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EASL Recommendations on Treatment of Hepatitis C 2016

SUMMARY

European Association for the Study of the Liver

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Methodology

These EASL recommendations have been prepared by a panel of experts chosen by the EASL Governing Board. The recommendations were approved by the EASL Governing Board. The recommendations have been based as far as possible on evidence from existing publications and presentations at international meetings, and, if evidence was unavailable, the experts' personal experiences and opinion. Wherever possible, the level of evidence and recommendation are cited. The evidence and recommendations have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated [7]. The quality of the evidence in the recommendations has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2) (Table 1). The recommendations thus consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted.
These recommendations are necessarily based on currently licensed drugs. They will be updated regularly, following approval of new drug regimens by the European Medicines Agency and other national European agencies.

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 3 months later to confirm definitive clearance (**A1**).
- HCV core antigen is a surrogate marker of HCV replication and can be used instead of HCV RNA to diagnose acute or chronic infection when HCV RNA assays are not available or not affordable (core antigen assays are slightly less sensitive than HCV RNA assays for detection of viral replication) (**A1**).

2. Screening for chronic hepatitis C

- Screening strategies for HCV infection should be defined according to the local epidemiology of HCV infection, ideally within the framework of national plans (**A1**).
- Screening for HCV infection is presently based on the detection of anti-HCV antibodies (**A1**).
- Whole blood sampled on dried blood spots can be used as an alternative to serum or plasma obtained by venipuncture (**A1**).
- Rapid diagnostic tests using serum plasma, fingerstick whole blood or crevicular fluid (saliva) as matrices can be used instead of classical enzyme immunoassays to facilitate anti-HCV antibody screening and improve access to care (**A1**).
- If anti-HCV antibodies are detected, HCV RNA, or alternatively HCV core antigen if HCV RNA assays are not available or not affordable, should be determined 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 extrahepatic manifestations and death (**A1**).
- The endpoint of therapy is undetectable HCV RNA in blood by a sensitive assay (lower limit of detection ≤15 IU/ml) 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment (**A1**).
- Undetectable HCV core antigen 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment is an alternative endpoint of therapy in patients with detectable HCV core antigen prior to therapy if HCV RNA assays are not available or not affordable (**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**).

4. Pre-therapeutic assessment

4.1. Search for other causes of liver disease
4.2. Assessment of liver disease severity

- 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 treatment regimen and post-treatment surveillance must 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**).
- Cardiac and renal function should be ascertained (**A1**).

4.3. HCV RNA or HCV core antigen detection/ quantification
4.4. HCV genotype determination
4.5. HCV resistance testing

- HCV RNA detection and quantification should be made by a sensitive assay with a lower limit of detection of ≤15 IU/ml (**A1**).
- If HCV RNA testing is not available or not affordable, HCV core antigen detection and quantification by EIA can be used as a surrogate marker of HCV replication (**A1**).
- The HCV genotype and genotype 1 subtype (1a or 1b) must be assessed prior to treatment initiation and will determine the choice of therapy, among other parameters (**A1**).
- Systematic testing for HCV resistance prior to treatment is not recommended. Indeed, this obligation would seriously limit access to care and treatment regimens can be optimized without this information (**B1**).
- Physicians who have easy access to a reliable test assessing HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93) can use these results to guide their decisions, as specified in these recommendations. The test should be based on population sequencing (reporting RASs as "present" or "absent") or deep sequencing with a cut-off of 15% (only RASs that are present in more than 15% of the sequences generated must be considered) (**B1**).

5. Contraindications to therapy

6. Indications for treatment: who should be treated?

- All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV must be considered for therapy (**A1**).
- Treatment should be considered without delay in patients with significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4), including decompensated (Child-Pugh B or C) cirrhosis, in 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), in patients with HCV recurrence after liver transplantation, and in 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) (**A1**).
- Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score ≥18-20 should be transplanted first and treated after transplantation. If the waiting time is more than 6 months, these patients can be treated before transplantation (**B1**).
- Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities (**B2**).
- National elimination plans require the development of economic partnerships and planning to expedite unrestricted access to treatment (**B1**).

7. Available drugs in Europe in 2016

- Numerous and complex drug-drug interactions are possible with the HCV DAAs. Therefore, the potential for drug-drug interactions should be considered in all patients undergoing treatment with DAAs. This requires a thorough drug-drug interaction risk assessment prior to starting therapy and before starting other medications during treatment (**A1**).
- The prescribing information for each DAA contains important information on drug-drug interactions. Summary data on key interactions can be found in Tables 4A-4F in this document. A key Internet resource is www.hep-druginteractions.org where recommendations are regularly updated (**A1**).
- Drug-drug interactions are a key consideration in treating HIV-HCV co-infected patients and it is vital that close attention is paid to anti-HIV drugs that are contraindicated, not recommended or require dose adjustment with particular DAA regimens (**A1**).
- Patients should be educated on the importance of adherence to therapy, following the dosing recommendations and reporting the use of over-the-counter medications, medications bought via the Internet, and use of party or recreational drugs (**B1**).

8. 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**).
- IFN-free regimens are the best options in HCV-monoinfected and in HIV-coinfected patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, because of their virological efficacy, ease of use and tolerability (**A1**).
- The same IFN-free treatment regimens can be used in HIV-co-infected patients as in patients without HIV infection, as the virologi-cal results of therapy are identical. Treatment alterations or dose adjustments may be needed in case of interactions with antiretroviral drugs (**A1**).

8.1. Treatment of HCV genotype 1 infection

Genotype 1, Option 1: Sofosbuvir/ledipasvir

- Patients infected with HCV genotype 1 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**A1**).
- Treatment can 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 in patients with F3 fibrosis (**B1**).
- Treatment-experienced, DAA-naïve patients infected with genotype 1b with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**A1**).
- Treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**A1**).
- If reliable NS5A resistance testing is performed, treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis who have NS5A RASs that confer high-level resistance to ledipasvir (M28A/G/T, Q30E/G/H/K/R, L31M/V, P32L/S, H58D, and/or Y93C/H/N/S) detected at baseline should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks with ribavirin, whereas those without ledipasvir RASs at baseline can be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**B1**).
- Treatment-experienced, DAA-naïve patients infected with genotype 1a with contraindications 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**).

Genotype 1, Option 2: Sofosbuvir/velpatasvir

- Patients infected with HCV genotype 1 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).

Genotype 1, Option 3: Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir

- Patients infected with HCV genotype 1 can 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), and dasabuvir (250 mg) (one tablet twice daily) (**A1**).
- Patients infected with subtype 1b with or without compensated cirrhosis should receive the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 12 weeks without ribavirin (**A1**).
- Treatment-naïve patients infected with subtype 1b without cirrhosis can receive the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 8 weeks without ribavirin, with caution in patients with F3 fibrosis (**B1**).
- Patients infected with subtype 1a without cirrhosis should receive the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir 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 compensated cirrhosis should receive the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**A1**).

Genotype 1, Option 4: Grazoprevir/elbasvir

- Patients infected with HCV genotype 1 can be treated with the fixed-dose combination of grazoprevir (100 mg) and elbasvir (50 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve and treatment-experienced patients infected with subtype 1b with or without compensated cirrhosis should receive the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**A1**).
- If no NS5A resistance testing is performed, treatment-naïve and treatment-experienced patients infected with subtype 1a with or without compensated cirrhosis with an HCV RNA level >800,000 IU/ml (5.9 $\log_{10}$ IU/ml) at baseline should receive the combination of grazoprevir and elbasvir for 16 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients infected with subtype 1a with or without compensated cirrhosis with an HCV RNA level ≤800,000 IU/ml (5.9 $\log_{10}$ IU/ml) at baseline should receive the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**B1**).
- If reliable NS5A resistance testing is performed, treatment-naïve and treatment-experienced patients infected with subtype 1a with or without compensated cirrhosis should receive the combination of grazoprevir and elbasvir for 16 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) if their HCV RNA level is >800,000 IU/ml and NS5A RASs that confer resistance to elbasvir (M28A/G/T, Q30D/E/G/H/K/L/R, L31F/M/V, H58D and/or Y93C/H/N/S) are present at baseline. Patients infected with subtype 1a with or without compensated cirrhosis with an HCV RNA level ≤800,000 IU/ml and those with an HCV RNA level >800,000 IU/ml without elbasvir NS5A RASs at baseline should receive the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**B1**).

Genotype 1, Option 5: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 1 can be treated with a combination of sofosbuvir (400 mg) in one tablet and daclatasvir (60 mg) in another tablet administered once daily (**A1**).
- The dose of daclatasvir must be adjusted to 30 mg in HIV-coinfected patients receiving ritonavir- or cobicistat-boosted atazanavir or cobicistat-boosted elvitegravir, and to 90 mg in HIV-coinfected patients receiving efavirenz (**B1**).
- Treatment-naïve patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**A1**).
- Treatment-experienced, DAA-naïve patients infected with genotype 1b with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**A1**).
- Based on data with the equivalent sofosbuvir and ledipasvir combination, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis receiving the combination of sofosbuvir and daclatasvir for 12 weeks (**C2**).
- If reliable NS5A resistance testing is performed, treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis with NS5A class RASs detected at baseline should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with ribavirin, whereas those without NS5A class RASs at baseline can be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**C2**).
- Treatment-experienced, DAA-naïve patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the combination of sofosbuvir and daclatasvir for 24 weeks without ribavirin (**B1**).

8.2. Treatment of HCV genotype 2 infection

Genotype 2, Option 1: Sofosbuvir/velpatasvir

- Patients infected with HCV genotype 2 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).

Genotype 2, Option 2: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 2 can be treated with a combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (**B1**).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B1**).

8.3. Treatment of HCV genotype 3 infection

Genotype 3, Option 1: Sofosbuvir/velpatasvir

- Patients infected with HCV genotype 3 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily, with or without ribavirin (**A1**).
- Treatment-naïve patients without cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).
- If no NS5A resistance testing is performed, treatment-experienced patients without cirrhosis, as well as treatment-naïve and treatment-experienced patients with compensated cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**A1**).
- If reliable NS5A resistance testing is performed, treatment-experienced patients without cirrhosis, as well as treatment-naïve and treatment-experienced patients with compensated cirrhosis, with the NS5A RAS Y93H detectable at baseline should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients without the NS5A RASs Y93H at baseline should receive the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).
- NS5A resistance testing for HCV genotype 3 may be technically challenging, so that a reliable result is not guaranteed in all cases (**B2**).
- Patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the combination of sofosbuvir and velpatasvir for 24 weeks without ribavirin (**C1**).

Genotype 3, Option 2: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 3 can be treated with a combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (**A1**).
- Treatment-naïve patients infected with HCV genotype 3 without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B1**).
- If no NS5A resistance testing is performed, treatment-experienced patients infected with HCV genotype 3 without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B1**).
- If reliable NS5A resistance testing is performed, treatment-experienced patients without cirrhosis with the NS5A RAS Y93H detectable at baseline should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients without the NS5A RASs Y93H at baseline should receive the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B1**).
- Treatment-naïve and treatment-experienced patients infected with HCV genotype 3 with cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**C1**).
- Patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the combination of sofosbuvir and daclatasvir for 24 weeks without ribavirin (**C1**).

8.4. Treatment of HCV genotype 4 infection

Genotype 4, Option 1: Sofosbuvir/ledipasvir

- Patients infected with HCV genotype 4 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**A1**).
- Treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B1**).
- Treatment-experienced patients with or without compensated cirrhosis with contraindications 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**).

Genotype 4, Option 2: Sofosbuvir/velpatasvir

- Patients infected with HCV genotype 4 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).

Genotype 4, Option 3: Ombitasvir/paritaprevir/ritonavir

- Patients infected with HCV genotype 4 can 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), without dasabuvir (**A1**).
- Patients infected with HCV genotype 4 with and without compensated cirrhosis should be treated with the fixed-dose combination of ombitasvir, paritaprevir and ritonavir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**A1**).

Genotype 4, Option 4: Grazoprevir/elbasvir

- Patients infected with HCV genotype 4 can be treated with the fixed-dose combination of grazoprevir (100 mg) and elbasvir (50 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve patients infected with genotype 4 with or without compensated cirrhosis should receive the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**A1**).
- By analogy to genotype 1a patients, treatment-experienced patients infected with genotype 4 with or without compensated cirrhosis with an HCV RNA level at baseline >800,000 IU/ml should receive the combination of grazoprevir and elbasvir for 16 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B2**).

Genotype 4, Option 5: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 4 can be treated with the combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (**B2**).
- Treatment-naïve patients with or without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B2**).
- Based on data with other combinations, treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B2**).
- In treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered (**B2**).

Genotype 4, Option 6: Sofosbuvir and simeprevir

- Patients infected with HCV genotype 4 can be treated with the combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) (**A1**).
- Treatment-naïve patients with or without cirrhosis should be treated with the combination of sofosbuvir and simeprevir for 12 weeks without ribavirin (**A1**).
- Based on data with other combinations, treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and simeprevir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B1**).
- In treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered (**C1**).

8.5. Treatment of HCV genotype 5 or 6 infection

Genotype 5 or 6, Option 1: Sofosbuvir/ledipasvir

- Patients infected with HCV genotype 5 or 6 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**B1**).
- Based on data in patients infected with HCV genotype 1, treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and ledipasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B1**).
- Treatment-experienced patients with or without compensated cirrhosis with contraindications 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**).

Genotype 5 or 6, Option 2: Sofosbuvir/velpatasvir

- Patients infected with HCV genotype 5 or 6 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).

Genotype 5 or 6, Option 3: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 5 or 6 can be treated with the combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (**B1**).
- Treatment-naïve patients with or without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B2**).
- Based on data with other combinations, treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B2**).
- In treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered (**B2**).

9. Treatment of patients with severe liver disease with or without an indication for liver transplantation and patients in the post-liver transplant setting

- IFN-free regimens are the only options in HCV-monoinfected and in HIV-coinfected patients with decompensated (Child-Pugh B or C) cirrhosis, with or without an indication for liver transplantation, and in patients after liver transplantation because of their virological efficacy, ease of use and tolerability (**A1**).
- The same IFN-free treatment regimens can be used in HIV-co-infected patients as in patients without HIV infection. Treatment alterations or dose adjustments may be needed in case of interactions with antiretroviral drugs (**B1**).

9.1. Patients with decompensated cirrhosis, no HCC, with an indication for liver transplantation

- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score <18-20 can be treated prior to liver transplantation. 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**).
- Protease inhibitors should not be used in patients with Child-Pugh B or C decompensated cirrhosis (**A1**).
- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score <18-20 can be treated with one of the following combinations: sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). In these patients, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance (**A1**).
- Patients with decompensated cirrhosis, no HCC and a MELD score <18-20 infected with HCV genotype 1, 4, 5 or 6 should be treated with sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, for 12 weeks with ribavirin (**A1**).
- Patients with decompensated cirrhosis, no HCC and a MELD score <18-20 infected with HCV genotype 2 should be treated with sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, for 12 weeks with ribavirin (**B1**).
- Patients with decompensated cirrhosis, no HCC and a MELD score <18-20 infected with HCV genotype 3 should be treated with sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, for 24 weeks with ribavirin (**B1**).
- Patients with decompensated cirrhosis with contraindications 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), the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), or the combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin (**B1**).
- 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**).
- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18-20 should be transplanted first, without antiviral treatment. HCV infection should be treated after liver transplantation (**B1**).
- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18-20 can be treated before transplantation if the waiting time on the transplant list exceeds 6 months, depending on the local situation (**B1**).

9.2. Patients with HCC, without cirrhosis or with compensated cirrhosis, with an indication for liver transplantation

- In patients with HCC awaiting liver transplantation with an indication for antiviral treatment, treatment can be initiated as soon as possible in order to complete a full treatment course before transplantation (**B1**).
- Patients with HCC who have no or compensated (Child-Pugh A) cirrhosis awaiting liver transplantation should be treated prior to liver transplantation, according to the general recommendations in patients with no or compensated cirrhosis and no HCC (**B1**).

9.3. Post-liver transplantation recurrence

- All patients with post-transplant recurrence of HCV infection should be considered for therapy (**A1**).
- Treatment should be initiated early after liver transplantation, ideally as early as possible when the patient is stabilized (generally after the first 3 months post-transplant), because the SVR12 rates diminish in patients with advanced post-transplant liver disease (**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 urgent antiviral treatment (**A1**).
- Patients with post-transplant recurrence of HCV genotype 1, 4, 5 or 6 infection without cirrhosis (F0-F3), with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir, or the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**A1**).
- Patients with post-transplant recurrence of HCV genotype 2 without cirrhosis (F0-F3), with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**B1**).
- Patients with post-transplant recurrence of HCV genotype 3 should be treated with the combination of sofosbuvir and daclatasvir for 24 weeks regardless of the stage of liver disease, with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**B1**).
- Patients with post-transplant recurrence of all HCV genotypes without cirrhosis (F0-F3), with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis could be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (24 weeks in patients with genotype 3 and decompensated (Child-Pugh B or C) cirrhosis) with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), as soon as the results of on-going studies, particularly drug-drug interactions with immunosuppressant drugs, have been presented (**C2**).
- In patients with decompensated cirrhosis, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance (**B1**).
- Patients with contraindications 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), the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), or the combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin (**B1**).
- The need for ribavirin in post-liver transplant patients without cirrhosis or with compensated (Child-Pugh A cirrhosis) has not been demonstrated and needs further exploration (**C2**).

9.4. 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 should be treated urgently (**A1**).
- Protease inhibitors should not be used in patients with Child-Pugh B and are contraindicated in patients with Child-Pugh C decompensated cirrhosis (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation should be treated with one of the following combinations: sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). In these patients, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation infected with HCV genotype 1, 4, 5 or 6 should be treated with sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir for 12 weeks with ribavirin (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation infected with HCV genotype 2 should be treated with sofosbuvir and velpatasvir or sofosbuvir and daclatasvir for 12 weeks with ribavirin (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation infected with HCV genotype 3 should be treated with sofosbuvir and velpatasvir or sofosbuvir and daclatasvir for 24 weeks, with ribavirin (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation with contraindications 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), the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), or the combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin (**B2**).
- Due to the limited amount of safety data reported in patients with decompensated cirrhosis, frequent clinical and laboratory assessment is necessary (**B2**).

9.5. 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 recommendations above, according to the HCV genotype, prior therapy and severity of underlying liver disease (unless antiviral therapy proves to be harmful in future studies) (**B2**).

10. Treatment of special groups

10.1. HBV co-infection

- Patients with HBV coinfection should be treated with the same regimens, following the same rules as HCV monoinfected patients (**B1**).
- If chronic hepatitis B or "occult" HBV infection is detected, concurrent HBV nucleoside/nucleotide analogue therapy is indicated (**B1**).

10.2. Immune complex-mediated manifestations of chronic hepatitis C

- Antiviral therapy should be considered for the treatment of mixed cryoglobulinemia and renal disease associated with chronic HCV infection, according to the above recommendations. Careful monitoring for adverse events is mandatory (**B1**).
- The indication of rituximab in HCV-related renal disease must be discussed by a multidisciplinary team (**B1**).
- Treatment of HCV-associated lymphoma should utilise IFN-free regimens as appropriate, but the effect of an SVR on the overall prognosis is not yet known (**B1**).

10.3. Patients with co-morbidities

10.3.1. Patients with renal impairment, including haemodialysis patients

- Patients with mild to moderate renal impairment (eGFR ≥30 ml/min/1.73 m^2) with HCV infection should be treated according to the general recommendations. No dose adjustments of HCV DAAs are needed, but these patients should be carefully monitored (**A1**).
- Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) and patients with end-stage renal disease on haemodialysis should be treated in expert centres, with close monitoring by a multidisciplinary team (**B1**).
- Sofosbuvir should be used with caution in patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease because no dose recommendation can currently be given for these patients (**B1**).
- Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 1a should be treated with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks or with the combination of grazoprevir and elbasvir for 12 weeks, with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline (**B1**).
- Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 1b should be treated with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks or with the combination of grazoprevir and elbasvir for 12 weeks, without ribavirin (**A1**).
- Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 4 should be treated with the combination of ritonavir-boosted paritaprevir and ombitasvir for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline, or with the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**B1**).
- In patients receiving ribavirin, haemoglobin levels should be carefully and frequently monitored and ribavirin administration should be interrupted in case of severe anaemia (haemoglobin <8.5 g/dl). The use of erythropoietin and, eventually, blood transfusion, may be useful in patients with severe ribavirin-induced anaemia (**B1**).
- Patients with cirrhosis, and those with a contraindication or who do not tolerate ribavirin, may benefit from 24 weeks of these therapies without ribavirin (**B2**).
- If treatment is urgently needed in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 2, these patients should receive the fixed-dose combination of sofosbuvir and velpatasvir, or the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin. Renal function may worsen and should be carefully monitored and treatment should be interrupted immediately in case of deterioration (**B1**).
- If treatment is urgently needed in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 3, these patients should receive the fixed-dose combination of sofosbuvir and velpatasvir, or the combination of sofosbuvir and daclatasvir for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline, or for 24 weeks without ribavirin. Renal function may worsen and should be carefully monitored and treatment should be interrupted immediately in case of deterioration (**B1**).
- The risks versus benefits of treating patients with end-stage renal disease and an indication for kidney transplantation before or after renal transplantation require individual assessment (**B2**).

10.3.2. Non-hepatic solid organ transplant recipients

- Solid organ transplant recipients, including kidney, heart, lung, pancreas or small bowel recipients should be treated for their HCV infection after transplantation, provided that their life expectancy exceeds one year (**A1**).
- Patients infected with HCV genotype 1, 4, 5 or 6 infection should be treated with the fixed-dose combination of sofosbuvir and ledipasvir, the fixed-dose combination of sofosbuvir and velpatasvir (if the drug-drug interaction profile with immunosuppressants is favourable in on-going studies), or the combination of sofosbuvir and daclatasvir according to the general recommendations, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**B1**).
- Patients infected with HCV genotype 2 should be treated with the fixed-dose combination of sofosbuvir and velpatasvir (if the drug-drug interaction profile with immunosuppressants is favourable in on-going studies) or the combination of sofosbuvir and daclatasvir according to the general recommendations, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**B1**).
- Patients infected with HCV genotype 3 should be treated with the fixed-dose combination of sofosbuvir and velpatasvir (if the drug-drug interaction profile with immunosuppressants is favourable in on-going studies) or the combination of sofosbuvir and daclatasvir according to the general recommendations, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**B1**).

10.3.3. Active drug addicts and patients on stable maintenance substitution

- PWIDs should be routinely and voluntarily tested for anti-HCV antibodies and if negative, annually (**A1**).
- 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**).
- 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 (**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 contraindication for liver transplantation and individuals on opioid substitution should not be advised to reduce or stop therapy (**B1**).

10.3.4. 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 transfusion support may be required (**B2**).

10.3.5. 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**).

11. Treatment monitoring

11.1. 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**).
- Measurement of HCV core antigen levels by EIA can be used as an alternative to HCV RNA level measurement to monitor treatment efficacy during and after therapy when HCV RNA assays are not available or not affordable (**A1**).
- In patients treated with an IFN-free regimen, HCV RNA or HCV core antigen levels should be measured at baseline, between week 2 and 4 for assessment of adherence (optional), at end-of-treatment (week 8, 12, 16 or 24 in patients treated 8, 12, 16 or 24 weeks, respectively), and 12 or 24 weeks after the end of therapy (SVR12 or SVR24, respectively) (**A2**).
- Monitoring of treatment efficacy can be simplified in order to improve access to care by measuring HCV RNA or HCV core antigen levels only at baseline and 12 or 24 weeks after the end of therapy (SVR12 or SVR24, respectively) (**A2**).

11.2. Monitoring of treatment safety

- The patients receiving an IFN-free regimen should be assessed for clinical side effects at each visit (**A1**).
- Haematological side effects should be assessed at weeks 2 and 4 of therapy and at 4 to 8 week intervals thereafter in patients receiving ribavirin (**A1**).
- ALT levels should be assessed at weeks 4, 8 and 12 of therapy, and at week 24 in patients receiving 24 weeks of treatment, as well as at 12 or 24 weeks post-treatment (**A1**).
- Renal function should be checked regularly in patients receiving sofosbuvir, especially in those with reduced eGFR (**A1**).
- Monitoring for rashes and indirect bilirubin elevations without ALT elevations should be performed in patients receiving simeprevir (**A1**).
- Monitoring for indirect bilirubin increases should be performed in patients receiving the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (**A1**).
- No dose adjustment of sofosbuvir and ledispavir, velpatasvir, daclatasvir or simeprevir is required in patients with mild, moderate or severe renal impairment (**B1**).
- The use of sofosbuvir is not recommended in patients with eGFR <30 ml/min/1.73 m^2. If no other option is available and treatment is urgently needed, the appropriate dose of sofosbuvir is not yet established; thus close monitoring of renal function is required and treatment should be interrupted if the renal function deteriorates (**B1**).
- No dose adjustment of sofosbuvir and ledipasvir, velpatasvir or daclatasvir is required for patients with mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (**A1**).
- Higher exposures have been observed with the protease inhibitors in patients with severe hepatic impairment and their use is not recommended in patients with Child-Pugh B and contraindicated in patients with Child-Pugh C decompensated cirrhosis (**B1**).
- 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**).
- An increase in ALT levels on treatment should prompt a test for HBs antigen and/or HBV DNA (**B1**).

11.3. Monitoring of 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**).

11.4. Treatment dose reductions

- The dose of ribavirin should be adjusted downward by 200 mg at decrements if the haemoglobin level drops below 10 g/dl. Ribavirin administration should be stopped if the haemoglobin levels drops below 8.5 g/dl (**A1**).
- Treatment should be promptly stopped in case of ALT flare >10 times the upper limit of normal values (**A1**).
- Treatment should be promptly stopped in case of severe bacterial infection at any site, regardless of the neutrophil count, especially in patients with decompensated cirrhosis (**A1**).
- Treatment should be stopped in case of severe adverse events of unclear origin (**B2**).

12. 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 and patient activation assessment 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 should be considered 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**).

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

- Non-cirrhotic patients with SVR should be retested for ALT and HCV RNA (or HCV core antigen) at 48 weeks post-treatment, then discharged if ALT is normal and HCV RNA is negative (**A1**).
- Patients with advanced fibrosis (F3) and cirrhotic patients with SVR should undergo surveillance for HCC every 6 months by means of ultrasound (**A1**).
- 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 (**A1**).
- The risk of reinfection should be explained, to positively modify risk behaviour (**A1**).
- 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 (**A1**).

14. Retreatment of non-sustained virological responders

14.1. Retreatment of patients who failed after a double combination of pegylated IFN-α and ribavirin

14.2. Retreatment of genotype 1 patients who failed after a triple combination of pegylated IFN-α, ribavirin, and telaprevir, boceprevir or simeprevir

14.3. Retreatment of patients who failed after an IFN-free regimen (all genotypes)

- Patients who failed after pegylated IFN-α and ribavirin combination treatment must be retreated according to the above recommendations by HCV genotype (**A1**).
- Patients infected with HCV genotype 1 who failed after a triple combination regimen of pegylated IFN-α, ribavirin and telaprevir, boceprevir or simeprevir should be retreated with the IFN-free combination of sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, with ribavirin for 12 weeks (**A1**).
- Patients who failed on a DAA-containing regimen should be retreated with an IFN-free regimen for 12 weeks with weight-based ribavirin if they have no, mild or moderate fibrosis (METAVIR score F0 to F2), for 24 weeks with ribavirin if they have extensive fibrosis (F3) or cirrhosis, unless otherwise specified below (**B1**).
- Patients who failed on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus pegylated IFN-α and ribavirin can be retreated with a combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), sofosbuvir and velpatasvir (all genotypes), ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), ritonavir-boosted paritaprevir and ombitasvir (genotype 4), grazoprevir and elbasvir (genotypes 1 or 4; 24 weeks in F0-F2 patients with HCV RNA >800,000 IU/ml), sofosbuvir plus daclatasvir (all genotypes), or sofosbuvir plus simeprevir (genotype 4) (**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 ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir (**B1**).
- Patients infected with HCV genotype 1 or 4 who failed on a regimen containing an NS5A inhibitor, such as ledipasvir, velpatasvir, ombitasvir, elbasvir or daclatasvir, should be retreated with a combination of sofosbuvir, ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), with a combination of sofosbuvir, ritonavir-boosted paritaprevir and ombitasvir (genotype 4), with a combination of sofosbuvir, grazoprevir and elbasvir (genotypes 1 and 4) or with a combination of sofosbuvir, simeprevir and daclatasvir (genotypes 1 or 4), for 12 weeks (genotype 1b or 4 patients with METAVIR score F0 to F2) or 24 weeks (all patients with genotype 1a; genotype 1b and 4 patients with METAVIR score F3 or with compensated cirrhosis) with ribavirin. Treatment should be administered with caution in patients with extensive fibrosis (METAVIR score F3) or compensated cirrhosis due to a possible risk of severe adverse events of some of these combinations (**B1**).
- Patients infected with HCV genotype 2, 3, 5 or 6 who failed on a regimen containing an NS5A inhibitor, such as ledipasvir, velpatasvir or daclatasvir, should be retreated with a combination of sofosbuvir and velpatasvir for 24 weeks with ribavirin (**B1**).
- Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available (**A1**).
- The utility of HCV resistance testing prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown. If reliable resistance testing is performed, retreatment can be guided by probabilities of response according to the resistance profile observed in the context of an experienced multidisciplinary team (**B2**).

15. 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 of 1 to 2 years (**A1**).
- HCC surveillance every 6 months must be continued indefinitely in patients with advanced fibrosis (F3) and cirrhosis (**A1**).

16. Treatment of acute hepatitis C

- Patients with acute hepatitis C should be treated with a combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6), a combination of sofosbuvir and velpatasvir (all genotypes), or a combination of sofosbuvir and daclatasvir (all genotypes) for 8 weeks without ribavirin (**B1**).
- Patients with acute hepatitis C and HIV coinfection and/or a baseline HCV RNA level >1 million IU/ml (6.0 log IU/ml) may need to be treated for 12 weeks with the same combination regimens (**B2**).
- SVR should be assessed at 12 and 24 weeks post-treatment, because late relapses have been reported (**B2**).
- There is no indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission (**B1**).

17. Perspective of new treatments

Conflict of interest

Jean-Michel Pawlotsky:

Grant and research support: Abbvie, and Gilead.

Advisory Boards: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.

Speaking and teaching: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.

Alessio Aghemo:

Advisory Boards: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.

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David Back:

Grant and research support: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck, and Viiv.

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Grant and research support: Abbvie, and Janssen.

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Grant and research support: Gilead.

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Grant and research support: Abbott Molecular, Abbvie, Gilead, Janssen, Qiagen, Roche, and Siemens.

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Speaking and teaching: Abbott Molecular, Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck, Qiagen, and Siemens.

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. Clinically relevant resistance-associated substitutions (RASs), i.e. RASs which, when detected at baseline by means of either population sequencing or deep sequencing with a cut-off of 15%, may influence the choice of first-line treatment regimen.

NS5A amino acid position	Ledipasvir RASs Genotype 1a Sofosbuvir/ Ledipasvir treatment	Elbasvir RASs Genotype 1a Grazoprevir/ Elbasvir treatment	NS5A RASs Genotype 3 Sofosbuvir/ Velpatasvir treatment
M28	M28A M28G M28T	M28A M28G M28T	
Q30	Q30E Q30G Q30H Q30K Q30R	Q30D Q30E Q30G Q30H Q30K Q30L Q30R	
L31	L31M L31V	L31F L31M L31V	
P32	P32L P32S		
H58	H58D	H58D	
Y93	Y93C Y93H Y93N Y93S	Y93C Y93H Y93N Y93S	Y93H

Table 3. Approved HCV DAAs in Europe in 2016 and ribavirin.

Product	Presentation	Posology
Sofosbuvir	Tablets containing 400 mg of sofosbuvir	One tablet once daily (morning)
Sofosbuvir/ledipasvir	Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily (morning)
Sofosbuvir/velpatasvir	Tablets containing 400 mg of sofosbuvir and 100 mg of velpatasvir	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)
Grazoprevir/elbasvir	Tablets containing 100 mg of grazoprevir and 50 mg of elbasvir	One tablet once daily (morning)
Daclatasvir	Tablets containing 30 or 60 mg of daclatasvir	One tablet once daily (morning)
Simeprevir	Capsules containing 150 mg of simeprevir	One capsule once daily (morning)
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 (or less if dose reduction needed)

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

		SOF	SOF/LDV	SOF/VEL	3D	GZR/EBR	DCV	SIM
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	■	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	■	●
	Etravirine	◆	◆	●	●	●	■	●
	Nevirapine	◆	◆	●	●	●	■	●
	Rilpivirine	◆	◆*	◆*	■	◆	◆	◆
Protease inhibitors	Atazanavir; atazanavir/r; atazanavir/cobicistat	◆	◆*	◆*	■‡	●	■	●
	Darunavir/r; darunavir/cobicistat	◆	◆*	◆*	■‡	●	◆	●
	Lopinavir/r	◆	◆*	◆*	●	●	◆	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	◆	■*	■*	●	●	■	●
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	◆	◆	◆	●	●	■	●
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir; /r, ritonavir.

Colour legend	
◆	No clinically significant interaction expected
■	Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring
●	These drugs should not be co-administered

Notes:
o Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
o 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.
* Known or anticipated increase in tenofovir concentrations in regimens containing tenofovir disoproxil fumarate. Caution and frequent renal monitoring.
‡ Atazanavir/cobicistat and darunavir/cobicistat are contraindicated with 3D

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

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

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.

Colour legend	
◆	No clinically significant interaction expected
■	Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring
●	These drugs should not be co-administered

Notes:
o Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
o 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.

	SOF	SOF/ LDV	SOF/ VEL	3D	GZR/ EBR	DCV	SIM
Atorvastatin	◆	■	■	●	■	■	■
Bezafibrate	◆	◆	◆	◆	◆	◆	◆
Ezetimibe	◆	◆	◆	■	◆	◆	◆
Fenofibrate	◆	■	■	◆	■	◆	◆
Fluvastatin	◆	■	■	■	■	■	◆
Gemfibrozil	◆	◆	◆	●	■	◆	◆
Lovastatin	◆	■	■	●	■	■	■
Pitavastatin	◆	■	■	■	◆	■	■
Pravastatin	◆	■	◆	■	◆	■	■
Rosuvastatin	◆	●	■	■	■	■	■
Simvastatin	◆	■	■	●	■	■	■

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir

Colour legend	
◆	No clinically significant interaction expected
■	Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring
●	These drugs should not be co-administered

Notes:
o Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
o 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.

		SOF	SOF/ LDV	SOF/ VEL	3D	GZR/ EBR	DCV	SIM
Anti-depressants	Amitriptyline	◆	◆	◆	■	◆	◆	◆
	Citalopram	◆	◆	◆	◆	◆	◆	◆
	Duloxetine	◆	◆	◆	◆	◆	◆	◆
	Escitalopram	◆	◆	◆	◆	◆	◆	◆
	Fluoxetine	◆	◆	◆	◆	◆	◆	◆
	Paroxetime	◆	◆	◆	◆	◆	◆	◆
	Sertraline	◆	◆	◆	■	◆	◆	◆
	Trazodone	◆	◆	◆	■	◆	◆	■
	Trimipramine	◆	◆	◆	◆	◆	◆	◆
	Venlafaxine	◆	◆	◆	■	◆	◆	◆
Anti-psychotics	Amisulpiride	◆	◆	◆	◆	◆	◆	◆
	Aripiprazole	◆	◆	◆	■	■	◆	■
	Chlorpromazine	◆	◆	◆	■	◆	◆	◆
	Clozapine	◆	◆	◆	■	◆	◆	■
	Flupentixol	◆	◆	◆	■	◆	◆	◆
	Haloperidol	◆	◆	◆	■	◆	◆	■
	Olanzapine	◆	◆	◆	■	◆	◆	◆
	Paliperidone	◆	■	◆	■	◆	■	■
	Quetiapine	◆	◆	◆	●	■	◆	■
	Risperidone	◆	◆	◆	■	◆	◆	■
	Zuclopentixol	◆	◆	◆	■	◆	◆	◆

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.

Colour legend	
◆	No clinically significant interaction expected
■	Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring
●	These drugs should not be co-administered

Notes:
o Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
o 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.

		SOF	SOF/ LDV	SOF/ VEL	3D	GZR/ EBR	DCV	SIM
Antiarrhythmics	Amiodarone	●	●	●	●	■	●	■
	Digoxin	◆	■	■	■	◆	■	■
	Flecainide	◆	◆	◆	■	◆	◆	■
	Vernakalant	◆	◆	◆	■	◆	◆	◆
Antiplatelet and anticoagulants	Clopidogrel	◆	◆	◆	■	◆	■	■
	Dabigatran	◆	■	■	■	■	■	■
	Ticagrelor	◆	■	■	●	■	◆	■
	Warfarin	◆	◆	◆	◆	◆	◆	◆
Beta blockers	Atenolol	◆	◆	◆	◆	◆	◆	◆
	Bisoprolol	◆	◆	◆	■	◆	◆	■
	Carvedilol	■	■	■	■	◆	■	■
	Propranolol	◆	◆	◆	◆	◆	◆	◆
Calcium channel blockers	Amlodipine	◆	■	■	■	■	■	■
	Diltiazem	◆	■	■	■	◆	■	■
	Nifedipine	◆	◆	◆	■	◆	■	■
Hypertension and heart failure agents	Aliskiren	◆	■	■	●	◆	■	■
	Candesartan	◆	◆	◆	■	■	◆	◆
	Doxazosin	◆	◆	◆	■	◆	◆	■
	Enalapril	◆	◆	◆	■	◆	◆	◆

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.

Colour legend	
◆	No clinically significant interaction expected
■	Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring
●	These drugs should not be co-administered

Notes:
o Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
o 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.

	SOF	SOF/ LDV	SOF/ VEL	3D	GZR/ EBR	DCV	SIM
Azathioprine	◆	◆	◆	◆	◆	◆	◆
Cyclosporine	◆	◆	◆	■	●	◆	●
Etanercept	◆	◆	◆	◆	■	◆	◆
Everolimus	◆	■	■	●	■	■	■
Mycophenolate	◆	◆	◆	■	◆	◆	◆
Sirolimus	◆	◆	◆	■	■	◆	■
Tacrolimus	◆	◆	◆	■	■	◆	■

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir

Colour legend	
◆	No clinically significant interaction expected
■	Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring
●	These drugs should not be co-administered

Notes:
o Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
o 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. IFN-free combination treatment regimens available as valuable options for each HCV genotype.

Combination regimen	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotypes 5 and 6
Sofosbuvir + ribavirin	No	Suboptimal	Suboptimal	No	No
Sofosbuvir/ledipasvir ± ribavirin	Yes	No	No	Yes	Yes
Sofosbuvir/velpatasvir ± ribavirin	Yes	Yes	Yes	Yes	Yes
Ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin	Yes	No	No	No	No
Ombitasvir/paritaprevir/ritonavir ± ribavirin	No	No	No	Yes	No
Grazoprevir/elbasvir ± ribavirin	Yes	No	No	Yes	No
Sofosbuvir + daclatasvir ± ribavirin	Yes	Yes	Yes	Yes	Yes
Sofosbuvir + simeprevir ± ribavirin	Suboptimal	No	No	Yes	No

Table 6. 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 pegylated IFN-α and ribavirin (treatment-experienced, DAA-naïve patients).

Patients	Treatment-naïve or -experienced	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir
Genotype 1a	Treatment-naïve	8-12 wk, no ribavirin	12 wk, no ribavirin	12 wk with ribavirin	No	12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml[b]	12 wk, no ribavirin	No
	Treatment-experienced	12 wk with ribavirin[a] or 24 wk, no ribavirin					12 wk with ribavirin[a] or 24 wk, no ribavirin	
Genotype 1b	Treatment-naïve	8-12 wk, no ribavirin	12 wk, no ribavirin	8-12 wk, no ribavirin	No	12 wk, no ribavirin	12 wk, no ribavirin	No
	Treatment-experienced	12 wk, no ribavirin		12 wk, no ribavirin				
Genotype 2	Both	No	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
Genotype 3	Treatment-naïve	No	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
	Treatment-experienced		12 wk with ribavirin[c] or 24 wk, no ribavirin				12 wk with ribavirin[c] or 24 wk, no ribavirin	
Genotype 4	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	No	12 wk with ribavirin	12 wk, no ribavirin	12 wk, no ribavirin	12 wk, no ribavirin
	Treatment-experienced	12 wk with ribavirin or 24 wk, no ribavirin				12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml	12 wk with ribavirin or 24 wk, no ribavirin	12 wk with ribavirin or 24 wk, no ribavirin
Genotype 5 or 6	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
	Treatment-experienced	12 wk with ribavirin or 24 wk, no ribavirin					12 wk with ribavirin or 24 wk, no ribavirin	

[a]Add ribavirin only in patients with RASs that confer high-level resistance to NS5A inhibitors at baseline if RAS testing available.
[b]Prolong to 16 weeks and add ribavirin only in patients with RASs that confer resistance to elbasvir at baseline if RAS testing available.
[c]Add ribavirin only in patients with NS5A RASs Y93H at baseline if RAS testing available.

Table 7. 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 pegylated IFN-α and ribavirin (treatment-experienced, DAA-naïve patients).

Patients	Treatment-naïve or -experienced	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir
Genotype 1a	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	24 wk with ribavirin	No	12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml[b]	12 wk, no ribavirin	No
	Treatment-experienced	12 wk with ribavirin[a] or 24 wk, no ribavirin					12 wk with ribavirin[a] or 24 wk, no ribavirin	
Genotype 1b	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	12 wk, no ribavirin	No	12 wk, no ribavirin	12 wk, no ribavirin	No
	Treatment-experienced							
Genotype 2	Both	No	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
Genotype 3	Treatment-naïve	No	12 wk with ribavirin[c] or 24 wk, no ribavirin	No	No	No	24 wk with ribavirin	No
	Treatment-experienced							
Genotype 4	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	No	12 wk with ribavirin	12 wk, no ribavirin	12 wk, no ribavirin	12 wk, no ribavirin
	Treatment-experienced	12 wk with ribavirin or 24 wk, no ribavirin				12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml	12 wk with ribavirin or 24 wk, no ribavirin	12 wk with ribavirin or 24 wk, no ribavirin
Genotype 5 or 6	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
	Treatment-experienced	12 wk with ribavirin or 24 wk, no ribavirin					12 wk with ribavirin or 24 wk, no ribavirin	

[a]Add ribavirin only in patients with RASs that confer high-level resistance to NS5A inhibitors at baseline if RAS testing available.
[b]Prolong to 16 weeks and add ribavirin only in patients with RASs that confer resistance to elbasvir at baseline if RAS testing available.
[c]Add ribavirin only in patients with NS5A RASs Y93H at baseline if RAS testing available.

Table 8. RASs shown to confer reduced susceptibility to the corresponding drug classes in in vitro assays and/or selected in patients who failed to achieve SVR on IFN-free regimens. These RASs and a number of other substitutions at the same positions may be present at retreatment baseline in patients who failed to achieve SVR, suggesting reduced susceptibility to drug(s) from the corresponding class(es) that may help guide retreatment decisions. Adapted from [30]

Drug class	Amino acid position	Genotype/subtype						
		1a	1b	2	3	4	5	6
Nucleotide analogue (sofosbuvir)	159	L159F	L159F	L159F	L159F			
	282	S282T/R	S282T	S282T	S282T	S282T	S282T	
	320	L320I/F/V						
	321	V321A			V321A			
NS5A inhibitors	24	K24G/N/R		T24A				Q24H
	26	K26E						
	28	M28A/G/T/S/V	L28M/T	L/F28M/V/S	M28T	L28S/V	L28I	F28L
	29		P29S					
	30	Q30C/D/E/G/H/I/K/L/Q/R/S/T/Y	R30G/H/P/Q/R	L30H/S	A30K/S	L30H		
	31	L31I/F/M/P/V	L31F/I/M/V	L31M/V	L31I/M/V	L31I/M	L31V	L31M/V
	32	P32L/S	P32F/L/S					P32L/S
	38	S38F						
	58	H58D/L/R	P58D/S			T58P/S		T58A/N/S
	62		Q/E62D					
	92	A92K/T	A92K					
	93	Y93C/F/H/L/N/R/S/T/W	Y93C/H/N/S	Y93H	Y93H	Y93H/R		V36I
Protease inhibitors	36	V36A/C/G/L/M	V36A/C/G/L/M					
	41	Q41R	Q41R					
	43	F43L	F43I/S/V					
	54	T54A/S	T54A/C/G/S					
	55	V55A/I	V55A					
	56	Y56H	Y56H/L	Y56H		Y56H		Y56H
	80	Q80H/K/L/R	Q80H/K/L/R					L80K/Q
	122	S122G/R	S122D/G/I/N/R/T					S122T
	155	R155G/I/K/M/S/T/W	R155C/G/I/K/Q/M/S/T/W					
	156	A156S/T/V	A156G/F/S/T/V					
	158	V158I	V158I					
	168	D168A/C/E/F/G/H/I/K/L/N/T/V/Y	D168A/C/E/F/G/H/I/K/L/N/T/V/Y		Q168R	D168V		D168E/Y
	170	I/V170F/T/V	I/V170A/L/T					I170V
	175		M175L					
Non-nucleoside palm-1 inhibitor (dasabuvir)	314	L314H						
	316	C316Y	C316H/N/Y/W					
	368		S368T					
	411		N411S					
	414	M414I/T/V	M414I/T/V					
	445		C445F/Y					
	446	E446K/Q						
	448	Y448C/H	Y448C/H					
	451	C451R						
	553	A553T	A553V					
	554	G554S	G554S					
	555	Y555H						
	556	S556G/R	S556G/R					
	557	G557R						
	558	G558R	G558R					
	559	D559G/N	D559G/N					
	561	Y561H/N						

Table 9. 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). 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

Failed treatment	Geno-type	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ Elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir	Sofosbuvir plus ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Sofosbuvir plus ombitasvir/ paritaprevir/ ritonavir	Sofosbuvir plus grazoprevir/ elbasvir	Sofosbuvir plus daclatasvir plus simeprevir
PegIFN-α with ribavirin and telaprevir, or boceprevir, or simeprevir	1	12 wk with ribavirin	12 wk with ribavirin	No	No	No	12 wk with ribavirin	No	No	No	No	No
Sofosbuvir alone, or sofosbuvir plus ribavirin, or sofosbuvir plus PegIFN-α and ribavirin	1	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	12 wk with ribavirin (F0-F2 with HCV RNA ≤800,000 (5.9 log) IU/ml) or 24 wk with ribavirin (F0-F2 with HCV RNA >800,000 (5.9 log) IU/ml and F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No
	2	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
	3	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
	4	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2 with HCV RNA ≤800,000 (5.9 log) IU/ml) or 24 wk with ribavirin (F0-F2 with HCV RNA >800,000 (5.9 log) IU/ml and F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No

Table 9. ***Continued.***

Failed treatment	Geno-type	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ Elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir	Sofosbuvir plus ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Sofosbuvir plus ombitasvir/ paritaprevir/ ritonavir	Sofosbuvir plus grazoprevir/ elbasvir	Sofosbuvir plus daclatasvir plus simeprevir
Sofosbuvir alone, or sofosbuvir plus ribavirin, or sofosbuvir plus PegIFN-α and ribavirin	5 or 6	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
Sofosbuvir and simeprevir	1	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
	4	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
NS5A inhibitor-containing regimen (ledipasvir, velpatasvir, ombitasvir, elbasvir, daclatasvir)	1a	No	No	No	No	No	No	No	24 wk with ribavirin	No	24 wk with ribavirin	24 wk with ribavirin
	1b	No	No	No	No	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)
	2	No	24 wk with ribavirin	No	No	No	No	No	No	No	No	No
	3	No	24 wk with ribavirin	No	No	No	No	No	No	No	No	No
	4	No	No	No	No	No	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)
	5 or 6	No	24 wk with ribavirin	No	No	No	No	No	No	No	No	No