir/cobicistat should not be used with this regimen because of the additional boosting effect **(B1)**

7. Treatment of chronic hepatitis C, including patients without cirrhosis and patients with compensated (Child-Pugh A) cirrhosis

- Indications for HCV treatment in HCV/HIV coinfected persons are identical to those in patients with HCV-monoinfection **(A1)**
- Notwithstanding the respective costs of these options, IFN-free regimens are the best options when available in HCV-monoinfected and in HIV-coinfected patients without cirrhosis or with compensated (Child-Pugh A) or decompensated (Child-Pugh B or C) cirrhosis, because of their virological efficacy, ease of use and tolerability **(A1)**
- The same IFN-free treatment regimens can be used in HIV-coinfected patients as in patients without HIV infection, as the virological results of therapy are identical **(A1)**

Treatment of HCV genotype 1 infection

Six treatment options are available in 2015 for patients infected with HCV genotype 1, including 2 IFN-containing regimens and 4 IFN-free regimens. The combination of sofosbuvir and ribavirin should not be used in patients infected with HCV genotype 1. In settings where none of the proposed options is available, the double combination of PegIFN-α and ribavirin, or the triple combination of PegIFN-α, ribavirin and either telaprevir or boceprevir, remain acceptable for selected patients likely to respond to these regimens until new DAAs become available and affordable; see prior EASL Clinical Practice Guidelines.

Genotype 1, IFN-containing Option 1

- Patients infected with HCV genotype 1 can be treated with a combination of weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(A1)**

Genotype 1, IFN-containing Option 2

- Patients infected with HCV genotype 1 can be treated with a combination of weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily simeprevir (150 mg) **(A1)**
- This combination is not recommended in patients infected with subtype 1a who have a detectable Q80K substitution in the NS3 protease sequence at baseline, as assessed by population sequencing (direct sequence analysis) **(A1)**
- Simeprevir should be administered for 12 weeks in combination with PegIFN-α and ribavirin. PegIFN-α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relapser patients, including cirrhotic patients, and for an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotic patients **(B1)**
- HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/ml at treatment week 4, week 12 or week 24 **(A2)**

Genotype 1, IFN-free Option 1

- Patients infected with HCV genotype 1 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily **(A1)**
- Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin **(A1)**
- Treatment may be shortened to 8 weeks in treatment-naïve patients without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 Log) IU/ml. This should be done with caution, especially in patients with F3 fibrosis, pending demonstration of the accuracy of HCV RNA level determination within this range of values and real-life confirmation that 8 weeks of treatment are sufficient to achieve high SVR rates **(B1)**
- Patients with compensated cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) **(A1)**
- Patients with compensated cirrhosis with contra-indications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir for 24 weeks without ribavirin **(B1)**
- Treatment with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin can be prolonged to 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 x 10^3/µl **(B2)**

Genotype 1, IFN-free Option 2

- Patients infected with HCV genotype 1 can be treated with an IFN-free regimen comprising the fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), and dasabuvir (250 mg) (one tablet twice daily) **(A1)**
- Patients infected with subtype 1b without cirrhosis should receive this combination for 12 weeks without ribavirin **(A1)**
- Patients infected with subtype 1b with cirrhosis should receive this combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) **(A1)**
- Patients infected with subtype 1a without cirrhosis should receive this combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) **(A1)**
- Patients infected with subtype 1a with cirrhosis should receive this combination for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) **(A1)**

Genotype 1, IFN-free Option 3

- Patients infected with HCV genotype 1 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) for 12 weeks **(A1)**
- Based on data with other IFN-free combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis **(B1)**
- In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered **(B1)**

Genotype 1, IFN-free Option 4

- Patients infected with HCV genotype 1 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks **(A1)**
- Based on data with other IFN-free combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis **(B1)**
- In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered **(B1)**

Treatment of HCV genotype 2 infection

The best first-line treatment option for patients infected with HCV genotype 2 is the IFN-free combination of sofosbuvir and ribavirin. Other options may be useful in the small number of patients who fail on this regimen. In settings where these options are not available, the combination of PegIFN-α and ribavirin remains acceptable, according to previously published EASL Clinical Practice Guidelines.

Genotype 2, Option 1

- Patients infected with HCV genotype 2 must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) for 12 weeks **(A1)**
- Therapy should be prolonged to 16 or 20 weeks in patients with cirrhosis, especially if they are treatment-experienced **(B1)**

Genotype 2, Option 2

- Cirrhotic and/or treatment-experienced patients can be treated with weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(B1)**

Genotype 2, Option 3

- Cirrhotic and/or treatment-experienced patients can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks **(B1)**

Treatment of HCV genotype 3 infection

Three treatment options are available for patients infected with HCV genotype 3. The combination of sofosbuvir and ribavirin is suboptimal, in particular in patients with cirrhosis who have previously failed IFN and ribavirin. Based on data with other genotypes and results in a small group of genotype 3-infected patients, the triple combination of PegIFN-α, ribavirin and sofosbuvir appears to be valuable. The IFN-free combination of sofosbuvir and daclatasvir, with or without ribavirin, is another attractive option for patients infected with HCV genotype 3.
Ledipasvir is considerably less potent against genotype 3 than daclatasvir in vitro; in clinical trials with ledipasvir, the respective roles of ledipasvir and ribavirin in combination with sofosbuvir cannot be determined in the absence of control arms with sofosbuvir and ribavirin alone. Thus, although this combination has been used, pending further studies in larger populations including appropriate control arms the combination of sofosbuvir plus ledipasvir is not recommended in patients infected with HCV genotype 3.
In settings where none of these options is available, the combination of PegIFN-α and ribavirin remains acceptable, according to previous EASL Clinical Practice Guidelines.

Genotype 3, Option 1

- Patients infected with HCV genotype 3 can be treated with a combination of weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(B1)**
- This combination is a valuable option in patients who failed to achieve an SVR after sofosbuvir plus ribavirin treatment **(B1)**

Genotype 3, Option 2

- Patients infected with HCV genotype 3 can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) for 24 weeks **(A1)**
- This therapy is suboptimal in treatment-experienced cirrhotic patients and in patients who failed to achieve an SVR after sofosbuvir plus ribavirin treatment, who should be offered an alternative treatment option **(B1)**

Genotype 3, Option 3

- Patients infected with HCV genotype 3 without cirrhosis can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks **(A1)**
- Treatment-naïve and treatment-experienced patients infected with HCV genotype 3 with cirrhosis should receive this combination with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) for 24 weeks, pending further data comparing 12 weeks with ribavirin and 24 weeks with and without ribavirin in this population **(B1)**

Treatment of HCV genotype 4 infection

Six treatment options are available in 2015 for patients infected with HCV genotype 4, including 2 IFN-containing regimens and 4 IFN-free regimens. In settings where none of these options is available, the combination of PegIFN-αand ribavirin remains acceptable; see prior EASL Clinical Practice Guidelines.

Genotype 4, IFN-containing Option 1

- Patients infected with HCV genotype 4 can be treated with a combination of weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(B1)**

Genotype 4, IFN-containing Option 2

- Patients infected with HCV genotype 4 can be treated with a combination of weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily simeprevir (150 mg) **(B1)**
- Simeprevir should be administered 12 weeks in combination with PegIFN-α and ribavirin. PegIFN-α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relapser patients, including cirrhotic patients, an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotic patients **(B1)**
- HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/ml at treatment week 4, week 12 or week 24 **(A2)**

Genotype 4, IFN-free Option 1

- Patients infected with HCV genotype 4 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily **(A1)**
- Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin **(A1)**
- Based on data in patients infected with HCV genotype 1, patients with compensated cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) **(B1)**
- Patients with compensated cirrhosis with contra-indications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir for 24 weeks without ribavirin **(B1)**
- Based on data in patients infected with HCV genotype 1, treatment with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin can be prolonged to 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 x 10^3/µl **(B1)**

Genotype 4, IFN-free Option 2

- Patients infected with HCV genotype 4 without cirrhosis can be treated with an IFN-free regimen comprising the fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without dasabuvir **(A1)**
- Patients infected with HCV genotype 4 with cirrhosis should be treated with the fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without dasabuvir, pending further data **(B1)**

Genotype 4, IFN-free Option 3

- Patients infected with HCV genotype 4 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) 12 weeks **(B2)**
- Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis **(B2)**
- In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered **(B2)**

Genotype 4, IFN-free Option 4

- Patients infected with HCV genotype 4 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks **(B2)**
- Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis **(B2)**
- In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered **(B2)**

Treatment of HCV genotype 5 or 6 infection

The 3 treatment options for patients infected with HCV genotypes 5 or 6 are the triple combination of PegIFN-α, ribavirin and sofosbuvir, the IFN-free combination of sofosbuvir and ledipasvir, and the IFN-free combination of sofosbuvir and daclatasvir. In settings where none of these options is available, the combination of PegIFN-α and ribavirin remains acceptable.

Genotype 5 or 6, Option 1

- Patients infected with HCV genotype 5 or 6 can be treated with a combination of weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(B1)**

Genotype 5 or 6, Option 2

- Patients infected with HCV genotype 5 or 6 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily **(A1)**
- Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin **(B1)**
- Based on data in patients infected with HCV genotype 1, patients with compensated cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) **(B1)**
- Patients with compensated cirrhosis with contra-indications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir for 24 weeks without ribavirin **(B1)**
- Based on data in patients infected with HCV genotype 1, treatment with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin can be prolonged to 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 x 10^3/µl **(B1)**

Genotype 5 or 6, Option 3

- Patients infected with HCV genotype 5 or 6 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks **(B1)**
- Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis **(B1)**
- In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered **(B1)**

8. Treatment monitoring

Monitoring of treatment efficacy

- A real-time PCR-based assay with a lower limit of detection of ≤15 IU/ml should be used to monitor HCV RNA levels during and after therapy **(A1)**
- In patients treated with the triple combination of PegIFN-α, ribavirin and sofosbuvir for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12 (end of treatment), and 12 or 24 weeks after the end of therapy **(A2)**
- In patients treated with the triple combination of PegIFN-α, ribavirin and simeprevir (12 weeks plus 12 or 36 weeks of PegIFN-α and ribavirin alone), HCV RNA should be measured at baseline, week 4, week 12, week 24 (end of treatment in treatment-naïve patients and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy **(A2)**
- In patients treated with an IFN-free regimen, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment in patients treated 12 or 24 weeks, respectively), and 12 or 24 weeks after the end of therapy **(A2)**

Stopping (futility) rules

- With the triple combination of PegIFN-α, ribavirin and simeprevir, treatment should be stopped if HCV RNA level is ≥25 IU/ml at treatment week 4, week 12 or week 24 **(A2)**
- An immediate switch to another IFN-containing DAA-containing or to an IFN-free regimen without a protease inhibitor should be considered **(B1)**
- No futility rules have been defined for other treatment regimens **(A1)**

Monitoring treatment safety

- Women of childbearing potential and/or their male partners must use an effective form of contraception during ribavirin-containing treatment and for a period of 6 months after the treatment has concluded **(A1)**
- The patients receiving PegIFN-α and ribavirin should be assessed for clinical side effects at each visit, while the haematological side effects should be assessed at weeks 2 and 4 of therapy and at 4 to 8 week intervals thereafter **(A1)**
- Renal function should be checked regularly in patients receiving sofosbuvir **(B1)**
- Rashes and indirect bilirubin elevations without ALT elevations may be seen with simeprevir **(A1)**
- Indirect bilirubin increases are rarely observed with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir **(A1)**
- No dose adjustment of simeprevir, sofosbuvir and ledispavir or daclatasvir is required in patients with mild, moderate or severe renal impairment. The appropriate dose of sofosbuvir for patients with eGFR <30 ml/min/1.73 m^2 is not yet established **(B2)**
- No dose adjustment of sofosbuvir plus ledipasvir or daclatasvir is required for patients with mild, moderate or severe (Child-Pugh C) hepatic impairment **(B2)**
- Higher exposures have been observed with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir in patients with severe hepatic impairment and their safety in this group requires further study **(B2)**

Monitoring drug-drug interactions

- The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment **(A1)**
- When possible, an interacting co-medication should be stopped for the duration of HCV treatment or the interacting co-medication should be switched to an alternative drug with less interaction potential **(B1)**

9. Measures to improve treatment adherence

- HCV treatment should be delivered within a multidisciplinary team setting, with experience in HCV assessment and therapy **(A1)**
- HCV-infected patients should be counselled on the importance of adherence for attaining an SVR **(A1)**
- In patients with socioeconomic disadvantages and in migrants, social support services should be a component of HCV clinical management **(B2)**
- In persons who actively inject drugs, access to harm reduction programs is mandatory **(A1)**

- Peer-based support should be evaluated as a means to improve HCV clinical management **(B2)**
- Patients should be counselled to abstain from alcohol during antiviral therapy. Patients with on-going alcohol consumption during treatment should receive additional support during antiviral therapy **(A1)**
- HCV treatment can be considered also for patients actively using drugs, provided they wish to receive treatment and are able and willing to maintain regular appointments. Also, the potential for drug-drug interactions involving prescribed and non-prescribed drugs needs to be considered **(A1)**

10. Post-treatment follow-up of patients who achieve an SVR

- Non-cirrhotic patients with SVR should be retested for ALT and HCV RNA at 48 weeks post-treatment, then discharged if ALT is normal and HCV RNA is negative **(B1)**
- Cirrhotic patients, and probably also patients with advanced fibrosis (F3), with SVR should undergo surveillance for HCC every 6 months by means of ultrasound **(B1)**
- Guidelines for management of portal hypertension and varices should be implemented, though index variceal bleed is seldom seen in low-risk patients after the achievement of SVR (unless additional causes for on-going liver damage are present and persist) **(A2)**
- Patients with on-going drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection **(B1)**
- The risk of reinfection should be explained to individuals with on-going risk behaviour, to positively modify risk behaviour **(B1)**
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken in people who inject drugs or men who have sex with men with on-going risk behaviour **(B2)**

11. Retreatment of non-sustained virological responders

- Patients who failed after PegIFN-α and ribavirin combination treatment must be retreated like treatment-naïve patients, according to the above recommendations by HCV genotype **(A1)**
- Patients infected with HCV genotype 1 who failed after a triple combination regimen of PegIFN-α, ribavirin and either telaprevir or boceprevir should be retreated with the IFN-free combination of sofosbuvir and ledipasvir, or sofosbuvir and daclatasvir, with ribavirin for 12 weeks **(A1)**
- Recommendations for retreatment after failure of second-wave DAA-based anti-HCV regimens are based on indirect evidence and subject to change when more data become available **(A1)**
- Patients who failed on a second-wave DAA-containing regimen, with or without PegIFN-α, with or without ribavirin, should be retreated with an IFN-free regimen for 12 weeks with weight-based ribavirin. Extending therapy to 24 weeks with ribavirin may be considered, especially in patients with advanced liver disease, including extensive fibrosis (F3) and cirrhosis (F4) **(B2)**
- Patients who failed on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus PegIFN-α and ribavirin can be retreated with a combination of sofosbuvir plus simeprevir (genotype 1 or 4), sofosbuvir plus daclatasvir (all genotypes) or sofosbuvir plus ledipasvir (genotypes 1, 4, 5 or 6), or with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), or with ritonavir-boosted paritaprevir and ombitasvir (genotype 4) **(B2)**
- Patients infected with HCV genotype 1 or 4 who failed on a regimen combining PegIFN-α, ribavirin and simeprevir should be retreated with a combination of sofosbuvir with daclatasvir or ledipasvir **(B2)**
- Patients who failed on a regimen combining PegIFN-α, ribavirin and daclatasvir should be retreated with a combination of sofosbuvir and simeprevir (if they are infected with genotype 1 or 4). Patients infected with other genotypes should be retreated with the combination of sofosbuvir and daclatasvir (genotypes 2, 3, 5 and 6) or with the combination of sofosbuvir and ledipasvir (genotypes 5 and 6) **(B2)**
- Patients infected with genotype 1 or 4 who failed on a regimen containing sofosbuvir and simeprevir should be retreated with a combination of sofosbuvir with daclatasvir or ledipasvir **(B2)**
- Patients who failed on a regimen containing sofosbuvir and daclatasvir or sofosbuvir and ledipasvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 and 4). Patients infected with other genotypes should be retreated with the combination of sofosbuvir and daclatasvir (genotypes 2, 3, 5 and 6) or with the combination of sofosbuvir and ledipasvir (genotypes 5 and 6) for 24 weeks **(B2)**

- Patients infected with genotype 1 who failed on the triple combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir should be retreated with a sofosbuvir-based regimen, e.g. sofosbuvir and simeprevir, sofosbuvir and daclatasvir or sofosbuvir and ledipasvir **(B2)**
- Patients infected with genotype 4 who failed on the double combination of ritonavir-boosted paritaprevir and ombitasvir should be retreated with a sofosbuvir-based regimen, e.g. sofosbuvir and simeprevir, sofosbuvir and daclatasvir or sofosbuvir and ledipasvir **(B2)**
- Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available **(A1)**
- The efficacy and safety of a triple combination regimen including sofosbuvir, an NS3 protease inhibitor and an NS5A protease inhibitor in patients who failed on a DAA-containing regimen is unknown **(B2)**
- The utility of HCV resistance testing (i.e. the determination of the sequence of the DAA target region) prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown **(B2)**

12. Treatment of patients with severe liver disease

Patients with decompensated cirrhosis without an indication for liver transplantation

- Patients with decompensated cirrhosis (Child-Pugh B and Child-Pugh C, up to 12 points) not on the waiting list for liver transplantation and without concomitant comorbidities that could impact their survival can be treated with the combination of sofosbuvir and ribavirin for 16-20 weeks (genotype 2), the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6), or the combination of sofosbuvir and daclatasvir (all genotypes), with weight-based ribavirin, for 12 weeks **(B1)**
- Patients with decompensated cirrhosis with contra-indications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), or the combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin **(B1)**

Patients with HCC without an indication for liver transplantation

- Although the long-term benefit of antiviral therapy to reduce the risk of HCC in patients undergoing resection or ablation for HCV-associated HCC is unknown, these patients frequently have advanced fibrosis and should receive appropriate antiviral therapy for their liver disease, following the guidelines above **(B2)**

Patients with an indication for liver transplantation

- In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection **(A1)**
- Treatment should be initiated as soon as possible in order to complete a full treatment course before transplantation and assess the effect of viral clearance on liver function, because significant improvement in liver function may lead to delisting selected cases **(B1)**
- Patients awaiting liver transplantation should be treated with an IFN-free regimen, in principle for 12 or 24 weeks, practically up to transplantation, with ribavirin **(A1)**
- Patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC can be treated with the combination of sofosbuvir and ribavirin for 16-20 weeks (genotype 2), with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a), with the combination of ritonavir-boosted paritaprevir and ombitasvir with ribavirin for 12 weeks (genotype 4), with the combination of sofosbuvir and simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), or with the combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes) **(B1)**
- Treatment with PegIFN-α, ribavirin and sofosbuvir for 12 weeks is acceptable in patients with compensated (Child-Pugh A) cirrhosis awaiting liver transplantation if IFN-free combinations are not available **(B2)**
- Patients with decompensated cirrhosis (Child-Pugh B or C) awaiting liver transplantation can be treated with the combination of sofosbuvir and ribavirin for 16-20 weeks (genotype 2), with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with the combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes); however, data are limited in patients with Child-Pugh C cirrhosis >12 points or with a MELD score >20 **(A1)**
- The optimal timing of treatment (i.e. before transplantation or post-transplantation) to maximize survival is still debatable and requires individual assessment **(B2)**
- Due to the limited amount of safety data reported in patients with decompensated cirrhosis awaiting liver transplantation, frequent clinical and laboratory assessment is necessary **(B2)**

Post-liver transplantation recurrence

- All patients with post-transplant recurrence of HCV infection should be considered for therapy **(A1)**
- Acute cholestatic hepatitis or the presence of moderate to extensive fibrosis or portal hypertension one year after transplantation predict rapid disease progression and graft loss and indicate more urgent antiviral treatment **(A1)**
- Patients with post-transplant recurrence of HCV should be treated with an IFN-free regimen, for 12 or 24 weeks with ribavirin **(A1)**
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis post-transplant can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with the combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes), without the need for immunosuppressant drug dose adjustments **(A1)**
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis post-transplant can be treated with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a with cirrhosis), with the combination of ritonavir-boosted paritaprevir and ombitasvir for 12 or 24 weeks with ribavirin (genotype 4 without or with cirrhosis, respectively), or with the combination of sofosbuvir and simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), with the need for immunosuppressant drug dose adjustments or, in the case of the sofosbuvir-simeprevir combination, the need to avoid cyclosporine A **(B1)**
- Patients with decompensated (Child-Pugh B or C) cirrhosis can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with the combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes). In these patients, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance **(B1)**
- No dose adjustment is required for tacrolimus or cyclosporine with sofosbuvir-ribavirin, sofosbuvir-ledipasvir or sofosbuvir-daclatasvir **(A2)**
- Because of significantly increased plasma concentrations of simeprevir, the concomitant use of simeprevir and cyclosporine A is not recommended in liver transplant recipients. No simeprevir dose changes are required with tacrolimus and sirolimus, but regular monitoring of their blood concentrations should be performed **(A2)**
- When using the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir, the tacrolimus dose must be adjusted to 0.5 mg once weekly or 0.2 mg every 3 days, while cyclosporine A dose must be adjusted to one-fifth of the daily dose given prior to HCV treatment once daily; prednisone use at doses ≤5 mg/day is permitted, but the use of mTOR inhibitors is not recommended **(A2)**

13. Treatment of special groups

HBV co-infection

- Patients should be treated with the same regimens, following the same rules as HCV monoinfected patients **(B1)**
- If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated **(B1)**

Immune complex-mediated manifestations of chronic hepatitis C

- Treatment of HCV-associated lymphoma should utilise new IFN-free regimens as appropriate, but the effect of an SVR on the overall prognosis is not yet known. The effect of new antiviral therapies together with B cell depletion requires further study. An interdisciplinary approach with close monitoring of liver function is required **(B1)**
- Appropriate antiviral therapy should be considered for the treatment of mixed cryoglobulinemia and renal disease associated with chronic HCV infection. The role of rituximab in HCV-related renal disease requires evaluation. The more rapid inhibition of HCV replication and high SVR rates will need correlation with the response of the renal injury and the cryoglublinemia. Careful monitoring for adverse events is mandatory **(B1)**

Haemodialysis patients

- Haemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy **(B1)**
- Haemodialysis patients should receive an IFN-free, if possible ribavirin-free regimen, for 12 weeks in patients without cirrhosis, for 24 weeks in patients with cirrhosis **(B1)**
- Simeprevir, daclatasvir, and the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir are cleared by hepatic metabolism and can be used in patients with severe renal disease **(A1)**
- Sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease until more data is available **(B2)**

- The need for dose adjustments for the approved HCV DAAs in patients on dialysis is unknown. No safety dosing and efficacy data is available in this population. These drugs should thus be used with extreme caution in patients with severe renal disease, and only in extreme life-threatening situations for patients on dialysis **(B1)**

Non-hepatic solid organ transplant recipients

- HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. Where possible, antiviral therapy should be given to potential transplant recipients before listing for renal transplantation. These patients should receive an IFN-free, if possible ribavirin-free regimen, for 12 weeks in patients without cirrhosis, for 24 weeks in patients with compensated (Child-Pugh A) cirrhosis, following the above recommendations. However, no safety and efficacy data is available in this population, and the need for dose adjustments for the new DAAs is unknown. These drugs should thus be used with extreme caution and sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease until more data is available **(B1)**
- In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an IFN-free regimen, following the above recommendations on treatment regimen and management of drug-drug interactions with cyclosporine and tacrolimus when appropriate **(B2)**

Active drug addicts and patients on stable maintenance substitution

- PWIDs should be routinely and voluntarily tested for HCV antibodies and if negative, every 6-12 months **(B1)**
- PWIDs should be provided with clean drug injecting equipment and access to opioid substitution therapy as part of widespread comprehensive harm reduction programs, including in prisons **(B1)**
- Pre-therapeutic education should include discussions of HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk, and harm reduction strategies **(B1)**
- PWIDs should be counselled to moderate alcohol intake, or to abstain if there is evidence of advanced liver disease **(A1)**
- PWIDs should be counselled to moderate cannabis use, or to abstain if there is evidence of advanced liver disease **(B2)**
- HCV treatment for PWIDs should be considered on an individualized basis and delivered within a multidisciplinary team setting **(A1)**
- Pre-therapeutic assessment should include an evaluation of housing, education, cultural issues, social functioning and support, finances, nutrition and drug and alcohol use. PWIDs should be linked into social support services and peer support, if available **(A1)**
- A history of intravenous drug use and recent drug use at treatment initiation are not associated with reduced SVR and decisions to treat must be made on a case-by-case basis **(B1)**
- Drug and alcohol users or any other patients with on-going social issues and/or history of psychiatric disease, and those with more frequent drug use during therapy, are at risk of lower adherence and reduced likelihood of achieving SVR. They need to be monitored more closely during therapy and need more intensive multidisciplinary support **(B1)**
- Evaluation of safety and efficacy of new IFN-containing and IFN-free regimens in PWIDs is needed **(C1)**
- PWIDs on opioid substitution therapy should receive an IFN-free regimen **(B1)**
- The anti-HCV regimens that can be used in PWIDs are the same as in non-PWIDs. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken. More data is needed with daclatasvir **(B1)**
- Awareness should be raised that liver transplantation is a therapeutic option in those with a history of intravenous drug use **(B1)**
- Opioid substitution therapy is not a contra-indication for liver transplantation and individuals on opioid substitution should not be advised to reduce or stop therapy **(B1)**

Haemoglobinopathies

- The indications for HCV therapy are the same in patients with and without haemoglobinopathies **(A1)**
- Patients with haemoglobinopathies should be treated with an IFN-free regimen, without ribavirin **(B1)**
- The anti-HCV regimens that can be used in patients with haemoglobinopathies are the same as in patients without haemoglobinopathies **(B1)**
- When the use of ribavirin is needed, careful monitoring is recommended, and blood transfusions may be required **(B2)**

Bleeding disorders

- The indications for HCV therapy are the same in patients with and without bleeding disorders **(A1)**
- Potential drug-drug interactions in HCV-HIV coinfected patients receiving antiretroviral agents requires careful selection of agents **(A1)**

14. Follow-up of untreated patients and of patients with treatment failure

- Untreated patients with chronic hepatitis C and those who failed prior treatment should be regularly followed **(A1)**
- Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals **(A1)**
- HCC surveillance must be continued indefinitely in patients with cirrhosis **(A1)**

15. Treatment of acute hepatitis C

- Based on existing data, PegIFN-α monotherapy (PegIFN-α2a, 180 µg/week or PegIFN-α2b, 1.5 µg/kg/week) for 12 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases **(A1)**
- PegIFN-α (PegIFN-α2a, 180 µg/week or PegIFN-α2b, 1.5 µg/kg/week) should be combined with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) for 24 weeks in patients with acute hepatitis C who are HIV-coinfected **(B1)**
- Although no data is available yet, IFN-free regimens can be used in these patients as they are expected to achieve high SVR rates. The same doses and durations as for patients with chronic hepatitis C can be used, without ribavirin, until new data indicate whether shorter and/or less intensive treatment is sufficient to achieve high infection cure rates **(B1)**
- There is no indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission **(B1)**

16. Conflict of interest

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Grant and research support: Gilead. Advisory Boards: Abbvie, Achillion, Bristol-Myers Squibb, Gilead, Janssen, Merck. Speaking and teaching: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck, and Roche.

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David Back
Grant and research support: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck, and Viiv. Advisory Boards: Abbvie, Gilead, Janssen, and Merck. Speaking and teaching: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.

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Christoph Sarrazin
Grant and research support: Abbott Molecular, Abbvie, Gilead, Janssen, Qiagen, Roche, and Siemens. Advisory Boards: Abbott Molecular, Abbvie, Achillion, Bristol-Myers Squibb, Gilead, Janssen, and Merck. Speaking and teaching: Abbott Molecular, Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck, Qiagen, and Siemens.

17. Tables

Table 1. Evidence grading used (adapted from the GRADE system).

Evidence quality	Notes	Grading
High	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain	C
Recommendation	**Notes**	**Grading**
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	2

Table 2. Indications for treatment of chronic hepatitis C in 2015: Who should be treated and when?

Treatment priority	Patient group
Treatment is indicated	• All treatment-naïve and treatment-experienced patients with compensated and decompensated liver disease
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 (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals)
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

Table 3. Approved HCV drugs in the European Union in 2015.

Product	Presentation	Posology
PegIFN-α2a	Solution for injection containing 180, 135 or 90 µg of PegIFN-α2a	Once weekly subcutaneous injection of 180 µg (or less if dose reduction needed)
PegIFN-α2b	Solution for injection containing 50 µg per 0.5 ml of PegIFN-α2b	Once weekly subcutaneous injection of 1.5 µg/kg (or less if dose reduction needed)
Ribavirin	Capsules containing 200 mg of ribavirin	Two capsules in the morning and 3 in the evening if body weight <75 kg or Three capsules in the morning and 3 in the evening if body weight ≥75 kg
Sofosbuvir	Tablets containing 400 mg of sofosbuvir	One tablet once daily (morning)
Simeprevir	Capsules containing 150 mg of simeprevir	One capsule once daily (morning)
Daclatasvir	Tablets containing 30 or 60 mg of daclatasvir	One tablet once daily (morning)
Sofosbuvir/ledipasvir	Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily (morning)
Paritaprevir/ombitasvir/ritonavir	Tablets containing 75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir	Two tablets once daily (morning)
Dasabuvir	Tablets containing 250 mg of dasabuvir	One tablet twice daily (morning and evening)

Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	•	•	•	•	•
	Didanosine	•	•	•	•	•
	Emtricitabine	•	•	•	•	•
	Lamivudine	•	•	•	•	•
	Stavudine	•	•	•	•	•
	Tenofovir	•	•	•	•	•
	Zidovudine	•	•	•	•	•
NNRTIs	Efavirenz	•	•	•	•*	•
	Etravirine	•	•	•	•	•
	Nevirapine	•	•	•	•	•
	Rilpivirine	•	•	•	•*	•
Protease inhibitors	Atazanavir; atazanavir/ritonavir	•	•	•	•*	•
	Darunavir/ritonavir; darunavir/cobicistat	•	•	•	•*	•
	Fosamprenavir	•	•	•	•*	•
	Lopinavir	•	•	•	•*	•
	Saquinavir	•	•	•	•*	•
Entry/ Integrase inhibitors	Dolutegravir	•	•	•	•	•
	Elvitegravir/cobicistat	•	•	•	•*	•
	Maraviroc	•	•	•	•	•
	Raltegravir	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.

*Known or anticipated increase in tenofovir concentrations with boosted regimens and with efavirenz and rilpivirine when given sofosbuvir plus ledipasvir: caution and frequent renal monitoring needed.

Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

- Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
- The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Table 4B. Drug-drug interactions between HCV DAAs and illicit recreational drugs.

	SIM	DCV	SOF	SOF/ LDV	3D
Amphetamine	•	•	•	•	•
Cannabis	•	•	•	•	•
Cocaine	•	•	•	•	•
Diamorphine	•	•	•	•	•
Diazepam	•	•	•	•	•
Gamma-hydroxybutyrate	•	•	•	•	•
Ketamine	•	•	•	•	•
MDMA (ecstasy)	•	•	•	•	•
Methamphetamine	•	•	•	•	•
Phencyclidine (PCP)	•	•	•	•	•
Temazepam	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.

Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

- Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
- The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Table 4C. Drug-drug interactions between HCV DAAs and lipid lowering drugs.

	SIM	DCV	SOF	SOF/ LDV	3D
Atorvastatin	•	•	•	•	•
Bezafibrate	•	•	•	•	•
Ezetimibe	•	•	•	•	•
Fenofibrate	•	•	•	•	•
Fluvastatin	•	•	•	•	•
Gemfibrozil	•	•	•	•	•
Lovastatin	•	•	•	•	•
Pitavastatin	•	•	•	•	•
Pravastatin	•	•	•	•	•
Rosuvastatin	•	•	•	•	•
Simvastatin	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.
Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

- Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
- The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Table 4D. Drug-drug interactions between HCV DAAs and central nervous system drugs.

		SIM	DCV	SOF	SOF/ LDV	3D
Anti-depressants	Amitriptyline	•	•	•	•	•
	Citalopram	•	•	•	•	•
	Duloxetine	•	•	•	•	•
	Escitalopram	•	•	•	•	•
	Fluoxetine	•	•	•	•	•
	Paroxetine	•	•	•	•	•
	Sertraline	•	•	•	•	•
	Trazodone	•	•	•	•	•
	Trimipramine	•	•	•	•	•
	Venlafaxine	•	•	•	•	•
Anti-psychotics	Amisulpiride	•	•	•	•	•
	Aripiprazole	•	•	•	•	•
	Chlorpromazine	•	•	•	•	•
	Clozapine	•	•	•	•	•
	Flupentixol	•	•	•	•	•
	Haloperidol	•	•	•	•	•
	Olanzapine	•	•	•	•	•
	Quetiapine	•	•	•	•	•
	Risperidone	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.
Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

- Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
- The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Table 4E. Drug-drug interactions between HCV DAAs and cardiovascular drugs.

		SIM	DCV	SOF	SOF/ LDV	3D
Antiarrythmics	Amiodarone	•	•	•	•	•
	Digoxin	•	•	•	•	•
	Flecainide	•	•	•	•	•
	Vernakalant	•	•	•	•	•
Antiplatelet and antico-agulants	Clopidogrel	•	•	•	•	•
	Dabigatran	•	•	•	•	•
	Warfarin	•	•	•	•	•
Beta blockers	Atenolol	•	•	•	•	•
	Bisoprolol	•	•	•	•	•
	Propranolol	•	•	•	•	•
Calcium channel blockers	Amlodipine	•	•	•	•	•
	Diltiazem	•	•	•	•	•
	Nifedipine	•	•	•	•	•
Hypertension and heart failure agents	Aliskiren	•	•	•	•	•
	Candesartan	•	•	•	•	•
	Doxazosin	•	•	•	•	•
	Enalapril	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.
Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

- Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
- The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Table 4F. Drug-drug interactions between HCV DAAs and immunosuppressants.

	SIM	DCV	SOF	SOF/ LDV	3D
Azathioprine	•	•	•	•	•
Cyclosporine	•	•	•	•	•
Etanercept	•	•	•	•	•
Everolimus	•	•	•	•	•
Mycophenolate	•	•	•	•	•
Sirolimus	•	•	•	•	•
Tacrolimus	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.
Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

- Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
- The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Table 5. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN-α and ribavirin (RBV)

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	8-12 wk, without RBV	12 wk with RBV	No	12 wk without RBV	12 wk without RBV
Genotype 1b					12 wk without RBV			
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV
Genotype 4	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk without RBV	No	No	No	12 weeks without RBV

Table 6. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN-α and ribavirin (RBV)

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

Table 7. Treatment recommendations for retreatment of HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C who failed to achieve an SVR on prior antiviral therapy containing one or several DAA(s).

Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
PegIFN-α, RBV and either telaprevir or boceprevir	Genotype 1	12 wk with RBV	No	No	No	12 wk with RBV
Sofosbuvir alone, in combination with RBV or in combination with PegIFN-α and RBV	Genotype 1	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	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
	Genotype 2 or 3	No	No	No	No	12 weeks with RBV or 24 weeks with RBV if F3 or cirrhosis
	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	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	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	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
PegIFN-α, RBV and simeprevir	Genotype 1 or 4	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
PegIFN-α, RBV and daclatasvir	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
Sofosbuvir and simeprevir	Genotype 1 or 4	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

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

Currently, there is limited data to firmly support these retreatment recommendations, which are based on indirect evidence and consideration of HCV genotype, known resistance profiles of the previously administered drugs, number of drugs used, use of ribavirin, treatment duration. Thus, these recommendations are subject to change when more data become available.