Clinical Practice Guidelines

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EASL Recommendations on Treatment of Hepatitis C 2018☆

European Association for the Study of the Liver*

Summary

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, with approximately 71 million chronically infected individuals worldwide. Clinical care for patients with HCV-related liver disease has advanced considerably 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 European Association for the Study of the Liver Recommendations on Treatment of Hepatitis C describe the optimal management of patients with acute and chronic HCV infections in 2018 and onwards.

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Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide.[1] The long-term natural history of HCV infection is highly variable. The hepatic injury can range from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). There are approximately 71 million chronically infected individuals worldwide,[1,2] many of whom are unaware of their infection, with important variations according to the geographical area. 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.

The primary goal of HCV therapy is to cure the infection, *i.e.* to achieve a sustained virological response (SVR) defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion. An SVR corresponds to a cure of the HCV infection, with a very low chance of late relapse. An SVR is generally associated with normalisation of liver enzymes and improvement or disappearance of liver necroinflammation and fibrosis in patients without cirrhosis. Patients with advanced fibrosis (METAVIR score F3) or cirrhosis (F4) remain at risk of life-threatening complications. However, hepatic fibrosis may regress and the risk of complications such as hepatic failure and portal hypertension is reduced after an SVR. Recent data suggest that the risk of HCC and liver-related mortality is significantly reduced, but not eliminated, in patients with cirrhosis who clear HCV compared to untreated patients and non-sustained virological responders, especially in the presence of cofactors of liver morbidity, such as the metabolic syndrome, harmful alcohol consumption and/or concurrent hepatitis B virus (HBV) infection.[3–9] HCV is also associated with a number of extra-hepatic manifestations and viral elimination induces reversal of most of them with reduction of all-cause mortality.[10–16]

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 current optimal management of patients with acute and chronic HCV infections. These recommendations apply to therapies that have been approved by the European Medicines Agency and other national European agencies at the time of their publication.

Methodology

These EASL recommendations have been prepared by a panel of experts chosen by the EASL Governing Board. The recommendations are primarily based on evidence from existing publications and presentations at international meetings. In the absence of such evidence, the experts' personal experiences and opinions have been considered. 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.[17] The strength of recommendations reflects the quality of underlying evidence. 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). Thus, the recommendations 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. The recommendations have been approved by the EASL Governing Board.

Diagnosis of acute and chronic hepatitis C

Anti-HCV antibodies are detectable in serum or plasma by enzyme immunoassay (EIA) in the vast majority of patients with HCV infection, but EIA results may be negative in early acute

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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

hepatitis C and in profoundly immunosuppressed patients. Following spontaneous or treatment-induced viral clearance, anti-HCV antibodies persist in the absence of HCV RNA, but may decline and finally disappear in some individuals.[18–20]

The diagnosis of acute and chronic HCV infection is based on the detection of HCV RNA in serum or plasma by a sensitive, exclusively qualitative, or both qualitative and quantitative, molecular method. An assay with a lower limit of detection ≤15 international units (IU)/ml is recommended. However, the vast majority of patients with an indication for anti-HCV therapy have an HCV RNA level above 50,000 IU/ml.[21] There is an important need for diagnostic nucleic acid assays that are cheap (less than US$5-10) and thus applicable for large-scale diagnosis in low-to middle-income areas, as well as in specific settings in high-income countries. Such HCV RNA assays should have a lower limit of detection ≤1,000 IU/ml (3.0 Log_{10} IU/ml). In such settings, the exceptionally low risk of a false-negative result with these assays, in a small percentage of infected individuals, is outweighed by the benefit of scaling up access to diagnosis and care to a larger population. Indeed, a study in patients with chronic hepatitis C due to HCV genotype 1 found only 4 patients out of 2,472 (0.16%) with an HCV RNA level below 1,000 IU/ml.[22]

HCV core antigen in serum or plasma is a marker of HCV replication. Core antigen detection can be used instead of HCV RNA detection to diagnose acute or chronic HCV infection. HCV core antigen assays are less sensitive than HCV RNA assays (lower limit of detection equivalent to approximately 500 to 3,000 HCV RNA IU/ml, depending on the HCV genotype[23–25]). As a result, the HCV core antigen becomes detectable in serum or plasma a few days after HCV RNA in patients with acute hepatitis C. In rare cases, the core antigen is undetectable in the presence of HCV RNA.[26]

The diagnosis of acute hepatitis C can only be made confidently if recent seroconversion to anti-HCV antibodies can be documented, since there is no serological marker which establishes that HCV infection is in the *de novo* acquired acute phase. Not all patients with acute hepatitis C will be anti-HCV antibody-positive at diagnosis. In these cases, acute hepatitis C can be suspected if the clinical signs and symptoms are compatible with acute hepatitis (alanine aminotransferase [ALT] level >10 times the upper limit of normal, and/or jaundice) in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent source of transmission is identifiable. In all cases, HCV RNA (or HCV core antigen) can be detected during the acute phase, although their levels may vary widely and there may be interludes (up to several weeks) of undetectable HCV RNA (or HCV core antigen). Thus, HCV RNA-negative (or HCV core antigen-negative) individuals should be retested for HCV RNA (or HCV core antigen) 12 and 24 weeks after a negative result to confirm definitive clearance.

HCV reinfection can occur after spontaneous or treatment-induced HCV clearance, essentially if patients at high risk of infection are re-exposed. Reinfection is defined by the reappearance of HCV RNA (or HCV core antigen) after an SVR and the demonstration that infection is caused by a different HCV strain (different genotype or distantly related strain by phylogenetic analysis if the genotype is the same). Reinfection should be suspected in cases of a post-SVR12 or -SVR24 recurrence of HCV infection, if risk behaviours have continued.

The diagnosis of chronic hepatitis C is based on the detection of both anti-HCV antibodies and HCV RNA (or HCV core antigen). Spontaneous viral clearance rarely occurs beyond 4 to 6 months after a newly acquired infection,[27] so the diagnosis of chronic hepatitis C can be made after this time period.

Recommendations

- All patients with suspected HCV infection should be tested for anti-HCV antibodies in serum or plasma as first-line diagnostic test (**A1**).
- In the case of suspected acute hepatitis C, in immunocompromised patients and in patients on haemodialysis, HCV RNA testing in serum or plasma should be part of the initial evaluation (**A1**).
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method with a lower limit of detection ≤15 IU/ml (**A1**).
- In low- and middle-income countries, and in specific settings in high-income countries, a qualitative HCV RNA assay with a lower limit of detection ≤1,000 IU/ml (3.0 Log_{10} IU/ml) can be used to provide broad affordable access to HCV diagnosis and care (**B2**).
- Anti-HCV antibody-positive, HCV RNA-negative individuals should be retested for HCV RNA 12 and 24 weeks later to confirm definitive clearance (**A1**).
- HCV core antigen in serum or plasma is a marker of HCV replication that can be used instead of HCV RNA to diagnose acute or chronic HCV infection when HCV RNA assays are not available and/or not affordable (**A1**).

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Screening for chronic hepatitis C

A major barrier to HCV elimination still results from the fact that a substantial proportion of patients with chronic HCV infection are unaware of their infection, with large variations across different regions, countries and risk populations. In addition, accurate HCV prevalence and incidence data are needed to analyse the magnitude of the pandemic in different regions and to design public health interventions. Thus, HCV screening is required to identify infected individuals and engage them in care and treatment.

Different screening strategies have been implemented in different regions, based on the local epidemiology. Groups at higher risk of HCV infection can be identified and should be tested. In regions where the majority of patients belong to a well-defined age group, birth cohort testing has proven efficacious, with limitations.[28,29] Systematic one-time testing has been recommended in countries with high endemicity and/or with the goal of complete eradication. The optimal regional or national screening approaches should be determined.

Screening for HCV infection is based on the detection of anti-HCV antibodies. In addition to EIAs, rapid diagnostic tests (RDTs) can be used to screen for anti-HCV antibodies. RDTs use various matrices, including serum and plasma, but also fingerstick capillary whole blood or oral (crevicular) fluid, facilitating screening without the need for venipuncture, tube centrifugation, freezing and skilled labour. RDTs are simple to perform at room temperature without specific instrumentation or extensive training.[30–32]

If anti-HCV antibodies are detected, the presence of HCV RNA (or alternatively HCV core antigen if HCV RNA assays are not available and/or not affordable) should be determined to identify patients with ongoing infection. Currently, most laboratories use a two-step approach that includes phlebotomy and an antibody test in step 1, and phlebotomy and a test for HCV RNA in step 2. As a result, a substantial fraction of patients with anti-HCV antibodies never receive confirmatory HCV RNA testing. Therefore, reflex testing for HCV RNA should be applied whenever possible when anti-HCV antibodies are detected.[33]

Dried blood spots can be used to collect whole blood specimens for EIA detection of anti-HCV antibodies in a central laboratory.[34–36] A second spot on the same card can be used to test for HCV RNA, allowing for reflex testing to be performed in anti-HCV antibody-positive samples.

A cartridge-based point-of-care HCV RNA assay has received World Health Organization (WHO) prequalification.[37] Such assays have the potential to simplify testing algorithms, increase diagnosis rates, and facilitate linkage to treatment, especially in low- and middle-income areas and in difficult-to-reach populations, such as people who inject drugs (PWID). Depending upon relative costs, a direct test for HCV RNA and near-patient testing could be considered to replace screening based on anti-HCV antibody testing by the direct identification of viremic patients.

Recommendations

- 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 strategies for HCV infection may include screening of populations at risk of infection, birth cohort testing, and general population testing in areas of intermediate to high seroprevalence (≥2%–5%) (**B2**).
- Screening for HCV infection should be based on the detection of anti-HCV antibodies in serum or plasma by means of enzyme immunoassay (**A1**).
- Anti-HCV antibody screening should be offered with linkage to prevention, care and treatment (**A1**).
- Whole blood sampled on dried blood spots can be used as an alternative to serum or plasma obtained by venipuncture for anti-HCV antibody testing, after shipment to a central laboratory where the enzyme immunoassay will be performed (**A2**).
- RDTs using serum, plasma, fingerstick whole blood or crevicular fluid (saliva) as matrices can be used instead of classical enzyme immunoassays at the patient's care site to facilitate anti-HCV antibody screening and improve access to care (**A2**).
- If anti-HCV antibodies are detected, the presence of HCV RNA, or alternatively HCV core antigen (if HCV RNA assays are not available and/or not affordable) in serum or plasma should be determined to identify patients with ongoing infection (**A1**).
- Whole blood sampled on dried blood spots can be used as an alternative to serum or plasma obtained by venipuncture for HCV RNA testing, after shipment to a central laboratory where the molecular test will be performed (**A2**).
- Reflex testing for HCV RNA in patients found to be anti-HCV antibody-positive should be applied to increase linkage to care (**B1**).
- Anti-HCV antibody screening for HCV infection can be replaced by a point-of-care HCV RNA assay with a lower limit of detection ≤1,000 IU/ml (3.0 Log_{10} IU/ml) or HCV core antigen testing, if such assays are available and the screening strategy proves to be cost-effective (**C2**).

Goals and endpoints of HCV therapy

The goal of therapy is to cure HCV infection in order to: (i) prevent the complications of HCV-related liver and extra-hepatic diseases, including hepatic necroinflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extra-hepatic manifestations and death; (ii) improve quality of life and remove stigma; (iii) prevent onward transmission of HCV.

The endpoint of therapy is an SVR, defined by undetectable HCV RNA in serum or plasma 12 weeks (SVR12) or 24 weeks (SVR24) after the end of therapy, as assessed by a sensitive molecular method with a lower limit of detection ≤15 IU/ml. Both SVR12 and SVR24 have been accepted as endpoints of therapy by regulators in Europe and the United States, given that their concordance is >99%.[38] In settings where sensitive HCV RNA assays are not available and/or not affordable, a qualitative assay with a lower limit of detection ≤1,000 IU/ml (3.0 Log_{10} IU/ml) can be used to assess the virological response; in this case, the response should be assessed at week 24 post-treatment (SVR24).

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Long-term follow-up studies have shown that an SVR corresponds to a definitive cure of HCV infection in the vast majority of cases.[39] Undetectable HCV core antigen 24 weeks after the end of therapy can be used as an alternative to HCV RNA testing to define the SVR24, respectively, in patients with detectable core antigen before treatment.[23,24,26,40]

In patients with advanced fibrosis (METAVIR score F3) and cirrhosis (F4), an SVR reduces the rate of decompensation and will also reduce, but not abolish, the risk of HCC.[8] Thus, in these patients, surveillance for HCC must be continued.

Recommendations

- The goal of therapy is to cure HCV infection, in order to: (i) prevent the complications of HCV-related liver and extra-hepatic diseases, including hepatic necroinflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extra-hepatic manifestations and death; (ii) improve quality of life and remove stigma; and (iii) prevent onward transmission of HCV (**A1**).
- The endpoint of therapy is undetectable HCV RNA in serum or plasma by a sensitive assay (lower limit of detection ≤15 IU/ml) 12 weeks (SVR12) or 24 weeks (SVR24) after the end of treatment (**A1**).
- Undetectable HCV core antigen in serum or plasma 24 weeks (SVR24) after the end of treatment can be used as an alternative endpoint of therapy in patients with detectable HCV core antigen prior to therapy, if HCV RNA assays are not available and/or not affordable (**A1**).
- Undetectable HCV RNA in serum or plasma 24 weeks (SVR24) after the end of treatment, using a qualitative HCV RNA assay with a lower limit of detection ≤1,000 IU/ml (3.0 Log_{10} IU/ml), can be used as an alternative endpoint of therapy in areas where sensitive HCV RNA assays are not available and/or not affordable (**B1**).
- In patients with advanced fibrosis and cirrhosis, surveillance for HCC must be continued because an SVR will reduce, but not abolish, the risk of HCC (**A1**).

Pre-therapeutic assessment

Liver disease severity must be assessed, and baseline virological parameters that will be useful for tailoring therapy should be determined.

Search for other causes of liver disease

Other causes of chronic liver disease, or factors which are likely to affect the natural history or progression of liver disease and therapeutic choices, should be systematically investigated. All patients should be tested for other blood-borne viruses, particularly hepatitis B virus (HBV), and for human immunodeficiency virus (HIV). HBV and hepatitis A virus (HAV) vaccination should be proposed for patients who are not protected. Alcohol consumption should be assessed and quantified, and specific counselling to stop harmful alcohol consumption should be given. In addition, HCV may cause a variety of extra-hepatic manifestations which need to be considered in the work-up of HCV-infected patients. Thus, assessments should be carried out for possible comorbidities, including alcoholism, cardiac disease, renal impairment, autoimmunity, genetic or metabolic liver diseases (for instance genetic hemochromatosis, diabetes mellitus or obesity) and the possibility of drug-induced hepatotoxicity.

Assessment of liver disease severity

Assessment of liver disease severity is necessary prior to therapy. Identifying patients with cirrhosis (METAVIR score F4) or advanced (bridging) fibrosis (METAVIR score F3) is of particular importance, as the choice of treatment regimen and the post-treatment prognosis depend on the stage of fibrosis. Assessment of the stage of fibrosis is not required in patients with clinical evidence of cirrhosis. Patients with cirrhosis need to be assessed for portal hypertension, including oesophageal varices. Patients with advanced fibrosis and those with cirrhosis need continued post-treatment surveillance for HCC every 6 months. Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT levels.

In chronic hepatitis C, non-invasive methods should be used instead of liver biopsy to assess liver disease severity prior to therapy. Liver stiffness measurement can be used to assess liver fibrosis and the presence of portal hypertension in patients with chronic hepatitis C. Consideration must be given to factors that may adversely affect its performance, such as obesity, high ALT levels, or post-prandial testing. Well-established panels of fibrosis biomarkers can also be applied. Both liver stiffness measurement and biomarkers perform well in the identification of cirrhosis or no fibrosis, but they perform less well in resolving intermediate degrees of fibrosis.[41] Cut-offs used with common non-invasive markers to establish the different stages of fibrosis in patients with chronic hepatitis C prior to therapy are shown in Table 2.[42–47] In low- and middle-income countries, as well as in settings where treatment expands outside of specialty clinics, aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4) are generally available, simple and cheap, and the information they provide is reliable. Notably, non-invasive tools should not be used to assess the fibrosis stage after therapy, as they are unreliable in this setting.

The combination of blood biomarkers or the combination of liver stiffness measurement and a blood test improve accuracy.[48,49] Liver biopsy may be required in cases of known or suspected mixed aetiologies (*e.g.* metabolic syndrome, alcoholism or autoimmunity).

Recommendations

- The contribution of comorbidities to the progression of liver disease must be evaluated and appropriate corrective measures implemented (**A1**).
- Liver disease severity must be assessed prior to therapy (**A1**).
- Patients with cirrhosis must be identified, as their treatment regimen must be adjusted and post-treatment surveillance for HCC is mandatory (**A1**).
- Post-treatment surveillance for HCC must also be performed in patients with advanced fibrosis (METAVIR score F3) (**B1**).

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Table 2. Non-invasive marker cut-offs for prediction of stages of fibrosis, including F3 (advanced fibrosis) and F4 (cirrhosis).

Test	Stage of fibrosis	Number of patients	Cutoff	AUROC	Sensitivity	Specificity	PPV	NPV	Ref.
FibroScan®	F3	560 HCV-positive	10 kPa[a]	0.83	72%	80%	62%	89%	42
	F4	1,855 HCV-positive	13 kPa[a]	0.90–0.93	72–77%	85–90%	42–56%	95–98%	42,44,47
ARFI (VTQ®)	F3	2,691 (including 1,428 HCV-positive)	1.60–2.17 m/s	0.94 (95% CI 0.91–0.95)	84% (95% CI 80–88%)	90% (95% CI 86–92%)	n.a.	n.a.	46
	F4	2,691 (including 1,428 HCV-positive)	2.19–2.67 m/s	0.91 (95% CI 0.89–0.94)	86% (95% CI 80–91%)	84% (95% CI 80–88%)	n.a.	n.a.	46
Aixplorer®	F3	379 HCV-positive	9 kPa[a]	0.91	90% (95% CI 72–100%)	77% (95% CI 78–92%)	n.a.	n.a.	45
	F4	379 HCV-positive	13 kPa[a]	0.93	86% (95% CI 74–95%)	88% (95% CI 72–98%)	n.a.	n.a.	45
Fibrotest®	F4	1,579 (including 1,295 HCV-positive)	0.74	0.82–0.87	63–71%	81–84%	39–40	93–94	44,47
FIB-4	F4	2,297 HCV-positive	1–45[b] 3.25[b]	0.87* (0.83–0.92)	90% 55%	58% 92%	n.a.	n.a.	43
APRI	F4	16,694 HCV-positive	1.0[b] 2.0[b]	0.84* (0.54–0.97)	77% 48%	75% 94%	n.a.	n.a.	43

APRI, aspartate aminotransferase to platelet ratio index; ARFI, acoustic radiation force impulse; AUROC, area under the receiver operating characteristic curve; FIB-4, fibrosis-4; n.a., not applicable; NPV, negative predictive value; PPV, positive predictive value.
[a] Scales for liver stiffness cut-offs (in kPa) are different between FibroScan® and Aixplorer®.
[b] Two cut-offs are provided for FIB-4 and for APRI, respectively, with their own sensitivities and specificities.
* Median (range).

- Fibrosis stage must be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional aetiologies (**A1**).
- Renal function (creatinine/estimated glomerular filtration rate [eGFR]) should be ascertained (**A1**).
- Extra-hepatic manifestations of HCV infection should be identified in case of symptoms (**A1**).
- HBV and HAV vaccination should be proposed to patients who are not protected (**A1**).

HCV RNA or HCV core antigen detection/quantification

HCV RNA detection or detection/quantification in serum or plasma is indicated for patients who undergo antiviral treatment. HCV RNA assessment should be made by a reliable sensitive assay, and HCV RNA levels should be expressed in IU/ml.

HCV core antigen detection and quantification by means of EIA can be performed when HCV RNA tests are not available and/or not affordable. HCV core antigen quantification should be made with a reliable assay and core antigen levels should be expressed in fmol/L.

HCV genotype determination

Together with prior treatment experience and the presence of cirrhosis, the HCV genotype, including genotype 1 subtype (1a or 1b), is still useful to tailor the treatment regimen and its duration. Genotyping/subtyping should be performed with an assay that accurately discriminates subtype 1a from 1b, *i.e.* an assay using the sequence of the 5′ untranslated region plus a portion of another genomic region, generally the core-coding or the NS5B-coding regions.[50] The most widely used method is based on reverse hybridization with the line probe assay. A kit based on deep sequencing will soon be available.[51]

With pan-genotypic HCV drug regimens, it is possible to treat individuals without identifying their HCV genotype and subtype. This may be particularly useful in regions where virological tests are not available or their cost exceeds that of antiviral treatment, or to simplify therapy in other regions, in order to improve access to care.

HCV resistance testing

No standardized tests for resistance of HCV to approved drugs are available as purchasable kits. Resistance testing mostly relies on in-house techniques based on population sequencing (Sanger sequencing) or deep sequencing.[52] A limited number of laboratories have made such tests available in Europe and elsewhere. HCV resistance testing may be technically difficult, in particular for genotypes other than 1 and 4, and the performances of the available in-house assays vary widely. A kit based on deep sequencing is currently at the developmental stage.

Access to reliable HCV resistance testing is limited and there is no consensus on the techniques, interpretation and reporting of these tests. In addition, highly efficacious treatments are now available for patients with detectable pre-existing resistance-associated substitutions (RASs) at baseline. Thus, systematic testing for HCV resistance prior to treatment in direct-acting antiviral (DAA) drug-naïve individuals is not recommended.[53]

The current EASL recommendations suggest treatment regimens that do not necessitate any resistance testing prior to first-line therapy. In areas where these regimens are not available or not reimbursed, physicians who have easy access to reliable resistance tests can use these results to guide their decisions, according to the EASL Recommendations for Treatment of Hepatitis C 2016.[54]

Recommendations

- HCV RNA detection and quantification in serum or plasma should be made by a sensitive assay with a lower limit of detection of ≤15 IU/ml (**A1**).

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- In low- and middle-income countries and in specific settings in high-income countries, a qualitative HCV RNA assay with a lower limit of detection of ≤1,000 IU/ml can be used if more sensitive quantitative assays are not available and/or not affordable (**B1**).
- If HCV RNA testing is not available and/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 to determine the choice of therapy and its duration, among other parameters (**A1**).
- Treatment with new pangenotypic regimens can be initiated without knowledge of the genotype and subtype in areas where genotype determination is not available and/or not affordable, or to simplify treatment access (**B1**).
- Testing for HCV resistance prior to treatment is not recommended (**B1**).
- In areas where only regimens that require optimisation based on pre-treatment resistance testing are available, and physicians have easy access to a reliable test that evaluates HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93), these analyses can guide decisions, as specified in the EASL Recommendations for Treatment of Hepatitis C 2016 (**B2**).

Contraindications to therapy

Contraindications to treatment with a DAA are few. The use of certain cytochrome P450 (CYP)/P-glycoprotein (P-gp) inducing agents (such as carbamazepine and phenytoin) are contraindicated with all regimens, due to the risk of significantly reduced concentrations of DAA and therefore high risk of virological failure. Other concomitant medicine-related contraindications are discussed below. Treatment regimens comprising an NS3-4A protease inhibitor, such as ritonavir-boosted paritaprevir, grazoprevir, glecaprevir or voxilaprevir, must not be used in patients with Child-Pugh B or C decompensated cirrhosis, because of the substantially higher protease inhibitor concentrations in these patients and the related risk of toxicity.

Sofosbuvir should be used with caution in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) if no alternative treatment option is available, as the pharmacokinetics and safety of sofosbuvir-derived metabolites in patients with severe renal dysfunction are still being ascertained.

Recommendations

- The use of certain cytochrome P450 (CYP)/P-glycoprotein (P-gp) inducing agents (such as carbamazepine and phenytoin) are contraindicated with all regimens, due to the risk of significantly reduced concentrations of DAA (**A1**).
- Treatment regimens comprising a protease inhibitor must not be used in patients with Child-Pugh B or C decompensated cirrhosis or in patients with previous episodes of decompensation (**A1**).
- In patients with an eGFR <30 ml/min/1.73 m^2, sofosbuvir should only be used if no alternative treatment approved for use in patients with severe renal impairment is available (**B1**).

Indications for treatment: who should be treated?

All treatment-naïve and -experienced patients with HCV infection, who are willing to be treated and who have no contraindications for treatment, should be treated.

Treatment must be considered without delay in patients with significant fibrosis (METAVIR score F2 or F3) or cirrhosis (METAVIR score F4), including decompensated cirrhosis; 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); patients with HCV recurrence after liver transplantation; patients at risk of a rapid evolution of liver disease because of concurrent comorbidities (non-liver solid organ or stem cell transplant recipients, HBV coinfection, diabetes); and individuals at high risk of transmitting HCV PWIDs, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals). PWIDs and men who have sex with men with high-risk sexual practices should be made aware of the risk of reinfection and should apply preventive measures after successful treatment.

Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score ≥18–20 will benefit from transplantation first and antiviral treatment after transplantation, because the probability of significant improvement in liver function and delisting is low.[55–60] However, patients with a MELD score ≥18–20 with a waiting time before transplantation expected to be more than 6 months can be treated for their HCV infection.

Treatment is generally not recommended in patients with limited life expectancy because of non–liver-related comorbidities.

Recommendations

- All patients with HCV infection must be considered for therapy, including treatment-naïve patients and individuals who failed to achieve SVR after prior treatment (**A1**).
- Treatment should be considered without delay in patients with significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4), including compensated (Child-Pugh A) and 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, in patients at risk of a rapid evolution of liver disease because of concurrent comorbidities (non-liver solid organ or stem cell transplant recipients, HBV coinfection, diabetes) and in individuals at risk of transmitting HCV (PWID, men who have sex with men with high-risk sexual practices, women of childbearing

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age who wish to get pregnant, haemodialysis patients, incarcerated individuals) (**A1**).

- Patients with decompensated (Child-Pugh B or C) cirrhosis and an indication for liver transplantation with a MELD score ≥18–20 should be transplanted first and treated after transplantation (**B1**).
- If the waiting time on a liver transplant list is more than 6 months, patients with decompensated (Child-Pugh B or C) cirrhosis with a MELD score ≥18–20 can be treated before transplantation, although the clinical benefit for these patients is not well established (**B2**).
- Treatment is generally not recommended in patients with limited life expectancy due to non-liver-related comorbidities (**B2**).

Available drugs in Europe in 2018

The HCV drugs available in Europe are listed in this paragraph and in Table 3. Their known pharmacokinetic profiles and how this impacts drug-drug interactions are presented. For a more comprehensive listing of drug-drug interactions, see Tables 4A–G, and www.hep-druginteractions.org for a comprehensive list of over 700 co-medications. For additional information on the disposition of individual DAAs, refer to the Summary of Product Characteristics.

Sofosbuvir

Sofosbuvir should be administered at the dose of 400 mg (one tablet) once per day, with or without food. Approximately 80% of sofosbuvir is renally excreted, whereas 15% is excreted in faeces. The majority of the sofosbuvir dose recovered in urine is the dephosphorylation-derived nucleoside metabolite GS-331007 (78%), while 3.5% is recovered as sofosbuvir. Renal clearance is the major elimination pathway for GS-331007, with a large part actively secreted. Thus, currently, no sofosbuvir dose recommendation can be given for patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease because of higher exposures (up to 20-fold) of GS-331007. However, there is accumulating evidence on safe use of sofosbuvir-based regimens in patients with an eGFR <30 ml/min/1.73 m^2, including patients on haemodialysis.[61] Sofosbuvir exposure is not significantly changed in patients with mild liver impairment, but it is increased 2.3-fold in those with moderate liver impairment.

Sofosbuvir is well tolerated over 12 to 24 weeks of administration. The most common adverse events (≥20%) observed in combination with ribavirin were fatigue and headache. Slight elevations of creatine kinase, amylase and lipase without clinical impact were also observed.

Sofosbuvir is not metabolised by cytochrome P450, but is transported by P-gp. Drugs that are potent P-gp inducers significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect. Thus, sofosbuvir should not be administered with known inducers of P-gp, such as rifampicin, carbamazepine, phenytoin or St. John's wort. Other potential interactions may occur with rifabutin, rifpentine and modafinil. No significant drug-drug interactions have been reported in studies with the antiretroviral agents emtricitabine, tenofovir, rilpivirine, efavirenz, darunavir/ritonavir and raltegravir, and there are no potential drug-drug interactions with other antiretrovirals.

Sofosbuvir-based regimens are contraindicated in patients who are being treated with the anti-arrhythmic amiodarone because of the risk of life-threatening arrhythmias. Indeed, bradycardia has been observed within hours to days of starting the DAA, but cases have been observed up to 2 weeks after initiating HCV treatment. The mechanism of interaction and the role of other co-medications (*e.g.* β-blockers) is still unclear, although a number of potential mechanisms have been proposed involving P-gp inhibition, protein binding displacement and direct effects of sofosbuvir and/or other DAAs on cardiomyocytes or ion channels. Toxicity is likely the result of a combination of mechanisms. Because of the long half-life of amiodarone, an interaction is possible for several months after discontinuation of amiodarone. If the patient has no cardiac pacemaker *in situ*, waiting 3 months after discontinuing amiodarone before starting a sofosbuvir-based regimen is recommended. Sofosbuvir-containing regimens have also been implicated in cardiac toxicity in the absence of amiodarone, but this remains controversial. In the absence of specific drug-drug interaction data, caution should be exercised with antiarrhythmics other than amiodarone.

Sofosbuvir and ledipasvir

Sofosbuvir and ledipasvir are available in a two-drug fixed-dose combination containing 400 mg of sofosbuvir and 90 mg of ledipasvir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with or without food.

Table 3. HCV DAAs approved in Europe in 2018 and recommended in this document.

Product	Presentation	Posology
Pangenotypic drugs or drug combinations		
Sofosbuvir	Tablets containing 400 mg of sofosbuvir	One tablet once daily
Sofosbuvir/velpatasvir	Tablets containing 400 mg of sofosbuvir and 100 mg of velpatasvir	One tablet once daily
Sofosbuvir/velpatasvir/voxilaprevir	Tablets containing 400 mg of sofosbuvir, 100 mg of velpatasvir and 100 mg of voxilaprevir	One tablet once daily
Glecaprevir/pibrentasvir	Tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir	Three tablets once daily
Genotype-specific drugs or drug combinations		
Sofosbuvir/ledipasvir	Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily
Paritaprevir/ombitasvir/ritonavir	Tablets containing 75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir	Two tablets once daily
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

DAA, direct-acting antiviral; HCV, hepatitis C virus.

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Table 4A. Drug-drug interactions between HCV DAAs and antiretroviral drugs.

		SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir disoproxil fumarate	◆	■	■	◆	◆	■	◆
	Tenofovir alafenamide	◆	◆	◆	■	◆	■	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	●	●
	Etravirine	◆	◆	●	●	●	●	●
	Nevirapine	◆	◆	●	●	●	●	●
	Rilpivirine	◆	◆	◆	■	◆	◆	◆
Protease inhibitors	Atazanavir/ritonavir	◆	◆*	◆*	■	●	●	●
	Atazanavir/cobicistat	◆	◆*	◆*	●	●	●	●
	Darunavir/ritonavir	◆	◆*	◆*	■	●	■*	●
	Darunavir/cobicistat	◆	◆*	◆*	●	●	◆*	●
	Lopinavir/ritonavir	◆	◆*	◆*	●	●	●	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	◆	■*	■*	●	●	■*	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	◆	◆	◆	●	●	◆	◆
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; LDV, ledipasvir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

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 coadministered.

Notes: 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.

*Known or anticipated increase in tenofovir concentrations in regimens containing tenofovir disoproxil fumarate. Caution and frequent renal monitoring.

Biliary excretion of unchanged ledipasvir is the major route of elimination with renal excretion being a minor pathway (accounting for approximately 1%), whereas sofosbuvir is principally excreted renally, as noted above. Following administration of sofosbuvir/ledipasvir, the median terminal half-lives of sofosbuvir and its predominant metabolite GS-331007 were 0.5 and 27 h, respectively. Neither sofosbuvir nor ledipasvir are substrates for hepatic uptake transporters; GS-331007 is not a substrate for renal transporters.

Ledipasvir plasma exposure (area under the curve [AUC]) was similar in patients with severe hepatic impairment and control patients with normal hepatic function. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to ledipasvir.

While no dose adjustment of sofosbuvir and ledipasvir is required for patients with mild or moderate renal impairment, the safety of the sofosbuvir-ledipasvir combination has not been assessed in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or end-stage renal disease requiring haemodialysis, but there is growing evidence of acceptable risk-benefit.[62] Relative to patients with normal renal function (eGFR >80 ml/min/1.73 m^2), the sofosbuvir AUC was 61%, 107% and 171% higher in patients with mild, moderate and severe renal impairment, while the GS-331007 AUC was 55%, 88% and 451% higher, respectively. Thus, no dose adjustment is required for patients with mild or moderate renal impairment, but no dose recommendation can currently be given for patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease. Pangenotypic drug combinations that are not cleared by the kidney are available, thus obviating the need for sofosbuvir-based regimens where appropriate drugs are available.

The most common adverse reactions reported with this combination were fatigue and headache.

Since the combination contains ledipasvir and sofosbuvir, any interactions identified with the individual drugs will apply to the combination. The potential (limited) interactions with sofosbuvir have been previously outlined. Since both ledipasvir and sofosbuvir are transported by intestinal P-gp and breast

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Table 4B. Drug-drug interactions between HCV DAAs and illicit/recreational drugs or drugs of abuse.

	SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r +DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
Amphetamine	◆	◆	◆	■	◆	◆	◆
Cannabis	◆	◆	◆	■	◆	◆	◆
Cocaine	◆	◆	◆	■	◆	◆	◆
Diamophine	◆	◆	◆	■	◆	◆	◆
Diazepam	◆	◆	◆	■	◆	◆	◆
Fentanyl	◆	◆	◆	◆	■	◆	■
Gamma-hydroxybutyrate	◆	◆	◆	■	■	◆	■
Ketamine	◆	◆	◆	■	◆	◆	◆
MDMA (ecstasy)	◆	◆	◆	■	◆	◆	◆
Mefedrone	◆	◆	◆	■	◆	◆	◆
Methadone	◆	◆	◆	◆	◆	◆	◆
Methamphetamine	◆	◆	◆	■	◆	◆	◆
Oxycodone	◆	◆	◆	■	■	◆	■
Phencyclidine (PCP)	◆	◆	◆	■	◆	◆	◆
Temazepam	◆	◆	◆	◆	◆	◆	◆

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

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 coadministered.

Notes: 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.

	SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
Atorvastatin	◆	■	■	●	■	●	●
Bezafibrate	◆	◆	◆	◆	◆	◆	
Ezetimibe	◆	◆	◆	■	◆	■	■
Fenofibrate	◆	◆	◆	◆	◆	◆	◆
Fluvastatin	◆	■	■	■	■	●	■
Gemfibrozil	◆	◆	◆	●	■	◆	■
Lovastatin	◆	■	■	●	■	●	●
Pitavastatin	◆	■	■	■	◆	●	■
Pravastatin	◆	■	◆	■	◆	■	■
Rosuvastatin	◆	●	■	■	■	●	■
Simvastatin	◆	■	■	●	■	●	●

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

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 coadministered.

Notes: 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.

cancer resistance protein (BCRP), any co-administered drugs that are potent P-gp inducers will not only decrease sofosbuvir but also ledipasvir plasma concentrations, leading to reduced therapeutic effect. Although co-administration with drugs that inhibit P-gp and/or BCRP may increase the exposure of sofosbuvir and ledipasvir, clinical consequences are unlikely.

Ledipasvir may also be the perpetrator of drug interactions by inhibiting P-gp and/or BCRP, potentially increasing the

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

		SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
Anti-depressants	Amitriptyline	◆	◆	◆	■	◆	◆	◆
	Citalopram	◆	◆	◆	◆	◆	◆	◆
	Duloxetine	◆	◆	◆	◆	◆	◆	◆
	Escitalopram	◆	◆	◆	◆	◆	◆	◆
	Fluoxetine	◆	◆	◆	◆	◆	◆	◆
	Paroxetime	◆	◆	◆	◆	◆	◆	◆
	Sertraline	◆	◆	◆	■	◆	◆	◆
	Trazodone	◆	◆	◆	■	◆	◆	◆
	Venlafaxine	◆	◆	◆	■	◆	◆	◆
Anti-psychotics	Amisulpiride	◆	◆	◆	◆	◆	◆	◆
	Aripiprazole	◆	◆	◆	■	■	◆	■
	Chlorpromazine	◆	◆	◆	■	◆	◆	◆
	Clozapine	◆	◆	◆	■	◆	◆	■
	Flupentixol	◆	◆	◆	■	◆	◆	◆
	Haloperidol	◆	◆	◆	■	◆	◆	◆
	Olanzapine	◆	◆	◆	■	◆	◆	◆
	Paliperidone	◆	■	◆	◆	◆	■	■
	Quetiapine	◆	◆	◆	●	■	◆	■
	Risperidone	◆	◆	◆	■	◆	◆	◆
	Zuclopentixol	◆	◆	◆	■	◆	◆	◆

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

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 coadministered.

Notes: 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.*

intestinal absorption of co-administered drugs. Thus, caution is warranted with well-studied P-gp substrates such as digoxin and dabigatran, but also potentially with other drugs which are, in part, transported by these proteins (*e.g.* aliskerin, amlodipine, buprenorphine, carvedilol, cyclosporine). Co-administration of amiodarone with sofosbuvir/ledipasvir is contraindicated because of a serious risk of symptomatic or even fatal bradycardia or asystole (see above, mechanism of interaction is unknown). The use of rosuvastatin is also not recommended (because of potential inhibition of hepatic OATP by ledipasvir) and interactions with other statins cannot be excluded. It is important to monitor carefully for statin-related adverse reactions. Since ledipasvir solubility decreases as pH increases, drugs that increase gastric pH (antacids, H2-receptor antagonists, proton pump inhibitors) are likely to decrease concentrations of ledipasvir. H2-receptor antagonists can be given simultaneously or 12 h apart at a dose not exceeding that equivalent to famotidine 40 mg and proton pump inhibitors can be given simultaneously, at a dose comparable to omeprazole 20 mg (Table 5). Real-world data have suggested slightly reduced SVR rates in patients receiving high-dose proton pump inhibitors, reinforcing the need for caution when treating patients on such drugs with sofosbuvir and ledipasvir.[63]

Sofosbuvir/ledipasvir may be given with all antiretrovirals. However, because of an increase in tenofovir disoproxil fumarate (TDF) concentrations when a pharmacokinetic enhancer (ritonavir or cobicistat) is present in an antiretroviral regimen, these combinations (*i.e.* atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir, elvitegravir/cobicistat, atazanavir/cobicistat, darunavir/cobicistat, all in combination with tenofovir disoproxil fumarate/emtricitabine) should be used with caution, with frequent renal monitoring if other alternatives are not available. The interaction is not mitigated by staggering administration by 12 h. Tenofovir levels are also increased in efavirenz-containing regimens and caution is required. The recent approval of tenofovir alafenamide (TAF), which results in considerably lower plasma tenofovir levels, means that there is less concern about an interaction leading to increased tenofovir exposure.

Sofosbuvir and velpatasvir

Sofosbuvir and velpatasvir are available in a two-drug fixed-dose combination containing 400 mg of sofosbuvir and 100 mg of velpatasvir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with or without food.

Velpatasvir is metabolised *in vitro* by CYP2B6, CYP2C8 and CYP3A4. However, because of the slow turnover, the vast majority of drug in plasma is the parent drug. Importantly, velpatasvir is transported by P-gp and BCRP and, to a limited extent, by organic anion transporting polypeptide (OATP) 1B1. Biliary excretion of the parent drug is the major route of elimination. The median terminal half-life of velpatasvir following administration of sofosbuvir and velpatasvir is approximately 15 h.

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

		SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
Anti-arrhythmics	Amiodarone	●	●	●	●	■	●	■
	Digoxin	◆	■	■	■	◆	■	■
	Vernakalant	◆	◆	◆	■	◆	◆	◆
	Flecainide	◆	◆	◆	■	◆	◆	◆
Beta-blockers	Atenolol	◆	◆	◆	◆	◆	◆	◆
	Bisoprolol	◆	◆	◆	■	◆	◆	◆
	Carvedilol	◆	■	■	■	◆	■	■
	Propranolol	◆	◆	◆	◆	◆	◆	◆
Calcium channel blockers	Amlodipine	◆	■	■	■	◆	◆	◆
	Diltiazem	◆	■	■	■	◆	■	■
	Nifedipine	◆	◆	◆	■	◆	◆	◆
Hypertension and heart failure agents	Aliskiren	◆	■	■	●	◆	●	●
	Losartan	◆	◆	◆	◆	◆	◆	◆
	Doxazosin	◆	◆	◆	■	◆	◆	◆
	Enalapril	◆	◆	◆	■	◆	■	■

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

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 coadministered.

Notes: 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.*

Velpatasvir plasma exposure (AUC) is similar in subjects with moderate and severe hepatic impairment compared to subjects with normal hepatic function. Cirrhosis (including decompensated cirrhosis) has no clinically relevant effect on velpatasvir exposure in a population pharmacokinetic analysis in HCV-infected individuals.

The pharmacokinetics of velpatasvir were studied in HCV-negative patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2). Relative to individuals with normal renal function, velpatasvir AUC was 50% higher, which was not considered to be clinically relevant.

The safety assessment of sofosbuvir and velpatasvir was based on pooled phase III data. Headache, fatigue and nausea were the most commonly reported adverse events, at as similar frequency to placebo-treated patients.

Because of the disposition profile of velpatasvir, there are some contraindications in relation to co-medications. Drugs that are potent P-gp or potent CYP inducers (*e.g.*, rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, St John's wort) are contraindicated, because of the decrease in sofosbuvir and/or velpatasvir exposure with the potential loss in efficacy. However, there are also drugs that are moderate P-gp or CYP inducers (such as modafinil) which can reduce velpatasvir exposure. Currently, this combination would not be recommended with sofosbuvir and velpatasvir.

Similar to ledipasvir, there is some concern about the inhibition of P-gp and/or BCRP by velpatasvir, such that there is an increase in exposure of a co-medication that is a substrate for these transporters. Current thinking is that the sofosbuvir and velpatasvir combination may be co-administered with P-gp, BCRP, OATP and CYP substrates, but there clearly needs to be some caution with co-medications that have a narrow therapeutic window and in which an increase in drug exposure could potentially have clinical consequences. The colour coding for sofosbuvir/velpatasvir in Tables 4A–G reflects this (*e.g.* for digoxin, dabigatran, ticagrelor, carvedilol, amlodipine, diltiazem, aliskiren).

Like ledipasvir, the solubility of velpatasvir decreases as pH increases. Therefore, it is important to be aware of the recommendations concerning the co-administration of antacids, H2-receptor antagonists and proton pump inhibitors. For most patients, proton pump inhibitors should be avoided during sofosbuvir/velpatasvir treatment. If considered necessary, sofosbuvir/velpatasvir should be given with food and taken 4 hours before the proton pump inhibitor, at a maximum dose comparable to omeprazole 20 mg (Table 5).

In HIV-HCV coinfected patients, sofosbuvir/velpatasvir may be given with most antiretrovirals, the exceptions being the inducing drugs efavirenz, etravirine and nevirapine. Efavirenz causes a 50% decrease in velpatasvir exposure. Sofosbuvir/velpatasvir also increases tenofovir exposure by inhibiting P-gp. This means that patients on a regimen containing TDF will need to be monitored for renal adverse events.

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

	SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
Azathioprine	◆	◆	◆	◆	◆	◆	◆
Cyclosporine	◆	◆	◆	■	●	●	■
Etanercept	◆	◆	◆	◆	◆	◆	◆
Mycophenolate	◆	◆	◆	■	◆	◆	◆
Sirolimus	◆	◆	◆	■	■	■	■
Tacrolimus	◆	◆	◆	■	■	■	■

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

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 coadministered.

Notes: 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 4G. Drug-drug interactions between HCV DAAs and antiplatelets and anticoagulants.

	SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
Clopidogrel	◆	◆	◆	■	◆	◆	◆
Dabigatran	◆	■	■	■	■	●	●
Ticagrelor	◆	■	■	●	■	■	■
Rivaroxaban	◆	■	■	●	■	■	■
Apixiban	◆	■	■	●	■	■	■
Edoxaban	◆	■	■	■	■	●	■
Warfarin	■	■	■	■	■	■	■

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

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 coadministered.

Notes: 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.

Sofosbuvir, velpatasvir and voxilaprevir

Sofosbuvir, velpatasvir and voxilaprevir are available in a three-drug fixed-dose combination containing 400 mg of sofosbuvir, 100 mg of velpatasvir and 100 mg of voxilaprevir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with food, as voxilaprevir plasma exposure (AUC) and maximum concentration (C_{max}) were 112% to 435%, and 147% to 680% higher, respectively, in the presence of food.

The specific pharmacokinetic information related to sofosbuvir and velpatasvir individually is discussed in previous sections. Voxilaprevir is metabolised *in vitro* by CYP3A4, with the vast majority of drug in plasma being the parent drug. Velpatasvir and voxilaprevir are both inhibitors of drug transporters P-gp, BCRP, OATP1B1 and OATP1B3. Biliary excretion of the parent drug is the major route of elimination for voxilaprevir. The median terminal half-life of voxilaprevir following administration of sofosbuvir, velpatasvir and voxilaprevir is approximately 33 h.

Table 5. Dose equivalence among proton pump inhibitors and H2 antagonists.

Drug family	Drug	Dose
Proton pump inhibitors (dose equivalent to omeprazole 20 mg once daily)	Omeprazole	20 mg once daily
	Lansoprazole	30 mg once daily
	Esomeprazole	20 mg once daily
	Pantoprazole	40 mg once daily
	Rabeprazole	20 mg once daily
H2 antagonists (dose equivalent to famotidine 20 mg twice daily)	Famotidine	20 mg twice daily
	Ranitidine	150 mg twice daily
	Cimetidine	300 mg three-four times daily
	Nizatidine	150 mg twice daily

The proton pump inhibitor doses shown in the Table are considered equivalent. The H2 antagonist doses shown in the Table are considered equivalent.

Population pharmacokinetic analysis of voxilaprevir in HCV-infected patients indicated that patients with compensated (Child-Pugh A) cirrhosis had 73% higher exposure of voxilaprevir than those without cirrhosis. Thus, no dose adjustment of

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sofosbuvir, velpatasvir and voxilaprevir is required for patients with compensated cirrhosis. The pharmacokinetics of single-dose voxilaprevir were also studied in patients with moderate and severe hepatic impairment (Child-Pugh B and C, respectively). Relative to patients with normal hepatic function, the voxilaprevir AUC was 3-fold and 5-fold higher in patients with moderate and severe hepatic impairment, respectively. Thus, the combination of sofosbuvir, velpatasvir and voxilaprevir is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and contraindicated in those with severe hepatic impairment (Child-Pugh C).

The pharmacokinetics of voxilaprevir were studied in HCV-negative patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2). Relative to subjects with normal renal function, voxilaprevir AUC was 71% higher in subjects with severe renal impairment, which was not considered to be clinically relevant.

The safety data of sofosbuvir, velpatasvir and voxilaprevir was based on data from phase II and III clinical trials. Headache, diarrhoea and nausea were the most commonly reported adverse events. The risk of gastrointestinal side effects is greater than with the combination of sofosbuvir and velpatasvir alone.

Because velpatasvir and voxilaprevir are both inhibitors of P-gp, BCRP, OATP1B1 and OATP1B3, co-administration of sofosbuvir, velpatasvir and voxilaprevir with medicinal products that are substrates of these transporters may increase the exposure of the co-medications. This means that those for which elevated plasma levels are associated with serious events are contraindicated and others may require dose adjustment or additional monitoring. Rosuvastatin is contraindicated because of a 19-fold increase in plasma exposure of the statin. As this effect is likely to be attributed more to the BCRP transporter, other drugs that are a BCRP substrate, including methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, sulfasalazine and topotecan, are also not recommended. Dabigatran is contraindicated because of a near 3-fold increase in AUC. This is caused by P-gp inhibition by both velpatasvir and voxilaprevir. Other substrates of P-gp may need to be dose-adjusted or monitored for increased exposure, including digoxin, ticagrelor, carvedilol, diltiazem and aliskiren. Similar caution is required with OATP1B inhibitors, such as cyclosporin, as voxilaprevir plasma exposure increases 19-fold, or with OATP1B substrates, such as edoxaban, as voxilaprevir inhibition is expected to increase the exposure of the factor Xa inhibitor. Neither of these combinations are recommended.

Concomitant use with medicinal products that are strong P-gp and/or strong CYP inducers such as rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital or phenytoin are contraindicated due to the decrease in sofosbuvir, velpatasvir and/or voxilaprevir exposure with the potential loss in efficacy. However, there are also drugs that are moderate P-gp or CYP inducers (such as modafinil, efavirenz, oxcarbazepine and others) which can also reduce exposure of this DAA and are not currently recommended.

For women of childbearing age, concomitant use with ethinylestradiol-containing contraception is contraindicated because of the risk of ALT elevations. Progestogen-containing contraception is allowed.

The solubility of velpatasvir decreases as pH increases. Therefore it is important to be aware of the recommendations concerning the co-administration of antacids, H2-receptor antagonists and proton pump inhibitors. Proton pump inhibitors can be given with sofosbuvir/velpatasvir/voxilaprevir at a dose that does not exceed doses comparable to omeprazole 20 mg (Table 5). Sofosbuvir/velpatasvir/voxilaprevir should be given with food and taken 4 hours before the proton pump inhibitor if possible.

In HIV-HCV coinfected patients, sofosbuvir/velpatasvir/voxilaprevir is not recommended with the inducing drugs efavirenz, etravirine and nevirapine, and the protease inhibitors atazanavir/ritonavir and lopinavir/ritonavir. Caution is required with twice daily darunavir/ritonavir, darunavir/cobicistat and atazanavir/cobicistat as there are no data. Efavirenz causes a 50% decrease in velpatasvir exposure and atazanavir causes a 4-fold increase in voxilaprevir exposure. Sofosbuvir/velpatasvir/voxilaprevir also increases tenofovir exposure by inhibiting P-gp. This means that patients on a regimen containing TDF need to be monitored for renal adverse events.

Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir

Paritaprevir is a protease inhibitor which is metabolised primarily by CYP3A4 and is given with a low dose of the CYP3A inhibitor ritonavir as a pharmacokinetic enhancer. This enables once daily administration and a lower dose than would be required without ritonavir. Ombitasvir is an NS5A inhibitor given in a fixed-dose combination with paritaprevir/ritonavir. The recommended dose of this combination is two tablets of ritonavir/paritaprevir/ombitasvir (50 mg/75 mg/12.5 mg per tablet) taken orally once daily with food. Dasabuvir is a non-nucleoside inhibitor of HCV RNA-dependent RNA polymerase administered in 250 mg tablets twice daily, in combination with ritonavir/paritaprevir/ombitasvir in genotype 1 patients.

Paritaprevir is excreted predominantly into the faeces. Ombitasvir shows linear kinetics, and is predominantly eliminated in the faeces. Dasabuvir is metabolised in the liver, and its predominant metabolite is mainly cleared via biliary excretion and faecal elimination with minimal renal clearance.

Pharmacokinetic results from hepatic impairment studies have shown that, in patients with severe hepatic impairment (Child-Pugh C), the AUC of paritaprevir was increased 9.5-fold, whereas ombitasvir was reduced 54% and dasabuvir was increased 3.3-fold. In Child-Pugh B, there is an increase in paritaprevir exposure of 62% with a decrease in ombitasvir of 30%. Thus, no dose adjustment is required for patients with mild hepatic impairment (Child-Pugh A), but the combination of ritonavir-boosted paritaprevir and ombitasvir with or without dasabuvir should not be used in patients with moderate hepatic impairment (Child-Pugh B) or in those with severe hepatic impairment (Child-Pugh C).

The AUC of paritaprevir was increased 45% in patients with severe renal impairment (creatinine clearance 15–29 ml/min), that of ritonavir 114%, and dasabuvir 50%. Currently, no dose adjustment is required for patients with mild, moderate or severe renal impairment. Paritaprevir, ombitasvir and dasabuvir can also be used in dialysis settings.

The most common side effects reported with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir were fatigue and nausea.

Paritaprevir is primarily metabolised by CYP3A4, whereas dasabuvir is primarily metabolised by CYP2C8 and ombitasvir undergoes hydrolysis. However, both ombitasvir and dasabuvir can be metabolised by CYP3A4. Transporters seem to play an important role in the disposition of these drugs, with paritaprevir inhibiting OATP1B1/B3, P-gp and BCRP. Dasabuvir and ritonavir may also inhibit P-gp and BCRP. Given the metabolic profile

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of the drugs and the presence of ritonavir, there is a potential for many drug-drug interactions. A comprehensive drug-drug interaction programme has been undertaken based on regulatory guidance from both the European Medicines Agency and the US Food and Drug Administration. It is important to consider the drug interaction profile of the compounds as a combination (either with or without dasabuvir), because the drugs have mutual effects on each other.

Ritonavir is a strong inhibitor of CYP3A4; thus, co-administration with drugs metabolised by this enzyme may result in markedly increased plasma concentrations. A number of drugs are contraindicated because elevated plasma exposure would lead to serious adverse events, including: alfuzosin, amiodarone, astemizole, terfenadine, cisapride, ergot derivatives, lovastatin, simvastatin, atorvastatin, oral midazolam, triazolam, quetiapine, quinidine, salmeterol, sildenafil when used for pulmonary arterial hypertension. Also contraindicated are enzyme inducers that might compromise virological efficacy, *e.g.* carbamazepine, phenytoin, phenobarbital, rifampicin, St John's wort, enzalutamide, and enzyme inhibitors that might increase paritaprevir exposure, *e.g.* azole antifungals, some macrolide antibiotics.

In addition to the contraindications, there are other drugs where caution needs to be exercised and there may be a requirement for a dosage adjustment, altered timing of administration or additional monitoring. Drug interactions need to be carefully considered in the setting of coinfection with HIV. Atazanavir and darunavir should be taken without ritonavir and other protease inhibitors are contraindicated. Efavirenz, etravirine and nevirapine are contraindicated, and rilpivirine should be used cautiously with repeat ECG monitoring. The exposure of raltegravir and dolutegravir may be increased, but this is not linked to safety issues. Cobicistat-containing regimens should not be used because of the additional boosting effect.

Grazoprevir and elbasvir

Grazoprevir and elbasvir are available in a two-drug fixed-dose combination containing 100 mg of grazoprevir and 50 mg of elbasvir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with or without food.

Grazoprevir and elbasvir are partially metabolised by CYP3A4, but no circulating metabolites are detected in plasma. The principal route of elimination is biliary and faecal with <1% recovered in urine. Grazoprevir is transported by P-gp and OATP1B1, while elbasvir is a substrate for P-gp. Both elbasvir (>99.9%) and grazoprevir (98.8%) are extensively bound to plasma proteins. The terminal half-life values are approximately 24 and 31 h, respectively.

Pharmacokinetic data from hepatic impairment studies in non-HCV-infected individuals have demonstrated a decrease in elbasvir AUC in Child-Pugh A (40%), Child-Pugh B (28%) and Child-Pugh C (12%) cirrhosis. In contrast, grazoprevir exposure is increased in Child-Pugh A (70%), Child-Pugh B (5-fold) and Child-Pugh C (12-fold) cirrhosis. Based on these data, there is a contraindication for elbasvir/grazoprevir in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

No dose adjustment is required in patients with mild, moderate or severe renal impairment (including patients on haemodialysis or peritoneal dialysis). There is an increase in elbasvir (65%) and grazoprevir (86%) exposure in non-HCV infected individuals with an eGFR <30 ml/min/1.73 m^2, but this is not considered to be clinically significant.

The safety of elbasvir/grazoprevir is based on phase II and III clinical studies with the most commonly reported adverse reactions being fatigue and headache. Rare cases (0.8%) of substantial ALT level elevations were reported, slightly more frequently in female, Asian and elderly patients. Less than 1% of subjects treated with elbasvir/grazoprevir with or without ribavirin discontinued treatment because of adverse events.

Since elbasvir and grazoprevir are substrates of CYP3A and P-gp, inducers of these proteins such as efavirenz, etravirine, phenytoin, carbamazepine, bosentan, modafinil and St John's wort may cause a marked decrease in plasma exposure of both DAAs and are therefore contraindicated. Strong inhibitors of CYP3A (*e.g.* boosted protease inhibitors, some azole antifungals), which may markedly increase plasma concentrations, are either contraindicated or not recommended. In addition to inhibition of CYP3A, grazoprevir plasma concentrations may also be markedly increased by inhibitors of OATP1B1 (including boosted protease inhibitors, cobicistat, cyclosporin, single-dose rifampicin). However, there is no effect of acid reducing agents on the absorption of either DAA.

The potential for grazoprevir/elbasvir to affect other medications is relatively low, although grazoprevir is a weak CYP3A inhibitor (approximately 30% increase in midazolam exposure) and elbasvir a weak inhibitor of P-gp. There needs to be some caution when co-administering drugs that use CYP3A and P-gp in their disposition, especially in the presence of a narrow therapeutic index (*e.g.* tacrolimus, some statins, dabigatran, ticagrelor), or drugs with large ranges such a quetiapine, where those on higher doses may need additional monitoring, dose reduction and/or ECG.

Based on the findings above, there are limitations on which antiretrovirals can be co-administered with elbasvir/grazoprevir. Currently the antiretrovirals that can be used are the nucleotide reverse transcriptase inhibitors abacavir, lamivudine, tenofovir (either as TDF or as TAF), emtricitabine, rilpivirine, raltegravir, dolutegravir and maraviroc (Table 4A).

Glecaprevir and pibrentasvir

Glecaprevir and pibrentasvir are available in a two-drug fixed-dose combination containing 100 mg of glecaprevir and 40 mg of pibrentasvir. The recommended dose is three tablets taken orally once daily with food, as glecaprevir plasma exposure increases 83%-163% in the presence of food compared to the fasted state.

Biliary excretion is the major route of elimination for glecaprevir and pibrentasvir. The half-lives of glecaprevir and pibrentasvir are approximately 6 and 23 h, respectively.

Population pharmacokinetic analysis in HCV-infected subjects showed that following administration of glecaprevir/pibrentasvir in HCV-infected individuals with compensated (Child-Pugh A) cirrhosis, exposure of glecaprevir was approximately 2-fold higher whilst pibrentasvir exposure was similar to patients without cirrhosis. When compared to patients with normal hepatic function, glecaprevir AUC was 33% higher in patients with compensated cirrhosis (Child-Pugh A), 100% higher in those with moderate hepatic impairment (Child-Pugh B), and increased to 11-fold in those with severe hepatic impairment (Child-Pugh C). Thus, glecaprevir/pibrentasvir is contraindicated in patients with Child-Pugh B or C.

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Glecaprevir/pibrentasvir was studied in HCV-negative individuals with mild, moderate, severe, or end-stage renal impairment not on dialysis and compared to subjects with normal renal function. The AUCs were increased by less than 56% in all patients, which was not clinically significant. Glecaprevir/pibrentasvir AUC was also similar with and without dialysis.

The safety of pibrentasvir and glecaprevir was evaluated in phase II and III clinical trials. Headache and fatigue were the most commonly reported adverse events.

Glecaprevir and pibrentasvir are inhibitors of P-gp, BCRP and OATP1B1 and OATP1B3. Co-administration with glecaprevir/pibrentasvir may increase the concentration of co-medications that are substrates of P-gp (*e.g.* dabigatran etexilate which is contraindicated because of a 2.4-fold increase in dabigatran exposure), BCRP (*e.g.* rosuvastatin which requires a dose reduction), or OATP1B1/3 (*e.g.* atorvastatin or simvastatin which are contraindicated). For other P-gp, BCRP, or OATP1B1/3 substrates, dose adjustment should be considered.

Glecaprevir/pibrentasvir concentrations may be decreased by strong P-gp and CYP3A inducing drugs such as rifampicin, carbamazepine, St. John's wort or phenytoin, leading to reduced therapeutic effect or loss of virologic response. Co-administration with these, or other potent inducers, is contraindicated. A similar effect cannot be ruled out with moderate inducers, such as oxcarbazepine and eslicarbazepine, and co-administration of these drugs is not recommended. Co-medications that inhibit P-gp and BCRP may increase plasma exposure of glecaprevir/pibrentasvir. Similarly OATP1B1/3 inhibitors, such as cyclosporin, darunavir and lopinavir, may also increase glecaprevir concentrations.

The potential for glecaprevir/pibrentasvir to affect other medications is relatively low, although glecaprevir is a weak CYP3A inhibitor (approximately 27% increase in midazolam exposure). There needs to be some caution when co-administering drugs that use CYP3A in their disposition in the presence of a narrow therapeutic index (*e.g.* tacrolimus) or drugs with large ranges such a quetiapine, whereas patients on higher doses may need additional monitoring, dose reduction and/or ECG.

For women of childbearing age, concomitant use with ethinylestradiol-containing contraception is contraindicated because of the risk of ALT elevations. Progestogen-containing contraception is allowed.

Similar to other DAAs, the solubility of glecaprevir decreases as pH increases. C_{max} of glecaprevir decreases on average by 64% when co-administered with omeprazole 40 mg. The license states that no dose changes are recommended. However, prescribing doses of omeprazole greater than 40 mg or equivalent (Table 5) with glecaprevir and pibrentasvir has not been studied and may lead to a greater decrease in glecaprevir concentrations.

In HIV-HCV coinfected patients, because of the mechanisms described above, glecaprevir/pibrentasvir is contraindicated with atazanavir-containing regimens and is not recommended with other HIV protease inhibitors. Similarly, the inducing non-nucleoside reverse transcriptase inhibitors efavirenz, etravirine and nevirapine are not recommended because of an expected reduction in plasma exposure of glecaprevir/pibrentasvir. All other antiretroviral drugs can be co-administered, including cobicistat when used with integrase inhibitor elvitegravir.

Recommendations

- Numerous and complex drug-drug interactions are possible with HCV DAAs. Therefore, a thorough drug-drug interaction risk assessment prior to starting therapy and before starting other medications during treatment is required in all patients undergoing treatment with DAAs, based on the prescribing information for each DAA (summary data on key interactions can be found in Tables 4A to G 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 coinfected patients, and close attention must be 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 other prescribed medications, over-the-counter medications, medications bought via the internet, and use of party or recreational drugs (**A1**).

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

In 2018 and onwards, because of their virological efficacy, ease of use, safety and tolerability, interferon (IFN)-free, ribavirin-free, DAA-based regimens are the best options in HCV-infected patients without cirrhosis (and in those with compensated [Child-Pugh A] and decompensated [Child-Pugh B and C] cirrhosis), including "treatment-naïve" patients (defined as patients who have never been treated for their HCV infection) and "treatment-experienced" patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin).

Indications depend on the HCV genotype/subtype, the severity of liver disease, and/or prior therapy. The indications are the same in HCV-monoinfected and HIV-coinfected patients. However, treatment alterations or dose adjustments may be needed in the latter, owing to drug-drug interactions (see above and Table 4A).

The panel recognises the heterogeneity of per capita incomes and health insurance systems across Europe and in other regions, and therefore the constraints that may necessitate continued utilisation of regimens described in previous versions of these recommendations but no longer recommended in 2018. In settings where none of the IFN-free, ribavirin-free options proposed in this document are available, options proposed in previous versions of these recommendations remain acceptable for patients likely to respond to these regimens until new DAAs become available and affordable; see prior EASL Recommendations on Treatment of Hepatitis C.[54,64–66]

It is hoped that the publication of up-to-date recommendations will guide reimbursement and discounting of drug costs in order to harmonize access and treatments across different countries and regions.

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Recommendations

- IFN-free, ribavirin-free, DAA-based regimens must be used in HCV-infected patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, including "treatment-naïve" patients (defined as patients who have never been treated for their HCV infection) and "treatment-experienced" patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; or pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin), because of their virological efficacy, ease of use, safety and tolerability (**A1**).
- The same IFN-free, ribavirin-free treatment regimens should be used in HIV-coinfected patients as in patients without HIV infection, as the virological results of therapy are identical. Treatment alterations or dose adjustments should be performed in case of interactions with antiretroviral drugs (**A1**).
- Whenever possible (same treatment duration, equivalent SVR rates), combination regimens comprising two drugs are preferred to triple combination regimens, in order to minimize the risk of side effects and drug-drug interactions (**B1**).

The IFN-free combination regimens that represent valuable options for each genotype/subtype are shown (Table 6). For each genotype/subtype, the available options are described below, followed by a summary of the data that support the given option, and summarised in Tables 7 and 8 for patients without cirrhosis and those with compensated (Child-Pugh A) cirrhosis, respectively.

By convention, the combination regimens listed start with fixed-dose pangenotypic combinations, followed by genotype-specific combinations (two-drug combinations followed by three-drug combinations; sofosbuvir-based followed by sofosbuvir-free).

Treatment of HCV genotype 1a infection

Four treatment options are available in 2018 for patients infected with HCV genotype 1a (Tables 6, 7 and 8). These options are considered equivalent, and their order of presentation does not indicate any superiority or preference, unless specified:

Sofosbuvir/velpatasvir.
Glecaprevir/pibrentasvir.
Sofosbuvir/ledipasvir.
Grazoprevir/elbasvir.

Recommendations

- The following regimens are recommended for the treatment of patients infected with genotype 1a, according to the below recommendations (**A1**):
  - o the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily;
  - o the fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in three tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, administered once daily with food;
  - o the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily;
  - o the fixed-dose combination of grazoprevir (100 mg) and elbasvir (50 mg) in a single tablet administered once daily).

Table 6. IFN-free, ribavirin-free combination treatment regimens available for treatment-naïve patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin), without cirrhosis or with compensated (Child-Pugh A) cirrhosis, recommended for each HCV genotype/subtype in 2018 and onwards.

Genotype	Pangenotypic regimens			Genotype-specific regimens		
	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
Genotype 1a	Yes	Yes	No*	Yes[a]	Yes[b]	No
Genotype 1b	Yes	Yes	No*	Yes	Yes	Yes
Genotype 2	Yes	Yes	No*	No	No	No
Genotype 3	Yes[c]	Yes	Yes[d]	No	No	No
Genotype 4	Yes	Yes	No*	Yes[a]	Yes[e]	No
Genotype 5	Yes	Yes	No*	Yes[a]	No	No
Genotype 6	Yes	Yes	No*	Yes[a]	No	No

DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

* Triple combination therapy efficacious but not useful due to the efficacy of double combination regimens.

[a] Treatment-naïve patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis.

[b] Treatment-naïve and treatment-experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis with an HCV RNA level ≤800,000 IU/ml (5.9 Log_{10} IU/ml).

[c] Treatment-naïve and treatment-experienced patients without cirrhosis.

[d] Treatment-naïve and treatment-experienced patients with compensated (Child-Pugh A) cirrhosis.

[e] Treatment-naïve patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis with an HCV RNA level ≤800,000 IU/ml (5.9 Log_{10} IU/ml).

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Table 7. Treatment recommendations for HCV-monoinfected or HCV/HIV-coinfected patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin).

Patients	Prior treatment experience	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
Genotype 1a	Treatment-naïve	12 wk	8 wk	No	8-12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	8 wk	No	No	12 wk (HCV RNA ≤800,000 IU/ml)	No
Genotype 1b	Treatment-naïve	12 wk	8 wk	No	8-12 wk	8 wk (F0-F2) 12 wk (F3)	8 wk (F0-F2) 12 wk (F3)
	Treatment-experienced	12 wk	8 wk	No	12 wk	12 wk	12 wk
Genotype 2	Treatment-naïve	12 wk	8 wk	No	No	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 3	Treatment-naïve	12 wk	8 wk	No	No	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 4	Treatment-naïve	12 wk	8 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 5	Treatment-naïve	12 wk	8 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 6	Treatment-naïve	12 wk	8 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

Table 8. Treatment recommendations for HCV-monoinfected or HCV/HIV-coinfected patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin).

Patients	Prior treatment experience	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
Genotype 1a	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	12 wk	No	No	12 wk (HCV RNA ≤800,000 IU/ml)	No
Genotype 1b	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk	12 wk
	Treatment-experienced	12 wk	12 wk	No	12 wk	12 wk	12 wk
Genotype 2	Treatment-naïve	12 wk	12 wk	No	No	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 3	Treatment-naïve	No	12 wk	12 wk	No	No	No
	Treatment-experienced	No	16 wk	12 wk	No	No	No
Genotype 4	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 5	Treatment-naïve	12 wk	12 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 6	Treatment-naïve	12 wk	12 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

Genotype 1a, Pangenotypic: Sofosbuvir/velpatasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 1a, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (**A1**).

Comments: This recommendation is based on the results of the phase III ASTRAL-1 trial in patients with HCV genotype 1 infection (22% with cirrhosis, 66% treatment-naïve, 34% treatment-experienced, 44% of whom exposed to previous DAA) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks. An SVR12 was observed in 98% (206/210; one relapse) of patients infected with genotype 1a.[67] These results were confirmed in real-world studies.[68,69]

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In the ASTRAL-5 trial in treatment-naïve or treatment-experienced patients with or without cirrhosis infected with genotype 1a and coinfected with HIV, the SVR12 rate with the same regimen was 95% (63/66; 2 relapses).[70]

The triple combination of sofosbuvir, velpatasvir and voxilaprevir administered for 8 weeks failed to achieve non-inferiority compared to sofosbuvir/velpatasvir for 12 weeks in the POLARIS-2 phase III trial, which included approximately 20% of patients with cirrhosis and 25% of treatment-experienced patients. The SVR12 rates in patients infected with genotype 1a were 92% (155/169; 14 relapses) after 8 weeks of sofosbuvir/velpatasvir/voxilaprevir and 99% (170/172; one relapse) after 12 weeks of sofosbuvir/velpatasvir.[71] Thus, the triple combination of sofosbuvir, velpatasvir and voxilaprevir for 8 weeks is not recommended in patients infected with HCV genotype 1a.

Genotype 1a, Pangenotypic: Glecaprevir/pibrentasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 1a without cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks (**A1**).
- Treatment-naïve and treatment-experienced patients infected with HCV genotype 1a with compensated (Child-Pugh A) cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (**A1**).

Comments: This recommendation is based on the results of two phase III trials in patients with HCV genotype 1a infection. In ENDURANCE-1, the SVR12 rate was 98% (150/152; one virological breakthrough, one non-virological failure) in treatment-naïve or treatment-experienced patients without cirrhosis receiving 8 weeks of glecaprevir/pibrentasvir, including 13 patients who were HIV-coinfected.[72] Treatment-naïve and treatment-experienced genotype 1a-infected patients with compensated cirrhosis were studied in the EXPEDITION-1 trial. The SVR12 rate was 98% (47/48; one relapse) after 12 weeks of glecaprevir/pibrentasvir.[73]

Genotype 1a, Genotype-specific: Sofosbuvir/ledipasvir

- Treatment-naïve patients infected with HCV genotype 1a, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks (**A1**).
- Treatment-naïve patients infected with HCV genotype 1a without cirrhosis can be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 8 weeks (**B2**).
- The combination of sofosbuvir and ledipasvir is not recommended in treatment-experienced patients infected with genotype 1a (**B1**).

Comments: This recommendation is based on the results of the three phase III trials ION-1, ION-3 and ION-4,[74–77] on *post hoc* analyses of pooled data from phase II and III clinical trials and on real-world data reported at international medical conferences or published.

In ION-1, treatment-naïve genotype 1a patients, including approximately 15% with compensated cirrhosis, achieved SVR12 in 98% (141/144; one relapse) of cases after 12 weeks of the fixed-dose combination of sofosbuvir and ledipasvir.[74] An integrated analysis of treatment-naïve genotype 1a patients with compensated cirrhosis treated with sofosbuvir/ledipasvir for 12 weeks in different phase II and III studies showed an overall SVR12 rate of 98% (84/86).[78]

In ION-4, an open-label study in treatment-naïve or treatment-experienced genotype 1a patients with or without cirrhosis who were coinfected with HIV and received an antiretroviral regimen of tenofovir and emtricitabine with efavirenz, rilpivirine or raltegravir, the SVR12 rate was 96% (240/250; 8 relapses).[77]

In ION-3 in treatment-naïve genotype 1a patients without cirrhosis, the SVR12 rates were 93% (159/171; 10 relapses) with sofosbuvir/ledipasvir for 8 weeks and 95% (163/172; 2 relapses) with sofosbuvir/ledipasvir for 12 weeks.[76] These results were confirmed by real-world studies from Europe and the United States in the same subgroup of patients, showing similarly high SVR12 rates. One study showed that shortening sofosbuvir and ledipasvir treatment duration can be applied to patients with an HCV RNA <6,000,000 IU/ml (6.8 Log_{10} IU/ml) at baseline.[79] A pooled analysis of patients from different real-world studies included 566 treatment-naïve genotype 1a-infected patients without cirrhosis; 527 of them were eligible to receive 8 weeks of sofosbuvir-ledipasvir, as per FDA labelling. The SVR12 rate was 98% (518/527; 9 relapses). Logistic regression analysis identified male sex, African-American origin and a fibrosis stage F3 as independent predictors of post-treatment relapse.[80] The effect of F3 fibrosis was not confirmed in later studies.[81,82]

SVR12 rates of the same order as in the clinical trials were observed in patients with or without compensated cirrhosis in real-world studies from various continents.

The combination of sofosbuvir and ledipasvir is not recommended in treatment-experienced patients infected with genotype 1a, because this regimen would require the addition of ribavirin, as explained in the EASL Recommendations for Treatment of Hepatitis C 2016.[54]

Genotype 1a, Genotype-specific: Grazoprevir/elbasvir

- Treatment-naïve and treatment-experienced patients infected with genotype 1a, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, with an HCV RNA level ≤800,000 IU/ml (5.9 Log_{10} IU/ml) at baseline should be treated with the fixed-dose combination of grazoprevir and elbasvir for 12 weeks (**B1**).
- The combination of grazoprevir and elbasvir is not recommended in patients infected with genotype 1a with an HCV RNA level >800,000 IU/ml (5.9 Log_{10} IU/ml) (**A1**).

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Comments: This recommendation is based on the results of three phase III trials and subsequent *post hoc* analyses of pooled phase II and III clinical trial data.

In the C-EDGE-TN trial, in treatment-naïve patients infected with genotype 1a receiving grazoprevir and elbasvir for 12 weeks, the SVR12 rate was 92% (144/157; one breakthrough and 12 relapses), with compensated cirrhosis having no effect on SVR12 rate.[83] In the open-label C-EDGE-COINFECTION trial, treatment-naïve patients coinfected with HIV with or without compensated cirrhosis were treated with grazoprevir and elbasvir for 12 weeks, with an SVR12 rate of 97% (139/144) in genotype 1a-infected patients.[84] In a pooled efficacy analysis of treatment-naïve patients with genotype 1a infection from phase II and III trials treated with grazoprevir/elbasvir for 12 weeks, the SVR12 rate was 99% (121/122) in patients with an HCV RNA level ≤800,000 IU/ml, with no influence of pre-existing NS5A RASs at baseline on SVR (unpublished data provided to the panel by Merck).

In treatment-experienced patients included in the C-EDGE-TE phase III trial, including approximately 30% of patients with compensated cirrhosis, the SVR12 rate in genotype 1a patients was 92% (55/60) after 12 weeks of grazoprevir/elbasvir.[85] In a pooled efficacy population of treatment-experienced patients with genotype 1a from phase II and III trials treated for 12 weeks, the SVR12 rate was 100% (14/14) in patients with an HCV RNA level ≤800,000 IU/ml (unpublished data provided to the panel by Merck).

With this regimen, the SVR12 rate was impacted by the presence of NS5A RASs at baseline in treatment-naïve and treatment-experienced patients with an HCV RNA level >800,000 IU/ml (unpublished data provided to the panel by Merck). Therefore, because resistance testing is not recommended prior to therapy, this regimen is not recommended in patients with an HCV RNA level >800,000 IU/ml.

Treatment of HCV genotype 1b infection

Five treatment options are available in 2018 for patients infected with HCV genotype 1b (Tables 6, 7 and 8). These options are considered equivalent, and their order of presentation does not indicate any superiority or preference, unless specified:

Sofosbuvir/velpatasvir.
Glecaprevir/pibrentasvir.
Sofosbuvir/ledipasvir.
Grazoprevir/elbasvir.
Ombitasvir/paritaprevir/ritonavir and dasabuvir.

Recommendations

- The following regimens are recommended for the treatment of patients infected with genotype 1b, according to the below recommendations (**A1**):
  - o the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily;
  - o the fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in three tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, administered once daily with food;
  - o the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily;
  - o the fixed-dose combination of grazoprevir (100 mg) and elbasvir (50 mg) in a single tablet administered once daily;
  - o 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).

Genotype 1b, Pangenotypic: Sofosbuvir/velpatasvir

- Treatment-naïve and treatment-experienced patients infected with genotype 1b, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (**A1**).

Comments: This recommendation is based on the results of the phase III ASTRAL-1 trial in patients with HCV genotype 1 infection (22% with cirrhosis, 66% treatment-naïve, 34% treatment-experienced, 44% of whom exposed to previous DAA) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks. An SVR12 was observed in 99% (117/118; one relapse) of patients infected with genotype 1b.[67] In the ASTRAL-5 trial in HIV-coinfected patients, the SVR12 rate with the same regimen was 92% (11/12; no virological failure) in treatment-naïve or treatment-experienced patients without cirrhosis or with compensated cirrhosis infected with genotype 1b.[70] These results were confirmed in real-world studies.[68,69]

Genotype 1b, Pangenotypic: Glecaprevir/pibrentasvir

- Treatment-naïve and treatment-experienced patients infected with genotype 1b without cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks (**A1**).
- Treatment-naïve and treatment-experienced patients infected with genotype 1b with compensated (Child-Pugh A) cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (**A1**).

Comments: This recommendation is based on the results of two phase III trials in patients with HCV genotype 1b infection. In ENDURANCE-1, the SVR12 rate was 100% (198/198) in treatment-naïve and treatment-experienced patients without cirrhosis receiving 8 weeks of glecaprevir/pibrentasvir, including two

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patients who were HIV-coinfected.[72] Treatment-naïve and treatment-experienced genotype 1b-infected patients with compensated cirrhosis were studied in the EXPEDITION-1 trial. The SVR12 rate was 100% (39/39) after 12 weeks of glecaprevir/pibrentasvir.[73]

Genotype 1b, Genotype-Specific: Sofosbuvir/ledipasvir

- Treatment-naïve and treatment-experienced patients infected with genotype 1b, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks (**A1**).
- Treatment-naïve patients infected with genotype 1b without cirrhosis can be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 8 weeks (**B1**).

Comments: This recommendation is based on the results of the four phase III trials ION-1, ION-2, ION-3 and ION-4[74–77] and several *post hoc* analyses of pooled data from phase II and III clinical trials.

In ION-1, treatment-naïve patients infected with HCV genotype 1b, including approximately 15% with compensated cirrhosis, achieved SVR12 in 100% (66/66) of cases after 12 weeks of the fixed-dose combination of sofosbuvir and ledipasvir.[74] An integrated analysis of genotype 1b patients with compensated cirrhosis treated with sofosbuvir/ledipasvir for 12 weeks in different phase II and III studies showed an overall SVR12 rate of 97% (72/74) in treatment-naïve and 96% (124/129) in treatment-experienced patients.[78]

In ION-2, in treatment-experienced patients (previously treated with pegylated IFN-α and ribavirin, or with pegylated IFN-α, ribavirin and either telaprevir or boceprevir), including approximately 20% with cirrhosis, the SVR12 rate was 87% (20/23; 3 relapses) in patients infected with HCV genotype 1b.[75]

In ION-4, an open-label study in treatment-naïve and treatment-experienced genotype 1b patients with or without cirrhosis who were coinfected with HIV and received an antiretroviral regimen of tenofovir and emtricitabine with efavirenz, rilpivirine or raltegravir, the SVR12 rate was 96% (74/77; 3 relapses).[77]

In ION-3 in treatment-naïve patients without cirrhosis (F3 fibrosis was present in only 13% of patients with genotype 1 who underwent liver biopsy), the SVR12 rate was 98% (42/43; one relapse) after 8 weeks of sofosbuvir/ledipasvir in patients infected with genotype 1b.[76] These results were confirmed by real-world studies from Europe and the United States in the same subgroup of patients, showing similarly high SVR12 rates. In a pooled analysis of patients from different real-world studies, the SVR12 rate after 8 weeks of sofosbuvir/ledipasvir as per FDA labelling was over 99% (235/237; 2 relapses) in genotype 1b patients.[80]

Similar SVR12 rates as those achieved in the clinical trials were observed in treatment-naïve and treatment-experienced patients with or without compensated cirrhosis in real-world studies from various continents.

Genotype 1b, Genotype-specific: Grazoprevir/elbasvir

- Treatment-naïve and treatment-experienced patients infected with genotype 1b, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of grazoprevir and elbasvir for 12 weeks (**A1**).
- Treatment-naïve patients infected with genotype 1b with F0-F2 fibrosis can be treated with the fixed-dose combination of grazoprevir and elbasvir for 8 weeks (**B2**).

Comments: This recommendation is based on the results of four phase III trials, and subsequent *post hoc* analyses of pooled phase II and III clinical trial data, as well as of the STREAGER trial with a shorter treatment duration.

In the C-EDGE-TN trial, in treatment-naïve patients infected with genotype 1b receiving grazoprevir and elbasvir for 12 weeks, the SVR12 rate was 99% (129/131; one relapse).[83] In the C-CORAL trial, performed in Russia and the Asia-Pacific region, the SVR12 rate was 98% (382/389; 5 relapses).[86] In the open-label C-EDGE-COINFECTION trial, treatment-naïve patients coinfected with HIV with or without compensated cirrhosis were treated with grazoprevir and elbasvir for 12 weeks. The SVR12 rate was 95% (42/44) in genotype 1b-infected patients.[84]

In treatment-experienced patients included in the C-EDGE-TE phase III trial, in which approximately a third of patients had compensated cirrhosis, the SVR12 rate in genotype 1b patients was 100% (34/34) after 12 weeks of grazoprevir/elbasvir.[85]

A pooled analysis of all phase II and III trials showed an SVR rate of 97% (1040/1070; 15 relapses and 15 virological failures) in patients infected with genotype 1b treated for 12 weeks with this regimen.[87]

In the STREAGER study, treatment-naïve genotype 1b-infected patients with a stage of fibrosis F0-F2 (excluding patients with advanced fibrosis or cirrhosis) treated with grazoprevir/elbasvir for 8 weeks achieved an SVR12 in 97% (66/68) of cases. Two patients relapsed post-treatment (updated data provided to the panel by Merck).[88]

Genotype 1b, Genotype-specific: Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir

- Treatment-naïve and treatment-experienced patients infected with genotype 1b, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 12 weeks (**A1**).
- Treatment-naïve patients infected with genotype 1b with F0-F2 fibrosis can be treated with the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 8 weeks (**B2**).

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Comments: This recommendation is based on the results of several phase III trials. In the PEARL-3 trial, the SVR12 rate was 99% (207/209) in treatment-naïve patients without cirrhosis infected with subtype 1b receiving the triple combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks.[89] In MALACHITE-1, the SVR12 rate in treatment-naïve patients without cirrhosis was 98% (81/83).[90] In the TURQUOISE-1 study in treatment-naïve patients without cirrhosis coinfected with HIV-1 and stable on antiretroviral treatment containing atazanavir or raltegravir, SVR12 was achieved in 100% (7/7) of genotype 1b patients.[91] Finally, in the GARNET study, the SVR12 rate was 97% (161/166) in treatment-naïve patients with genotype 1b infection and no cirrhosis (METAVIR score F0 to F3) after 8 weeks of treatment with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir. Among the 15 patients with F3 fibrosis included in this study, two experienced a virological failure.[92]

In treatment-experienced patients (pegylated IFN-α and ribavirin failures) without cirrhosis treated with this combination for 12 weeks in PEARL-2, SVR12 was achieved in 100% (95/95) of cases.[93] In the TOPAZ-1 study, treatment-naïve and treatment-experienced patients without cirrhosis receiving the same regimen achieved SVR12 in 99% (738/745; 3 virological failures) of cases.[94] A pooled analysis of several clinical trials showed a 99% SVR12 rate in 521 patients without cirrhosis (PEARL-2, PEARL-3, TOPAZ-2, MALACHITE-1).[95] Similarly high SVR12 rates were achieved in Asian patients infected with genotype 1b with this combination.[96]

In treatment-naïve and treatment-experienced patients with compensated cirrhosis included in the TURQUOISE-3 trial, SVR12 was achieved in 100% (60/60) of genotype 1b patients treated for 12 weeks with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir.[97]

Similar SVR12 rates as those achieved in the clinical trials were observed in a large number of real-world studies from various continents.

Treatment of HCV genotype 2 infection

Two first-line treatment options are available for patients infected with HCV genotype 2 (Tables 6, 7 and 8). These options are considered equivalent, and their order of presentation does not indicate any superiority or preference, unless specified:

Sofosbuvir/velpatasvir.

Glecaprevir/pibrentasvir.

Recommendations

- The following regimens are recommended for the treatment of patients infected with genotype 2, according to the below recommendations (**A1**):
  - o the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily;
  - o the fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in three tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, administered once daily with food.

Genotype 2, Pangenotypic: Sofosbuvir/velpatasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 2, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (**A1**).

Comments: This recommendation is based on the results of the phase III ASTRAL-2 trial in patients with HCV genotype 2 infection (14% with compensated cirrhosis, 86% treatment-naïve, 14% treatment-experienced) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, showing SVR12 in 99% (133/134) of patients.[98] In ASTRAL-1, the SVR12 rate was 100% (104/104) in treatment-naïve (two-thirds) and treatment-experienced (one-third) patients, who included approximately 30% with cirrhosis.[67] In the ASTRAL-5 trial in HIV-coinfected patients, the SVR12 rate with the same regimen was 100% (11/11) in genotype 2 patients.[70]

Genotype 2, Pangenotypic: Glecaprevir/pibrentasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 2 without cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks (**A1**).
- Treatment-naïve and treatment-experienced patients infected with HCV genotype 2 with compensated (Child-Pugh A) cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (**A1**).

Comments: This recommendation is in part based on the results of the phase II SURVEYOR-2 trial, showing an SVR12 rate of 98% (53/54; no virological failure) in treatment-naïve and treatment-experienced patients without cirrhosis infected with HCV genotype 2, receiving the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks.[99] These results were confirmed in the CERTAIN-2 trial, showing an SVR rate of 98% (127/129, no virological failure) in Japanese patients infected with genotype 2, receiving the same treatment regimen for 8 weeks.[100] In the EXPEDITION 2 trial, the SVR12 rate was 100% (12/12) after 8 weeks of glecaprevir/pibrentasvir in patients without cirrhosis with genotype 2 infection coinfected with HIV.[101]

In the EXPEDITION-1 trial, 12 weeks of glecaprevir/pibrentasvir yielded SVR12 in 100% (31/31) of treatment-naïve or treatment-experienced genotype 2-infected patients with compensated cirrhosis.[73] These results were confirmed in the CERTAIN-2 trial, showing an SVR rate of 100% (38/38) in Japanese patients with compensated cirrhosis infected with genotype 2 receiving the same treatment regimen for 12 weeks.[100]

Treatment of HCV genotype 3 infection

Three first-line treatment options are available for patients infected with HCV genotype 3 (Tables 6, 7 and 8). These options

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are considered equivalent, and their order of presentation does not indicate any superiority or preference, unless specified:
Sofosbuvir/velpatasvir.
Glecaprevir/pibrentasvir.
Sofosbuvir/velpatasvir/voxilaprevir.

Recommendations

- The following regimens are recommended for the treatment of patients infected with genotype 3, according to the below recommendations (**A1**):
  - the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily;
  - the fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in three tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, administered once daily with food;
  - the fixed-dose combination of sofosbuvir (400 mg), velpatasvir (100 mg) and voxilaprevir (100 mg) in a single tablet administered once daily with food.

Genotype 3, Pangenotypic: Sofosbuvir/velpatasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 3 without cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (**A1**).
- The combination of sofosbuvir and velpatasvir is not recommended in treatment-naïve and treatment-experienced patients infected with HCV genotype 3 with compensated (Child-Pugh A) cirrhosis, because suboptimal results have been reported with this combination (**B2**).

Comments: This recommendation is based on the results of the phase III ASTRAL-3 trial in patients with HCV genotype 3 infection (29% with compensated cirrhosis, 74% treatment-naïve, 26% treatment-experienced) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks. The SVR12 rates were 98% (160/163) in treatment-naïve patients without cirrhosis. Lower SVR12 rates were observed in patients who were treatment-experienced or had cirrhosis with this regimen: overall 90% (104/116; 12 virological failures); 93% (40/43) in treatment-naïve patients with compensated cirrhosis, 91% (31/34) in treatment-experienced patients without cirrhosis and 89% (33/37) in treatment-experienced patients with compensated cirrhosis.[98] Thus, the addition of a third drug to this regimen is necessary, at least in patients infected with genotype 3 with compensated cirrhosis, justifying the use of the triple combination of sofosbuvir, velpatasvir and voxilaprevir in this group (see below).

In the ASTRAL-5 trial in HIV-coinfected patients, the SVR12 rate with the same regimen was 92% (11/12).[70]

Genotype 3, Pangenotypic: Glecaprevir/pibrentasvir

- Treatment-naïve patients infected with HCV genotype 3, with no to moderate fibrosis (METAVIR score F0-F2), should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks (**A1**).
- Treatment-naïve patients infected with HCV genotype 3, with advanced fibrosis (METAVIR score F3), but without cirrhosis, can be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks (**B2**).
- Treatment-experienced patients infected with HCV genotype 3 without cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (**B1**).
- Treatment-naïve patients infected with HCV genotype 3 with compensated (Child-Pugh A) cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (**B1**).
- Treatment-experienced patients infected with HCV genotype 3 with compensated (Child-Pugh A) cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 16 weeks (**B1**).

Comments: This recommendation is based on the results of the phase III ENDURANCE-3 trial showing an SVR12 rate of 95% (149/157; 5 relapses, one virological breakthrough) in treatment-naïve patients without cirrhosis infected with HCV genotype 3 receiving the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks. However, only 17% of patients in this study had advanced fibrosis (METAVIR score F3), the remaining 83% having mild to moderate fibrosis (F0-F2).[102] Thus, more data must be generated to strengthen the recommendation of 8 weeks of glecaprevir and pibrentasvir as the ideal treatment duration in treatment-naïve patients with advanced (F3) fibrosis.In the EXPEDITION-2 trial, the SVR12 rate was 100% (22/22) after 8 weeks of glecaprevir/pibrentasvir in patients with genotype 3 infection coinfected with HIV without cirrhosis.[101] An integrated analysis of phase II and III trials in patients infected with genotype 3 showed an SVR12 rate of 95% (198/208; 6 virological failures) after 8 weeks of glecaprevir/pibrentasvir in treatment-naïve patients infected with genotype 3 without cirrhosis.[103]

In the same integrated analysis of phase II and III trials, the SVR12 rate after 12 weeks of glecaprevir/pibrentasvir in treatment-naïve patients with cirrhosis infected with genotype 3 was 97% (67/69; one virological breakthrough).[103] In the SURVEYOR-2 study, the SVR12 rates were 91% (20/22; 2 relapses) and 95% (21/22; 1 relapse) in treatment-experienced patients without cirrhosis treated for 12 or 16 weeks, respectively; they were 98% (39/40; no virological failure) in treatment-naïve patients with cirrhosis treated for 12 weeks and 96% (45/47; 2 virological failures) in treatment-experienced patients with cirrhosis treated for 16 weeks.[104] A pooled analysis of phase II and III clinical trials in patients infected with genotype 3 showed SVR12 rates of 96% (258/270) in treatment-naïve patients without cirrhosis treated for 12 weeks, 90% (44/49) in treatment-experienced patients without cirrhosis treated for 12 weeks, 96% (21/22) in treatment-experienced patients without

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cirrhosis treated for 16 weeks, 99% (64/65) in treatment-naïve patients with compensated cirrhosis treated for 12 weeks, and 94% (48/51) in treatment-experienced patients with compensated cirrhosis treated for 16 weeks.[105] Data with 12 weeks of treatment with glecaprevir and pibrentasvir in treatment-experienced patients with cirrhosis are needed.

Genotype 3, Pangenotypic: Sofosbuvir/velpatasvir/voxilaprevir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 3 with compensated (Child-Pugh A) cirrhosis should be treated with the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks (**B2**).

Comments: This recommendation is based on the results of the POLARIS-2 and -3 phase III trials. In POLARIS-2, which included approximately three-quarters of treatment-naïve and one-quarter of treatment-experienced patients and approximately 20% of individuals with cirrhosis, the SVR12 rate was 99% (91/92; no virological failure) after 8 weeks of the triple combination of sofosbuvir, velpatasvir and voxilaprevir.[71] In POLARIS-3, 8 weeks of the triple combination yielded a 96% SVR12 rate (106/110; 2 relapses) in treatment-naïve and treatment-experienced patients with compensated cirrhosis.[71] Because genotype 3 is more difficult-to-cure than other genotypes, and in the absence of data with 12 weeks of therapy, it appears to be safer to treat patients with genotype 3 infection who have cirrhosis for 12 weeks with this combination.

Treatment of HCV genotype 4 infection

Four treatment options are available in 2018 for patients infected with HCV genotype 4 (Tables 6, 7 and 8). These options are considered equivalent, and their order of presentation does not indicate any superiority or preference, unless specified:

Sofosbuvir/velpatasvir.
Glecaprevir/pibrentasvir.
Sofosbuvir/ledipasvir.
Grazoprevir/elbasvir.

Recommendations

- The following regimens are recommended for the treatment of patients infected with genotype 4, according to the below recommendations (**A1**):
  - o the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily;
  - o the fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in three tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, administered once daily with food;
  - o the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily;
  - o the fixed-dose combination of grazoprevir (100 mg) and elbasvir (50 mg) in a single tablet administered once daily.

Genotype 4, Pangenotypic: Sofosbuvir/velpatasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 4, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (**A1**).

Comments: This recommendation is based on the results of the phase III ASTRAL-1 trial in patients with HCV genotype 4 infection (23% with cirrhosis, 55% treatment-naïve, 45% treatment-experienced) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, showing SVR12 in 100% (116/116) of patients.[67] In the ASTRAL-5 trial in HIV-coinfected patients receiving the same treatment regimen, the SVR12 rate was 100% (4/4).[70]

Genotype 4, Pangenotypic: Glecaprevir/pibrentasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 4 without cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks (**A1**).
- Treatment-naïve and treatment-experienced patients infected with HCV genotype 4 with compensated (Child-Pugh A) cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (**A1**).

Comments: This recommendation is partly based on the results of the phase II SURVEYOR-2 trial showing an SVR12 rate of 93% (43/46; no virological failure) in treatment-naïve and treatment-experienced patients without cirrhosis infected with HCV genotype 4 receiving the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks.[99] In ENDURANCE-4, genotype 4 patients without cirrhosis treated for 12 weeks achieved SVR in 99% (75/76; no virological failures) of cases,[106] whereas in EXPEDITION-1, 100% (16/16) of patients with cirrhosis infected with genotype 4 achieved SVR12.[73]

In the EXPEDITION 2 trial, the SVR12 rate was 100% (16/16) after 8 weeks of glecaprevir/pibrentasvir in patients with genotype 4 infection coinfected with HIV without cirrhosis.[101]

Genotype 4, Genotype-specific: Sofosbuvir/ledipasvir

- Treatment-naïve patients infected with HCV genotype 4, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks (**B1**).

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- The combination of sofosbuvir and ledipasvir is not recommended in treatment-experienced patients infected with genotype 4 (**B1**).

Comments: The SYNERGY trial assessed the efficacy and safety of the combination of sofosbuvir and ledipasvir in patients with genotype 4 infection. After 12 weeks of therapy, 95% (20/21; no virological failure) of them achieved an SVR.[107] In another phase II trial, patients were treated with the combination of sofosbuvir and ledipasvir for 12 weeks. The SVR12 rates were 96% (21/22) in treatment-naïve and 91% (20/22) in treatment-experienced individuals; the split was 91% (31/34) in patients without cirrhosis and 100% (10/10) in those with cirrhosis.[108]

Genotype 4, Genotype-specific: Grazoprevir/elbasvir

- Treatment-naïve patients infected with genotype 4, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, with an HCV RNA level ≤800,000 IU/ml (5.9 Log_{10} IU/ml) at baseline should be treated with the fixed-dose combination of grazoprevir and elbasvir for 12 weeks (**A1**).
- The combination of grazoprevir and elbasvir is not recommended in patients infected with genotype 4 who are treatment-naïve with an HCV RNA level >800,000 IU/ml (5.9 Log_{10} IU/ml), or treatment-experienced regardless of their baseline HCV RNA level (**A1**).

Comments: This recommendation is based on the results of three phase III trials including a small number of patients infected with genotype 4 and on the analogy with data in patients infected with genotype 1. In the C-EDGE-TN trial, the SVR12 rate was 100% (18/18) in treatment-naïve patients infected with genotype 4 receiving grazoprevir and elbasvir for 12 weeks (including 12% with cirrhosis).[83] In the open-label C-EDGE-COINFECTION trial, treatment-naïve patients with HCV genotype 4 coinfected with HIV, with or without compensated cirrhosis, were treated with grazoprevir and elbasvir for 12 weeks. The SVR12 rate was 96% (27/28; one relapse).[84] In the C-CORAL trial, 3/3 treatment-naïve patients infected with genotype 4 achieved an SVR12 after 12 weeks of grazoprevir/elbasvir.[86] The SVR12 rate was 100% (11/11) in the C-EDGE CO-STAR trial in PWIDs on opioid substitution therapy receiving the same treatment regimen.[109]

Treatment of HCV genotype 5 infection

Three treatment options are available in 2018 for patients infected with HCV genotype 5 (Tables 6, 7 and 8). However, the number of patients infected with genotype 5 treated in all of the trials was limited, making it difficult to make strong recommendations once the data are broken down by cirrhosis and prior treatment. These options are considered equivalent, and their order of presentation does not indicate any superiority or preference, unless specified:

Sofosbuvir/velpatasvir.
Glecaprevir/pibrentasvir.
Sofosbuvir/ledipasvir.

Recommendations

- The following regimens are recommended for the treatment of patients infected with genotype 5, according to the below recommendations (**A1**):
  - the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily;
  - the fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in three tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, administered once daily with food;
  - the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily.

Genotype 5, Pangenotypic: Sofosbuvir/velpatasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 5, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (**B1**).

Comments: This recommendation is based on the results of the phase III ASTRAL-1 trial in patients with HCV genotype 5 (14% with cirrhosis, 69% treatment-naïve, 31% treatment-experienced) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, showing SVR12 in 97% (34/35) of them.[67]

Genotype 5, Pangenotypic: Glecaprevir/pibrentasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 5 without cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks (**B1**).
- Treatment-naïve and treatment-experienced patients infected with HCV genotype 5 with compensated (Child-Pugh A) cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (**B1**).

Comments: This recommendation is based on the results of the phase II SURVEYOR-2 trial in which 2/2 patients without cirrhosis infected with HCV genotype 5 receiving the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks achieved an SVR12.[99] In ENDURANCE-4, genotype 5 patients without cirrhosis treated for 12 weeks achieved SVR in 100% (26/26) of cases,[106] whereas in EXPEDITION-1, 2/2 patients infected with genotype 5 with cirrhosis achieved SVR12.[73]

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Genotype 5, Genotype-specific: Sofosbuvir/ledipasvir

- Treatment-naïve patients infected with HCV genotype 5 without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the combination of sofosbuvir and ledipasvir for 12 weeks (**B1**).
- The combination of sofosbuvir and ledipasvir is not recommended in treatment-experienced patients infected with genotype 5 (**B1**).

Comments: In a phase II trial, 41 treatment-naïve and treatment-experienced patients infected with HCV genotype 5, including 9 with compensated cirrhosis, were treated with sofosbuvir and ledipasvir without ribavirin for 12 weeks: 95% (39/41) achieved SVR12.[110]

Treatment of HCV genotype 6 infection

Three treatment options are available in 2018 for patients infected with HCV genotype 6 (Tables 6, 7 and 8). However, the number of patients infected with genotype 6 treated in all of the trials was limited, making it difficult to make strong recommendations once the data are broken down by cirrhosis and prior treatment. These options are considered equivalent, and their order of presentation does not indicate any superiority or preference, unless specified:

Sofosbuvir/velpatasvir.
Glecaprevir/pibrentasvir.
Sofosbuvir/ledipasvir.

Recommendations

- The following regimens are recommended for the treatment of patients infected with genotype 6, according to the below recommendations (**A1**):
  - o the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily;
  - o the fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in three tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, administered once daily with food;
  - o the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily.

Genotype 6, Pangenotypic: Sofosbuvir/velpatasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 6, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (**B1**).

Comments: This recommendation is based on the results of the phase III ASTRAL-1 trial in patients with HCV genotype 6 (15% with cirrhosis, 93% treatment-naïve, 17% treatment-experienced) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, of whom 100% (41/41) achieved SVR12.[67] These results were confirmed by a 97% (35/36; one relapse) SVR rate in a phase III trial in patients infected with genotype 6 from Singapore, Malaysia, Thailand and Vietnam.[111]

Genotype 6, Pangenotypic: Glecaprevir/pibrentasvir

- Treatment-naïve and treatment-experienced patients infected with HCV genotype 6 without cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks (**B1**).
- Treatment-naïve and treatment-experienced patients infected with HCV genotype 6 with compensated (Child-Pugh A) cirrhosis should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (**B1**).

Comments: This recommendation is partly based on the results of the phase II SURVEYOR-2 trial, showing an SVR12 rate of 90% (9/10; no virological failure) in treatment-naïve and treatment-experienced patients infected with HCV genotype 6 without cirrhosis, who received the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks.[99] In ENDURANCE-4, genotype 6 patients without cirrhosis treated for 12 weeks achieved SVR in 100% (19/19) of cases,[106] whereas in EXPEDITION-1, 100% (7/7) of patients infected with genotype 6 with cirrhosis achieved SVR12.[73]

In the EXPEDITION 2 trial, the SVR12 rate was 3/3 after 8 weeks of glecaprevir/pibrentasvir in patients with genotype 6 infection and HIV coinfection without cirrhosis.[101]

Genotype 6, Genotype-specific: Sofosbuvir/ledipasvir

- Treatment-naïve patients infected with HCV genotype 6, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the combination of sofosbuvir and ledipasvir for 12 weeks (**B1**).
- The combination of sofosbuvir and ledipasvir is not recommended in treatment-experienced patients infected with genotype 6 (**B1**).

Comments: The combination of sofosbuvir and ledipasvir administered for 12 weeks without ribavirin, in treatment-naïve and treatment-experienced patients infected with genotype 6, yielded an SVR rate of 96% (24/25).[112]

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Simplified treatment of chronic hepatitis C with pangenotypic drug regimens in patients without cirrhosis and in patients with compensated (Child-Pugh A) cirrhosis

With the approval of highly efficacious, safe and well-tolerated combination regimens, improving access to anti-HCV therapy has become a worldwide priority. However, many obstacles remain that reduce global benefit from the new IFN-free, ribavirin-free combination regimens. They include the numbers of infected individuals, the cost of biological tests, the amount of information needed to inform treatment decisions, and the relative complexity of the treatment strategies shown in the previous chapter.

The availability of new pangenotypic regimens now provides healthcare practitioners worldwide with the opportunity to considerably simplify, and thereby facilitate, treatment access while reducing its cost. Indeed, the use of sofosbuvir/velpatasvir or glecaprevir/pibrentasvir for 12 weeks in all patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, including treatment-naïve or treatment-experienced patients (as defined above) is expected to yield an SVR12 rate above 95%. The only information needed to start treatment with one of these regimens is the presence of HCV replication (as assessed by HCV RNA or HCV core antigen testing, as described above) and possible drug-drug interactions. The presence of advanced fibrosis (F3) or cirrhosis (F4) must be checked prior to therapy as it will determine whether the patient needs post-treatment surveillance for HCC, provided that treatment for HCC is available. A simple non-invasive marker score, such as FIB-4 or APRI, can be used for that purpose (see above, Table 2). A universal duration of 12 weeks ensures that this information is not needed to choose the treatment regimen. However, if the information is available and reliable, the combination of glecaprevir and pibrentasvir can be used for 8 weeks instead of 12 weeks in treatment-naïve patients without cirrhosis.

Licensed generic drugs and drugs agreed with the Medicines Patent Pool have been shown to generate similar results to the original compounds.[113] The presence of the drug at the appropriate dosage must be verified by the provider and guaranteed to the prescriber and patient. Indeed, effective and safe generics are a crucial resource in resource-limited countries.

Recommendation

- Simplified, pangenotypic anti-HCV treatment recommendations are now possible, thanks to the approval of highly efficacious, safe and well-tolerated pangenotypic anti-HCV drug regimens (**B1**).
- Pre-treatment assessment can be limited to proof of HCV replication (presence of HCV RNA or of HCV core antigen in serum or plasma) and the assessment of the presence or absence of cirrhosis by means of a simple non-invasive marker (such as FIB-4 or APRI) that determines whether the patient needs post-treatment follow-up (**B1**).
- Treatment-naïve and treatment-experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis can be treated with either the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, or the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks without testing genotype (**B1**).
- If cirrhosis can be reliably excluded by means of a non-invasive marker in treatment-naïve patients, the combination of glecaprevir and pibrentasvir can be administered for 8 weeks only (**A1**).
- Generic drugs can be used, provided that quality controls are met and guaranteed by the provider (**A1**).
- Possible drug-drug interactions should be carefully checked and dose modifications implemented when necessary (**A1**).
- Given the high SVR12 rates expected with these regimens across all groups of patients if adherent, checking SVR12 12 weeks after the end of treatment is dispensable (**B1**).
- Patients with high-risk behaviours and risk of reinfection should be tested for SVR12 and yearly thereafter whenever possible (**B1**).
- In patients with advanced fibrosis (F3) or compensated cirrhosis (F4), post-SVR surveillance for the diagnosis of HCC and linkage to care must be provided when treatment for HCC is available (**A1**).

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, DAA-based regimens are the most suitable options for patients with decompensated (Child-Pugh B or C) liver disease. Protease inhibitors are contraindicated for this group.

Recommendations

- 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, safety and tolerability (**A1**).
- Protease inhibitor-containing regimens are contraindicated in patients with decompensated (Child-Pugh B or C) cirrhosis (**A1**).

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

Liver transplantation is the treatment of choice for patients with end-stage liver disease. Hepatitis C recurrence because of graft infection is universal after transplantation in the absence of prevention,[114] and the life of the graft and survival are reduced in patients with recurrent hepatitis C.

Treatment of HCV infection pre-transplant in patients awaiting liver transplantation has two complementary goals: preventing liver graft infection after transplantation by achieving viral clearance, and stabilising or improving liver function before transplantation. In some regions, treatment of HCV infection increases access to marginal grafts which may not be made available to patients with ongoing HCV infection. Prevention of liver graft infection substantially facilitates post-transplant

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management. In addition, improvement of liver function denotes delisting of some patients.[115] However, with the exception of living-donor grafts, the duration of antiviral therapy is unpredictable in a patient on the waiting list, so the patient may be transplanted before the virus has been cleared. In addition, if delisted, the patient will keep a diseased liver with the risk of subsequent decompensation, HCC occurrence and death, potentially foregoing the opportunity to cure the liver disease and the infection, because cure of HCV infection can be achieved by therapy in the vast majority of patients after transplantation.

The use of protease inhibitors is contraindicated in patients with Child-Pugh B and C decompensated cirrhosis, because of substantially higher drug exposure, which is associated with toxicities in these patients. Protease inhibitors should also not be used in patients with compensated cirrhosis and a history of prior decompensation, as cases of decompensation have been reported on treatment.[116] Thus, treatment of patients with decompensated cirrhosis on the transplant list should be based on the combination of sofosbuvir and an NS5A inhibitor, namely sofosbuvir/ledipasvir or sofosbuvir/velpatasvir. If these regimens are not available, the combination of sofosbuvir and daclatasvir remains an acceptable option, according to the EASL Recommendations for Treatment of Hepatitis C 2016.[54]

In the SOLAR-1 trial, patients infected with genotype 1 or 4 with decompensated cirrhosis were treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 or 24 weeks with ribavirin. In Child-Pugh B patients, the SVR12 rates were 87% (26/30) and 89% (24/27) after 12 and 24 weeks of therapy, respectively; in Child-Pugh C patients, they were 86% (19/22) and 87% (20/23) after 12 and 24 weeks of therapy, respectively. The MELD and Child-Pugh scores improved in approximately half of treated patients.[55] The design of the SOLAR-2 trial was identical in patients infected with genotype 1 or 4 with decompensated cirrhosis who received the same treatment regimens. The SVR12 rates were 87% (20/23) and 96% (22/23) after 12 and 24 weeks of therapy, respectively, in Child-Pugh B patients; they were 85% (17/20) and 78% (18/23) after 12 and 24 weeks of therapy, respectively, in Child-Pugh C patients. The MELD and Child-Pugh scores improved in approximately half of treated patients.[56] The lower SVR rates in patients with decompensated cirrhosis as compared to patients with compensated cirrhosis in other studies were due to treatment discontinuations rather than virological failures. Despite the early improvement in MELD score, long-term data are limited to determine whether SVR is associated with clinical improvement in these patients.

In a real-world study based on the United Kingdom early access program, patients with decompensated cirrhosis infected with HCV genotype 1 were treated with sofosbuvir and ledipasvir, or with sofosbuvir and daclatasvir, for 12 weeks with or without ribavirin. The SVR12 rates were: 85% (11/13) after 12 weeks of sofosbuvir and ledipasvir without ribavirin; 91% (136/149) after 12 weeks of sofosbuvir and ledipasvir with ribavirin; 50% (2/4) after 12 weeks of sofosbuvir and daclatasvir without ribavirin; and 88% (30/34) after 12 weeks of sofosbuvir and daclatasvir with ribavirin. However, in patients with decompensated cirrhosis infected with genotype 3, the SVR12 rates were 60% (3/5) after 12 weeks of sofosbuvir and daclatasvir without ribavirin and 71% (75/105) after 12 weeks of sofosbuvir and daclatasvir with ribavirin.[117] Approximately one-third of patients improved their MELD scores, one-third had no change, and one-third suffered deteriorating liver function 12 weeks after treatment. Improvement in MELD score was more frequent in treated than in untreated patients. The proportion of patients with at least one decompensating event during the study period (baseline to week 12 post-treatment) was reduced in the treated compared to untreated group, apart from the subgroup with a baseline MELD score ≥15. Rates of new decompensation in patients with recompensated disease at baseline were significantly lower in the treated cohort (4% *vs.* 10%).[117] Longer-term follow-up of the same group of patients confirmed that treatment was clinically beneficial in patients with advanced liver disease.[118]

When considering the two SOLAR studies and the United Kingdom early access program study together, the proportion of patients who substantially improved their MELD scores after achieving SVR was modest. Only 24% (10/42) of patients with Child-Pugh B and 38% (13/34) of patients with Child-Pugh C cirrhosis had a MELD score improvement ≥3 points 12 weeks after the end of treatment when pooling results from SOLAR-1 and SOLAR-2. These results were comparable to those found in the United Kingdom early access program real-world study, showing MELD score improvements in only 17% (15/88) and 33% (3/9) of patients with Child-Pugh B and C cirrhosis, respectively.[119]

In the ASTRAL-4 study, patients with Child-Pugh B decompensated cirrhosis infected with genotypes 1 to 4 were randomized to receive the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, for 12 weeks with weight-based dosed ribavirin, or for 24 weeks without ribavirin. The SVR12 rates with these three treatment regimens, respectively, were: 88% (44/50), 94% (51/54) and 93% (51/55) in patients with genotype 1a infection; 89% (16/18), 100% (14/14) and 88% (14/16) in patients with genotype 1b infection; 100% (4/4), 100% (4/4) and 75% (3/4) in patients with genotype 2 infection; 50% (7/14), 85% (11/13) and 50% (6/12) in patients with genotype 3 infection; 100% (4/4), 100% (2/2) and 100% (2/2) in patients with genotype 4 infection. No arm with sofosbuvir, velpatasvir and ribavirin for 24 weeks was included in the study.[120] Of the patients with a baseline MELD score <15, 51% (114/223) had an improved MELD score at week 12 post-treatment, 22% (49/223) had no change in their MELD score, and 27% (60/223) had a worse MELD score. Of the patients who had a baseline MELD score ≥15, 81% (22/27) had an improved MELD score, 11% (3/27) had no change in their MELD score, and 7% (2/27) had a worse MELD score.[120] In these studies, the median MELD score improvement was 2 points (range: 1–17), not always followed by clinical improvement. Importantly, data are almost non-existent for patients with the most advanced forms of disease (Child-Pugh score >12 or MELD score >20), who were excluded from the studies.

Several studies assessed whether achieving an SVR prior to liver transplantation would lead to patients being removed from the transplantation list. In a multicentre European real-world study of patients receiving IFN-free, DAA-based therapy followed for a median duration of 52 weeks (interquartile range 33–67), 40% (41/103) of patients were transplanted, whereas only 20% (21/103) were delisted and an additional 13% (13/103) were put on hold. Patients with lower MELD scores were more likely to be delisted, while the median MELD score evolved from 15.5 to 14.0 ($p = 0.0008$) from start of DAA therapy to 24 weeks afterwards.[58] Among the 23.9% of patients who were delisted because of clinical improvement and followed-up for a median duration of 58 weeks, only 8.8% (3/34) had to be relisted because of re-decompensation. No HCC occurred.[121]

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In a French cohort study, including 18 transplant centres with a mean follow-up of 68 weeks (range: 12–95 weeks), 18% of patients (14/77) were delisted and 16% (12/77) improved.[57] In a similar Spanish study, 24% (29/122) of patients were delisted after DAA-based therapy. No patients with a baseline MELD score >20 were delisted.[60] Overall, the short-term benefits observed must be balanced with the respective risks of death on the waiting list and likelihood of transplantation. A recent US study combining real data and modelling suggested that treating HCV before instead of after liver transplantation would only increase life expectancy in patients with a MELD score ≤23–27, depending on the United Network for Organ Sharing region. Above a MELD score of 20, the life expectancy benefit of treating before liver transplantation in the model was always less than one year, arguing for transplanting individuals with very severe disease prior to HCV therapy.[59] Finally, pre-liver transplantation treatment was reported to be cost-effective for patients without HCC with a MELD score ≤20, while antiviral treatment after liver transplantation was cost-effective in patients with a MELD score >20.[122]

Recommendations

- Patients with decompensated (Child-Pugh B or C) cirrhosis should be treated in experienced centres with easy access to liver transplantation and close monitoring during therapy is required, with the possibility of stopping therapy with evidence of worsening decompensation during treatment (**A1**).
- Patients with decompensated (Child-Pugh B or C) cirrhosis, without HCC, awaiting liver transplantation with a MELD score <18–20 should 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 SVR on liver function, because significant improvement in liver function may lead to delisting in selected cases (**A1**).
- Protease inhibitors-containing regimens are contraindicated in patients with decompensated (Child-Pugh B or C) cirrhosis (**A1**).
- Patients with decompensated (Child-Pugh B or C) cirrhosis, without HCC, awaiting liver transplantation with a MELD score <18–20 can be treated with sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6), or with sofosbuvir and velpatasvir (all genotypes), with daily weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) for 12 weeks (**A1**).
- In patients with decompensated (Child-Pugh B or C) cirrhosis without HCC awaiting liver transplantation with a MELD score <18–20 treated with sofosbuvir and ledipasvir with ribavirin, or with sofosbuvir and velpatasvir with ribavirin, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance (**B1**).
- Patients with decompensated (Child-Pugh B or C) 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), or the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), for 24 weeks without ribavirin (**A1**).
- The higher risk of adverse events reported in patients with decompensated cirrhosis awaiting liver transplantation necessitates appropriately frequent clinical and laboratory assessments during and after HCV therapy (**B1**).
- 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 (**B2**).

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

In patients with HCC, without cirrhosis or with compensated cirrhosis, who have an indication for liver transplantation, the ideal timing for antiviral therapy (before or after liver transplantation) remains debated.[123,124] Lower SVR rates were reported in patients with HCC treated with regimens including sofosbuvir, sofosbuvir and ledipasvir, or ombitasvir and ritonavir-boosted paritaprevir plus dasabuvir, with or without ribavirin, than in patients without HCC or in patients with HCC treated after liver transplantation (74% *vs.* 91% and 94%, respectively).[125] Post-liver transplantation treatment of HCV was reported to be cost-effective in patients with HCC.[122] In patients with HCC, without cirrhosis or with compensated cirrhosis, who have an indication for liver transplantation, pre- or post-liver transplant antiviral treatment indications are similar to those in patients who do not have HCC, and depend on the HCV genotype, prior therapy and severity of liver disease (see general recommendations).

Recommendations

- In patients with HCC awaiting liver transplantation with an HCV infection, liver transplantation must be considered as the main therapeutic goal and the antiviral treatment decision must be made on a case-by-case basis through a multidisciplinary discussion (**A1**).
- Antiviral treatment can be initiated before liver transplantation to prevent recurrence of infection and post-transplant complications, provided that it does not interfere with the management of the patient on the waiting list (**A2**).
- Antiviral treatment can be delayed until after transplantation, with a high likelihood of SVR (**A2**).
- Patients with HCC without cirrhosis or with compensated (Child-Pugh A) cirrhosis awaiting liver

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transplantation should be treated, prior to or after liver transplantation, according to the general recommendations in patients without HCC (**A1**).

Post-liver transplantation recurrence

Recurrence of HCV infection is universal in patients with detectable HCV RNA at the time of liver transplantation.[114] The course of HCV-related liver disease is accelerated in liver transplant recipients and approximately one-third of them develop cirrhosis within 5 years following transplantation.[126–129] Overall, graft survival is 30% lower in HCV-infected compared to non-HCV-infected liver transplant recipients, because of recurrent HCV disease, but also extra-hepatic manifestations of HCV infection, management issues and complications of immunosuppression. Cure of HCV infection following liver transplantation has been shown to significantly improve post-transplant survival.[130,131] Patients with fibrosing cholestatic hepatitis and patients with moderate to extensive fibrosis or portal hypertension one year after transplantation are at high risk of graft loss, and require urgent antiviral therapy.[132,133]

In the SOLAR-1 trial, transplant recipients with HCV genotype 1 or 4 recurrence were treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 or 24 weeks with ribavirin. In patients treated for 12 weeks with ribavirin, the SVR12 rates were 96% (53/55) in those without cirrhosis, 96% (25/26) in those with compensated (Child-Pugh A) cirrhosis, 85% (22/26) in those with decompensated Child-Pugh B cirrhosis, and 60% (3/5) in those with Child-Pugh C decompensated cirrhosis. The SVR12 rates were not higher in patients treated for 24 weeks with ribavirin: 98% (55/56), 96% (24/25), 88% (23/26), and 75% (3/4), respectively.[55] Similar results were reported in the SOLAR-2 study in patients with genotype 1 receiving the same treatment regimens. In patients treated for 12 weeks with ribavirin, the SVR12 rates were 93% (42/45) in patients without cirrhosis, 100% (30/30) in those with compensated (Child-Pugh A) cirrhosis, 95% (19/20) in those with Child-Pugh B decompensated cirrhosis, and 50% (1/2) in those with Child-Pugh C decompensated cirrhosis. In patients treated for 24 weeks, the SVR12 rates were: 100% (44/44), 96% (27/28), 100% (20/20), and 80% (4/5), respectively. Twenty-five of the 27 patients infected with genotype 4 (93%) achieved SVR12.[56]

In another study, liver transplant recipients with HCV recurrence were treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin. The global SVR12 rate was 96% (76/79; 2 relapses). One genotype 1a patient out of 15 and one genotype 3 patient out of 35 relapsed.[134]

A number of real-world studies reported high SVR rates after treating liver transplant recipients with HCV recurrence with the combination of sofosbuvir and ledipasvir with or without ribavirin. Whether ribavirin is needed in all patients after liver transplantation in combination with sofosbuvir and ledipasvir, or with sofosbuvir and velpatasvir, remains to be determined.

Because of frequent drug-drug interactions and the need for immunosuppressant drug dose adjustments, treatment regimens including a protease inhibitor are not optimal for HCV treatment post-liver transplantation. However, in liver transplant recipients with impaired kidney function, the combination of glecaprevir and pibrentasvir for 12 weeks is an alternative to sofosbuvir-based regimens. In the MAGELLAN-2 study, 80 liver and 20 kidney transplant recipients on a stable immunosuppressive regimen were included. Prednisone/prednisolone was permitted at ≤10 mg/day and cyclosporine A at ≤100 mg/day at the time of screening. All but one patients achieved SVR12.[135]

Recommendations

- 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 stabilised (generally after the first 3 months post-transplant), because the SVR12 rates diminish in patients with advanced post-transplant liver disease (**A1**).
- Fibrosing cholestatic hepatitis or the presence of moderate to extensive fibrosis or portal hypertension one year after transplantation indicate urgent antiviral treatment because they predict rapid disease progression and graft loss (**A1**).
- Immunosuppressant drug levels during and after anti-HCV therapy must be monitored (**A1**).
- Patients with post-transplant HCV recurrence without cirrhosis, with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis can be treated with the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), or with the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes) (**A1**).
- Patients with post-transplant recurrence of HCV genotype 1, 4, 5 or 6 infection, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and ledipasvir or the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, without the need for pre-treatment immunosuppressant drug dose adjustments (**A1**).
- Patients with post-transplant recurrence of HCV genotype 2 or 3, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, without the need for pre-treatment immunosuppressant drug dose adjustments (**A1**).
- Patients with post-transplant recurrence of all HCV genotypes, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, with an eGFR <30 ml/min/1.73 m^2 can be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks. Immunosuppressant drug levels need to be monitored and adjusted as needed during and after the end of treatment (**B1**).
- Patients with post-transplant HCV recurrence with decompensated (Child-Pugh B or C) cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), or with the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), for 12 weeks with daily weight-based ribavirin (1,000 or 1,200 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 (**B1**).

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- Patients with decompensated (Child-Pugh B or C) cirrhosis and contraindications for ribavirin, or with poor tolerance to ribavirin on treatment, should be treated with the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6) or the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes) for 24 weeks without ribavirin (**B1**).

Patients with decompensated cirrhosis without an indication for liver transplantation

The main goal of anti-HCV therapy in patients with decompensated (Child-Pugh B or C) cirrhosis not on a transplant waiting list is to achieve improvement in liver function and survival. Several studies have demonstrated acceptably high SVR rates, equivalent in Child-Pugh B and C patients, in individuals with decompensated cirrhosis, together with an effect of therapeutic viral clearance on liver function, with significant improvements in bilirubin, albumin and international normalized ratio values and, as a result, in MELD and Child-Pugh scores in one-third to half of patients.[55,56,120,136,137] Similar results were reported in real-world studies.[57,58,117,121,138,139] Patients with Child-Pugh B cirrhosis benefited more from viral clearance in terms of adverse event-free survival at 15 months than those with Child-Pugh C cirrhosis.[117] The results of these studies were summarised earlier. Long-term clinical follow-up data are lacking.

Recommendations

- Patients with decompensated (Child-Pugh B and Child-Pugh C up to 12 points) cirrhosis not on the waiting list for liver transplantation and without concomitant comorbidities that could impact their survival should be treated urgently (**A1**).
- Protease inhibitors-containing regimens are contraindicated in patients with Child-Pugh B or C decompensated cirrhosis (**A1**).
- Patients with decompensated cirrhosis, not on the waiting list for liver transplantation, can be treated with the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6) or the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes) with daily weight-based ribavirin (1,000 or 1,200 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 should be treated with sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6) or with sofosbuvir and velpatasvir (all genotypes) for 12 weeks with ribavirin (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation with contraindications for ribavirin, or with poor tolerance to ribavirin on treatment, can receive the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), or the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes) for 24 weeks without ribavirin (**B2**).
- The higher risk of adverse events reported in patients with decompensated cirrhosis necessitates appropriately frequent clinical and laboratory assessments during and after HCV therapy (**B1**).

Patients with treated HCC without an indication for liver transplantation

HCV is a leading cause of HCC worldwide and the morbidity and mortality from HCV-associated HCC is increasing, especially in high-income areas. HCC occurs at an annual rate of 1–7% in patients with cirrhosis, but there is considerable heterogeneity in risk. The risk is related to the severity of fibrosis, gender, age, diabetes and alfa-foetoprotein level at treatment among other factors. An SVR has been shown to be associated with a reduction in all-cause mortality, liver mortality and a reduction in the risk of incident (*de novo*) HCC. The risk of HCC is not, however, eliminated by an SVR. DAA-based treatments in patients with cirrhosis have resulted in significant numbers of patients requiring follow-up. Several large cohort studies and meta-analyses have examined the relationship between SVR and reduction in the risk of HCC. They show that SVR is associated with a substantial reduction in the incidence of HCC in the mid- to long-term.[8,15,140–142] Substantial databases have also examined the risk and determinants of HCC patients cured with DAA-based treatments. In a retrospective cohort study, the outcome was examined in 17,836 HCV-positive patients treated with DAAs (SVR in 66.6% and 96.2% of patients treated with IFN- or DAA-based therapies, respectively) in Veterans Administration hospitals. Compared with patients without SVR, those with SVR had a significantly reduced *de novo* HCC risk.[143]

IFN has been shown to improve outcomes following ablation or resection of HCC. Whether the high rates of SVR achieved with new IFN-free regimens have an effect on the risk of recurrence following resection or ablation of HCC is currently debated. Indeed, unexpectedly frequent early HCC recurrence with a more aggressive course was reported in two retrospective studies in patients with HCV-related HCC who underwent curative procedures and were subsequently treated with IFN-free regimens and cured from HCV in most cases.[144,145] The statistical analysis has been examined and the data criticised. Definite estimate of the likelihood of HCC recurrence is difficult due to the high clinical biological and epidemiological heterogeneity of HCC. Using HCC treatment as a starting point (rather than DAA initiation), the actual probability by Kaplan-Meier of developing HCC recurrence at 6 and 12 months was 7% and 13%, at variance with the reported crude rate of 27%.[146] Because of the small number of patients, the retrospective character of the studies and the lack of control arms, the authors concluded that their observation should be taken as a note of caution and should prime a larger scale assessment.

Contradictory results were then published by other groups. At the time of writing these recommendations, several studies suggest an increase in HCC recurrence or *de novo* incidence after DAA-induced SVR,[144,145,147–150] whereas others do not report any change.[118,151–164] The most scientifically rigorous evaluation of HCC risk from DAA-based therapy would be randomized controlled trials among patients with cirrhosis (for occurrence

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risk) and patients with HCC following curative HCC management (for recurrence risk). However, such trials would raise important ethical concerns. A considerable body of data suggests that incident HCC is reduced by a DAA-induced SVR. A larger prospective study with appropriate risk stratification and longer-term follow-up would be needed to enable more accurate estimates of HCC recurrence risk and overall outcome in treated HCC, following DAA-based therapy. As hepatic decompensation is a major driver of death in patients with HCC, and liver function can improve in patients with cirrhosis, currently withholding treatment for HCV-positive patients with treated HCC is not warranted. However close surveillance and imaging is required in these patients.

Recommendations

- HCV treatment should not be withheld in patients with cirrhosis and these patients will require post-SVR HCC surveillance, because the risk of *de novo* or incident HCC is reduced but not abolished by SVR (**A1**).
- Whether antiviral therapy leads to a long-term survival benefit by reducing the risk of recurrent HCC in patients with treated HCV-associated HCC is unknown. However, these patients frequently have advanced fibrosis or cirrhosis and should receive appropriate antiviral therapy for their liver disease, while careful HCC surveillance is required in these patients (**B1**).

Treatment of special groups

HBV coinfection

In patients with HCV-HBV coinfection, the HBV DNA level is often low or undetectable, although it may fluctuate widely, and HCV is usually the main driver of chronic inflammatory activity. Patients should be carefully characterized for the replicative status of both HBV and HCV, and the presence of hepatitis D virus infection should be ascertained. When HCV RNA is present, HCV infection should be treated following the same rules as applied to HCV monoinfected patients.

There is a potential risk of HBV reactivation during or after HCV clearance, but the risk is unpredictable.[165,166] In a prospective study in 111 Taiwanese patients with HBV-HCV coinfection, defined as having detectable HBs antigen and HCV RNA, 100% of patients achieved SVR with the combination of sofosbuvir and ledipasvir for 12 weeks. Approximately two-thirds of them had an increase in the HBV DNA level not associated with signs or symptoms. Only 5 patients experienced a serum ALT increase of more than twofold the upper limit of normal and HBV treatment had to be initiated in 2 cases.[167]

Patients commencing DAA-based treatment for hepatitis C should be tested for HBs antigen, anti-HBc antibodies and anti-HBs antibodies. If HBs antigen is present, concurrent HBV nucleoside/nucleotide analogue therapy is indicated. In HBs antigen-negative, anti-HBc antibody-positive patients, serum ALT levels should be monitored, and both HBs antigen and HBV DNA should be tested if ALT levels do not normalise or rise during or after anti-HCV therapy. Monitoring of serum ALT levels is indicated in anti-HBs and anti-HBc antibody-positive patients.

Recommendations

- Patients with HBV-HCV coinfection should be treated with the same anti-HCV regimens, following the same rules as HCV monoinfected patients (**B1**).
- Patients coinfected with HCV and HBV fulfilling the standard criteria for HBV treatment should receive nucleoside/nucleotide analogue treatment according to the EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection (**A1**).
- Patients who are HBs antigen-positive should receive nucleoside/nucleotide analogue prophylaxis at least until week 12 post anti-HCV therapy and be monitored monthly if HBV treatment is stopped (**B1**).
- In patients who are HBs antigen-negative but anti-HBc antibody-positive, serum ALT levels should be monitored monthly, HBs antigen and HBV DNA should be tested if ALT levels do not normalise or rise during or after anti-HCV therapy, and nucleoside/nucleotide analogue therapy should be initiated if HBs antigen and/or HBV DNA are present (**B1**).
- HBs antigen-negative, anti-HBc antibody-positive patients undergoing anti-HCV treatment should be monitored monthly for ALT and tested for HBs antigen and HBV DNA in case of ALT elevation (**B1**).

Immune complex-mediated manifestations of chronic hepatitis C

Several severe systemic immune complex-mediated manifestations of chronic HCV infection have been described. Mixed cryoglobulinemia associated with clonal B lymphocyte expansion may cause a systemic vasculitis, in which multiple organs are involved as a result of vascular deposition of immune complexes. The treatment of mixed cryoglobulinemia relies on causal (antiviral) therapy and/or immunosuppressive therapy. Recent studies suggested that SVR induced by IFN-free regimens was associated with improvement of the clinical manifestations of mixed cryoglobulinemia.[168–174] Rituximab, an anti-CD20 monoclonal antibody, has been used for both skin and organ involvement.

There is a significant association between persistent hepatitis C and B-cell non-Hodgkin lymphoma. Diffuse large B-cell lymphoma is the most common. The disease is treated with standard-of-care R-CHOP regimens; the outcome with rituximab appears to be enhanced, although rituximab may enhance viral replication. Cases have been reported showing regression of low-grade lymphomas following SVR with an IFN-free regimen.[175–177] In a recent study, antiviral treatment with DAAs was found to be an independent predictor of disease-free survival when combined with specific chemotherapy.[178]

The association of chronic HCV infection and chronic renal disease is well established.[179] A spectrum of histopathological lesions has been reported, but the most frequent is type I membrano-proliferative glomerulonephritis, usually in the context of type II mixed cryoglobulinemia. Focal segmental glomerulosclerosis, vasculitic involvement and interstitial nephritis may also occur. Therapeutic approaches for HCV-associated renal disease include antiviral therapy, rituximab, plasma exchange,

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corticosteroids and cyclophosphamide. It is possible that the effective and rapid antiviral response observed with IFN-free antiviral regimens will improve outcome, although this is unproven. Some evidence exists for a benefit with rituximab in the management of HCV-induced renal disease. An interdisciplinary approach is recommended.

Recommendations

- Mixed cryoglobulinemia and renal disease associated with chronic HCV infection must be treated with IFN-free, ribavirin-free DAA-based anti-HCV combinations, according to the above recommendations. Careful monitoring for adverse events is mandatory (**B1**).
- The indication for rituximab in HCV-related renal disease must be discussed by a multidisciplinary team (**B1**).
- HCV-associated lymphoma should be treated with IFN-free, ribavirin-free regimens according to the above recommendations, in combination with specific chemotherapy, taking into account possible drug-drug interactions (**B1**).

Patients with renal impairment, including haemodialysis patients

HCV infection is prevalent in patients with renal impairment, including those with severe renal impairment (eGFR <30 ml/min/1.73 m^2) and those with end-stage renal disease who require haemodialysis or peritoneal dialysis. Diverse groups of patients with renal disease require consideration when treatment of hepatitis C is indicated. These include patients with chronic kidney disease (CKD) stage 4 with severely reduced renal function (eGFR = 15–29 ml/min/1.73 m^2) or those with CKD stage 5 (eGFR <15 ml/min/1.73 m^2 or on dialysis); post-renal transplant patients; patients with cirrhosis with renal impairment (chronic renal disease, hepatorenal syndrome, acute kidney injury, acute-on-chronic liver failure); post-liver transplant patients with calcineurin-induced renal impairment; or patients with mixed essential cryoglobulinemia with renal damage. In some of these groups, renal function could potentially improve with antiviral treatment. However, organ recovery may be delayed after an SVR in patients with cryoglobulinemia.[169] In the haemodialysis population, HCV infection is associated with an increased risk of all-cause and liver-related mortality. However, cardiovascular disease remains the main cause of death in dialysis patients irrespective of HCV status.

In patients with mild to moderate renal impairment (eGFR ≥30 ml/min/1.73 m^2), no dose adjustments are necessary for any of the approved DAA combinations. These patients should therefore be treated according to the general recommendations provided earlier.

In patients with severe renal dysfunction (eGFR <30 ml/min/1.73 m^2), the safety of sofosbuvir-based regimens has been questioned. Sofosbuvir is eliminated mainly by the renal route and its use in patients with CKD stage 4 or 5, or requiring haemodialysis, is out of the licence recommendations. Concerns have been raised because of the substantially higher concentrations of sofosbuvir and, most importantly, of its renally excreted metabolite GS-331007 in patients with renal impairment compared to those without (+103% and +501% AUC_T, respectively).[62] HCV-infected patients with CKD stage 4 or 5 were treated with sofosbuvir-based regimens when no other options were available and treatment was needed, without deterioration of their renal function in the majority of cases.[180] However, in the TARGET 2.0 real-world cohort study, progressive deterioration of renal function and renal symptoms were reported in patients with severe renal impairment receiving a sofosbuvir-based regimen, although efficacy was comparable to that observed in patients without renal impairment.[181] In patients with end-stage renal disease on haemodialysis, the concentrations of GS-331007 were 10-fold higher one hour before dialysis and 20-fold higher one hour after dialysis than in patients with normal renal function.[182] In another study, sofosbuvir and GS-331007 did not accumulate in patients undergoing haemodialysis.[61] Overall, the appropriate therapeutic dose of sofosbuvir in patients with advanced or end-stage renal disease has not been established.

Thus, patients with severe renal impairment, or those with end-stage renal disease on haemodialysis, should be treated for their HCV infection, and sofosbuvir-free regimens must be preferred. If there is no other choice than a sofosbuvir-based regimen, close monitoring is required and treatment should be rapidly interrupted if renal function deteriorates. For patients on dialysis, who already have end-stage renal disease, the optimal timing of treatment is an important consideration, *i.e.* pre- or post-renal transplantation if they are candidates for renal transplantation, while the risks *vs.* the benefits must be considered if renal transplantation is not possible.

Several clinical trials confirmed the efficacy and safety of sofosbuvir-free regimens in patients with severe renal impairment. In the RUBY-1 study, patients infected with genotype 1 without cirrhosis, with stage 4 or 5 CKD, were treated for 12 weeks with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir. The seven patients infected with genotype 1b were treated without ribavirin and all of them achieved SVR.[183]

In the C-SURFER trial, 122 patients infected with HCV genotype 1 (including 6% with cirrhosis) with stage 4 or 5 CKD, including 75% on haemodialysis, were treated with grazoprevir and elbasvir for 12 weeks without ribavirin. The SVR12 rate was 94% (115/122), with only one virological failure. The most common adverse events were headache, nausea, and fatigue, occurring at similar frequencies in patients receiving grazoprevir and elbasvir and in the deferred treatment group receiving placebo. The frequencies of renal system adverse events were comparable between treatment groups.[184] The safety and efficacy data for the treatment phase of the deferred treatment group has been reported, with an SVR rate of 98% (97/99).[185] A real-world study using the same regimen in American patients with various stages of CKD showed SVR was achieved in 97% (758/781) of patients with stage 3 and in 96% (714/747) of patients with stage 4 or 5 CKD.[186]

EXPEDITION-4 was a phase III trial conducted in patients with stage 4 or 5 CKD treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks. Among the 104 patients, 23 were infected with genotype 1a, 29 with genotype 1b, 2 with another genotype 1 subtype, 17 with genotype 2, 11 with genotype 3, 20 with genotype 4, 1 with genotype 5 and 1 with genotype 6. Twenty patients (19%) had compensated cirrhosis and 42% were treatment-experienced. The SVR12 rate was 98% (102/104), with both patients who did not achieve SVR having a non-virological failure.[187] An integrated analysis

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of phase II and III studies in which glecaprevir and pibrentasvir were administered for 12 weeks in 2,238 patients infected with genotypes 1 to 6 showed an overall SVR rate of 98% (2,188/2,238), with no difference between patients with CKD stage 1–3 (98%; 2,087/2,135) or stage 4–5 (98%; 101/103).[188]

HCV-associated liver damage may be accelerated by immunosuppression. For this reason, antiviral therapy should be considered for all haemodialysis patients who will be candidates for renal transplantation. Studies showing high efficacy and safety of IFN-free anti-HCV regimens in kidney transplant recipients suggest that these patients can be transplanted and treated for their HCV infection after kidney transplantation with a high probability of cure.[189–193] Decisions regarding timing of HCV treatment in relation to kidney transplantation should consider the type of donor (living or deceased), waiting list times by donor type, centre-specific policies for using or not kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis. If receiving a kidney from an HCV RNA-positive donor increases the chance of undergoing transplantation, the patient can be transplanted and treated for HCV infection after transplantation.[194]

Recommendations

- Patients with HCV infection and mild to moderate renal impairment (eGFR ≥30 ml/min/1.73 m^2) 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, only if an alternative treatment is not available, because no dose recommendation can currently be given for these patients (**B1**).
- Patients infected with all genotypes 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, should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 or 12 weeks, according to the general recommendations (**A1**).
- Patients infected with HCV genotype 1a and treatment-naïve patients infected with genotype 4 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 and with an HCV RNA level ≤800,000 IU/ml (5.9 Log_{10} IU/ml), can be treated with the combination of grazoprevir and elbasvir for 12 weeks (**A1**).
- Patients infected with HCV genotype 1b 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, can be treated with the combination of grazoprevir and elbasvir for 12 weeks, or with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks (**A1**).
- The risks *vs.* benefits of treating patients with end-stage renal disease and an indication for kidney transplantation before or after renal transplantation require individual assessment (**B1**).

Non-hepatic solid organ transplant recipients

HCV infection in kidney transplant recipients may be associated with an increased rate of liver fibrosis progression. Most cohorts of kidney transplant patients show that HCV positivity is associated with impaired renal graft and patient survival, particularly in patients with cirrhosis. Impaired graft survival partly reflects increased patient mortality. In addition, specific HCV-related causes such as glomerulonephritis and increased risk of diabetes will affect graft outcome. HCV positivity is associated with increased all-cause and liver-related mortality, though cardiovascular disease remains the main cause of patient death.[195] As cirrhosis is an important predictor of poor post-kidney transplant survival after kidney transplantation, it is advisable to assess the stage of liver fibrosis in all HCV-positive kidney transplant candidates.[115] For patients with established cirrhosis and portal hypertension who fail (or are unsuitable for) HCV antiviral treatment, combined liver and kidney transplantation must be considered.[196]

In a randomized clinical trial of patients who underwent renal transplantation, the fixed-dose combination of sofosbuvir and ledipasvir yielded SVR rates of 100% (57/57) and 100% (57/57) in patients infected with HCV genotype 1 or 4 treated for 12 or 24 weeks, respectively, without ribavirin. Treatment was well tolerated and no significant changes in eGFR were observed during and after treatment administration.[192] Other clinical trials and real-world studies reported high SVR rates and good safety in patients treated with various treatment regimens post-kidney transplantation.[189–191,193,197–200]

Data on HCV infection after heart transplantation are scarce and controversial, with studies showing unaltered or decreased survival rates in patients infected with HCV. Although the experience with DAAs in this setting is limited, the combinations of sofosbuvir with ledipasvir or daclatasvir were safe and effective in 12 patients with chronic HCV infection.[201] There is also limited experience with the treatment of lung transplant recipients, but sofosbuvir-based regimens appeared to be safe and efficacious in case reports.[202] No data are available on the impact of HCV infection and its treatment after pancreas or small bowel transplantation.

Experience accumulated with the treatment of liver transplant recipients suggests that organ recipients can be treated with the expectation of high SVR rates and acceptable safety. Combinations of sofosbuvir with an NS5A inhibitor, such as ledipasvir or velpatasvir, should be utilised because they do not require immunosuppressant drug dose adjustments. Patients with an eGFR <30 ml/min/1.73 m^2 can be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks, but immunosuppressant drug levels need to be adjusted as needed during and after the end of treatment.

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Recommendations

- Solid organ transplant recipients, including kidney, heart, lung, pancreas or small bowel recipients, should be treated for their HCV infection before or after transplantation, provided that their life expectancy exceeds one year (**A1**).
- Before kidney, heart, lung, pancreas or small bowel transplantation, patients on the waiting list can be treated according to the above general recommendations, according to the genotype, severity of liver disease and prior anti-HCV treatment (**A1**).
- After transplantation, solid organ transplant recipients, including kidney, heart, lung, pancreas or small bowel recipients should be treated with the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6) or with the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes) according to the general recommendations, without the need for immunosuppressant drug dose adjustments (**A1**).
- After transplantation, solid organ transplant recipients, including kidney, heart, lung, pancreas or small bowel recipients, with an eGFR <30 ml/min/1.73 m^2, can be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks. Immunosuppressant drug levels need to be monitored and adjusted as needed during and after the end of treatment (**B1**).

Recipients of an HCV-positive organ transplant

There is a huge disparity between the number of patients who need organ transplantation and the number of potential donors. Accepting grafts from anti-HCV antibody-positive, including HCV RNA-positive, donors increases access to organ transplantation. Anti-HCV antibody-positive donors that are HCV RNA-negative will increase substantially with the advent of highly efficacious DAA-based antiviral therapies.

In liver transplantation, HCV infection is generally transmitted when the donor is viremic. In contrast, transmission of HCV infection is unusual if the donor is anti-HCV antibody-positive, HCV RNA-negative. Rare cases of transmission have been reported, possibly because of acute infection in high-risk donors.[203] Data from the IFN era have shown that the use of infected liver grafts in HCV-positive recipients is safe and not associated with more frequent or more severe complications, except when the graft is from an old donor.[204] Thus, assessing graft quality is crucial when accepting anti-HCV antibody-positive grafts, through visual inspection and histological examination. New techniques, such as elastography or liquid biopsy, will become available for this purpose. Grafts with advanced fibrosis (F3) are declined, whereas those with no or mild fibrosis (F0-F1) are accepted. It is still unclear whether grafts with moderate fibrosis (F2) should be accepted for transplantation. Future data on fibrosis progression following early post-transplant therapy with new oral antivirals is needed before liberally accepting these grafts.

The use of anti-HCV antibody-positive organs has substantially increased since the approval of DAA-based combination regimens, although a substantial number of grafts are still discarded.[205] Some centres, particularly in areas with high HCV positivity rates in the context of the "opioid epidemic"[206] and high rates of mortality on the waiting list, have started using HCV RNA-positive livers into non-infected recipients, with good preliminary results. More safety data need to be generated in this setting. Meanwhile, the use of HCV-infected organs is an acceptable practice in patients at high risk of dying on the waiting list. In a recent study, a life expectancy benefit was observed in recipients with MELD scores ≥20, with the maximum benefit observed in those with a MELD score ≥28.[59] HCV-positive organs should not be offered to non-infected recipients with a MELD score <20 if access to anti-HCV therapy is not guaranteed.

Several studies have shown that transplantation of kidneys from HCV-positive donors into HCV-positive recipients reduces the waiting time, but is associated with a slightly increased risk of death, graft loss and severe liver disease compared to transplantation of HCV-negative kidneys. However, HCV-positive recipients transplanted with HCV-positive kidneys have better survival than patients remaining on the waiting list. In contrast, transplantation of HCV-negative recipients with HCV-positive kidneys was shown to be detrimental, and was thus formally contraindicated during the IFN treatment era. These policies may change with the availability of all-oral DAA-based therapies. Indeed, in a trial including 10 kidney transplant candidates transplanted with HCV genotype 1-infected kidneys, the median time on the waiting list before entering the trial once eligible was very short (58 days, interquartile range: 53–100) and all recipients achieved SVR after DAA-based treatment, with acceptable graft function at 6 months of follow-up.[194]

An informed consent must be signed by the recipient before transplanting an organ from a donor positive for anti-HCV antibodies, whether HCV RNA-positive or -negative.

Recommendations

- Organs from anti-HCV antibody-positive, HCV RNA-positive donors can be transplanted to HCV RNA-positive recipients (**B1**).
- The use of anti-HCV antibody-positive, HCV RNA-positive organs for HCV RNA-negative recipients is possible, provided that it is allowed local regulations, rigorous informed consent is obtained, and rapid post-transplant DAA therapy is guaranteed (**C2**).
- The use of liver grafts with moderate (F2) or advanced (F3) fibrosis is not recommended (**B2**).

People who inject drugs and patients receiving opioid substitution therapy

People with a history of injecting drug use include former injectors who have ceased injecting and recent/current PWIDs.[207] Some people with a history of injecting drug use receive opioid substitution therapy (OST), *e.g.* methadone or buprenorphine, for the management of their opioid dependence. In Europe, two-thirds of the HCV burden is attributable to injecting drug use.[208] The prevalence of chronic HCV infection among people who recently injected drugs is approximately 40%.[209]

Recommendations for HCV testing in this population are based on the high prevalence of infection,[210,211] the demonstra-

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tion that awareness of their HCV status induces sustained protective behavioural changes,[212,213] the potential public health benefit of reducing transmission by treating current drug users,[214–218] and the proven benefits of care and treatment in reducing HCV-related morbidity and mortality.[4,219] Evidence supporting the frequency of testing is limited. Because of the high incidence of HCV infection in PWIDs[211,220,221] and the benefits outlined above, HCV testing should be performed at least annually and following a high-risk episode in PWIDs.

It has been shown that OST is associated with a 50% reduction in the risk of new HCV acquisition, and this effect is increased to 74% by the concomitant use of clean drug injecting equipment.[222] However, the global coverage of OST and needle and syringe programmes interventions is low.[223] A combination of prevention strategies, including HCV treatment as prevention, are critical to substantially reduce HCV transmission and prevalence in these populations, especially in settings with high existing harm reduction coverage.[224]

The goals of HCV treatment in PWIDs are to prevent the complications of chronic hepatic and extra-hepatic HCV-associated disease like in any other group of HCV-infected patients, but also to prevent onward transmission of HCV. Treatment uptake has been low in this group, especially when IFN was the backbone of therapy.[225,226]

Among patients receiving OST and those with recent injecting drug use, DAA therapy has been demonstrated to be safe and effective and does not require specific methadone or buprenorphine dose adjustment. However, monitoring for signs of opioid toxicity or withdrawal should be undertaken.[109,227]

Post hoc analyses of phase II and III trials of DAA therapy demonstrated similar SVR rates in patients receiving and not receiving OST, respectively.[228–232] The C-EDGE CO-STAR trial randomized patients on OST infected with HCV genotype 1 or 4 to immediate treatment with grazoprevir and elbasvir or to deferred treatment. People with recent drug use were eligible for inclusion. SVR12 was achieved in 92% (184/201; 7 relapses, 5 reinfections) of patients in the immediate treatment arm compared to 90% (85/95; one virological breakthrough, one relapse, no reinfection) of patients in the deferred treatment arm.[109] The overall SVR12 rate was 91% (269/296), with similar efficacy and treatment adherence as in other phase III trials with the same combination regimen that excluded people with recent drug use.[83,84] Importantly, drug use at baseline (all drugs: 62%; non-cannabinoids: 47%) and during treatment (all drugs: 60%; non-cannabinoids: 47%) did not affect SVR or adherence.[109]

In the D3FEAT study, patients infected with HCV genotype 1 receiving OST and/or with recent injecting drug use (previous 6 months) received the combination of ombitasvir, ritonavir-boosted paritaprevir and dasabuvir with or without ribavirin for 12 weeks. Among the 87 participants (80% on OST, 58% with recent injecting drug use), 94% (82/87) completed 12 weeks of therapy and 91% (79/87) achieved SVR, with no virological failures. There was no impact of injecting drug use prior to or during therapy on SVR.[233]

Other studies evaluated the outcome of therapy in patients with recent injecting drug use. In a study of 174 participants who injected drugs in the last year, including 63% with compensated cirrhosis, 37% treatment-experienced, and 58% infected with genotype 1, 95% completed therapy and 93% (162/174) achieved SVR. There were 3 virological breakthroughs and one relapse.[234]

The SIMPLIFY study included only patients with recent (last 6 months) injecting drug use, receiving or not receiving OST. They were treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks. Study adherence was 94% and SVR 12 was obtained in 94% (97/103) of cases. There were no virological breakthroughs and one reinfection. Drug use within the month preceding the start of therapy was reported by 74 of patients. SVR12 in this subgroup was 96% and did not differ from that in patients who did not report drug use in the preceding month (94%). However, there were 4 deaths during the study period because of illicit drug overdose (5.0 per 100 person-years), highlighting the drug use comorbidity mortality risk in this population.[235] It is thus critical that HCV care in PWIDs be integrated within a framework that addresses drug-related harms, prevents overdose mortality, addresses social inequalities, and improves drug user health.

Real-world studies have confirmed the high rates of treatment completion (93%-100%), as well as the high SVR rates (80%-96%) in patients receiving OST.[236–243] In the German Hepatitis C registry study, SVR was lower in patients on OST than in those not receiving OST (85% and 91%, respectively), as a result of the higher rate of patients lost to follow-up in the former group. Thus, per-protocol SVR was similar in both groups (96% and 95%, respectively).[244]

The lack of treatment settings suitable for PWIDs is a major obstacle. Successful models have been multidisciplinary and often peer-supported in community-based clinics, drug treatment clinics, prisons, needle syringe programmes, supervised consumption rooms, specialized hospital-based clinics and primary care.[245]

HCV reinfection after treatment success has mostly been studied in patients who received IFN-based therapy.[246–251] The reinfection rates were in the order of 6 per 100 person-years of follow-up in patients who reported injecting drugs after the end of HCV treatment, and 2 per 100 person-years of follow-up among those who reported ever injecting drugs before.[249,250] After DAA treatment, the rate of persistent reinfections observed was 4.2 per 100 person-years in 74 patients included in the C-EDGE CO-STAR study who achieved SVR with grazoprevir and elbasvir and injected drugs post-SVR.[252] To date, no study had the power to identify risk factors for post-SVR reinfection, nor has any trial been conducted to explore the effect of interventions to reduce the risk of reinfection.

It is important to acknowledge without stigma that reinfection may occur. Thus, patients who injected drugs during the year preceding treatment should be offered ideally bi-annual, at least annual testing for reinfection after DAA-induced SVR. In addition, testing should be offered after particular episodes implying a high risk of reinfection. When reinfection is detected, a new course of HCV treatment should be offered, with a 3-month delay to allow for possible spontaneous clearance, except if urgent treatment is needed.

Aiming at eliminating HCV is crucial in PWIDs. Modelling suggests that such elimination can be achieved by scaling up treatment in this population.[253] The prevention benefits of treatment will be greatest when delivered in combination with OST and needle and syringes programmes.[254]

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Recommendations

- PWIDs should be routinely and voluntarily tested for anti-HCV antibodies and HCV RNA. PWIDs who are HCV RNA-negative should be tested for HCV RNA annually and following any high-risk injecting episode (**A1**).
- PWIDs should be provided with appropriate access to OST and clean drug injecting equipment as part of widespread comprehensive harm reduction programs, including in prisons (**A1**).
- All PWIDs who are infected with HCV have an indication for antiviral therapy, as DAA-based therapies are safe and effective in HCV-infected patients receiving OST, those with a history of injecting drug use and those who recently injected drugs (**A1**).
- HCV treatment should be offered to HCV-infected patients in prison (**B1**).
- Pre-therapeutic education should include discussions of HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk, and harm reduction strategies (**B1**).
- In patients on OST, DAA-based anti-HCV therapy does not require methadone or buprenorphine dose adjustment (**A1**).
- Harm reduction, education and counselling should be provided to PWIDs in the context of HCV treatment to prevent HCV reinfection following successful treatment (**B1**).
- Following SVR, monitoring for HCV reinfection ideally through bi-annual, at least annual HCV RNA assessment should be undertaken in PWIDs with an ongoing risk behaviour (**A1**).
- Retreatment should be made available, if reinfection is identified during post-SVR follow-up (**A1**).

Haemoglobinopathies and bleeding disorders

The most frequent haemoglobinopathy associated with chronic hepatitis C is thalassemia major, which requires frequent blood transfusions and is prevalent in countries where blood supply screening may be, or has been, suboptimal. Chronic HCV infection is also frequent in individuals with sickle cell anaemia, with a more rapid course of liver disease because of the concurrent iron overload.[255] Treatment has often been withheld in these patients because both pegylated IFN-α and ribavirin can cause anaemia.

Few trials with antiviral therapy have been published in this population, but there is no reason to consider that HCV DAAs are specifically contraindicated. For instance, in the C-EDGE IBLD study, the fixed-dose combination of grazoprevir and elbasvir was administered for 12 weeks without ribavirin in patients with haemoglobinopathies infected with genotypes 1a, 1b or 4. Approximately one patient out of four had cirrhosis. Patients with a haemoglobin level <7 g/dl were excluded. SVR12 was achieved in 95% (18/19) of patients with sickle cell anaemia and in 98% (40/41) of patients with β-thalassemia. On treatment, haemoglobin levels were maintained.[256] These results were confirmed in a real-life cohort study including 139 patients receiving sofosbuvir-based regimens who achieved SVR in 93% of cases (130/139; 5 relapses).[257]

Haemophilia is an inherited bleeding disorder caused by a deficiency of either factor VIII or IX in haemophilia A and B, respectively. Patients suffer spontaneous and traumatic bleeds. Treatment is based on intravenous replacement of these factors which, until recently, were prepared from plasma donations. People with haemophilia exposed to non-virally inactivated concentrates prior to 1985 had an almost 100% chance of being infected with HCV with their first exposure to concentrate. There are a number of other inherited bleeding disorders treated with concentrates, including von Willebrand disease, and deficiencies of fibrinogen and factors II, VII, X, XI and XIII.

Progression to end-stage liver disease in patients with haemophilia is similar to HCV-positive individuals in the general population. The investigation of chronic liver disease in haemophilia is the same as in non-haemophilic individuals. Transjugular liver biopsies have enhanced the safety of the procedure. Non-invasive methods can be utilised to monitor disease progression. Death from liver failure in HCV-positive individuals is among the commonest causes of death in patients with inherited bleeding disorders. The management of chronic hepatitis C in haemophilia is similar to the non-haemophilic population and HCV DAAs are applicable to patients with haemophilia. In a study with the fixed-dose combination of grazoprevir and elbasvir administered for 12 weeks without ribavirin, SVR12 was achieved in 91% (42/46) of patients with von Willebrand disease or haemophilia A or B.[256]

Over 100 liver transplants have been carried out in patients with haemophilia worldwide. Factor VIII/IX concentrate is administered immediately before the surgery, either by bolus injection or continuous infusion, and for the immediate postoperative period for 12–48 h, after which no further concentrate is required. Coinfection with HIV and HCV is not a contraindication to liver transplantation in haemophilia. The indications for liver transplantation in patients with haemophilia are the same as in those without haemophilia, but the procedure has the major advantage of producing a phenotypic cure of the haemophilia, as a result of factor VIII production by the transplanted liver.

Recommendations

- The indications for HCV therapy are the same in patients with and without haemoglobinopathies or bleeding disorders (**A1**).
- The IFN-free, ribavirin-free anti-HCV regimens that can be used in patients with haemoglobinopathies or bleeding disorders are the same as in patients without haemoglobinopathies or bleeding disorders (**B1**).

Adolescents and children

It is thought that approximately 3.5 million children globally, aged 1–15 years, are chronically infected with HCV. Mother-to-infant transmission is the major route of infection, but other

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sources of acquisition, including nosocomial transmission, occur in some countries. Adolescents are at risk via injecting drug use. The opioid epidemic in the United States has shown the ongoing risk of HCV transmission from mothers to their children. The transmission rates are higher from HIV-HCV coinfected mothers. All children born to HCV-infected women should be tested for HCV infection from the age of 18 months.

Cirrhosis and HCC are rare in children.[258] However, liver disease may progress during early life.[259] Individuals with thalassemia and iron overload, as well as those with HIV coinfection and childhood haematological or solid tumours receiving chemotherapy, may develop advanced hepatic fibrosis.[260] Childhood obesity may contribute to advancing liver disease.

There are numerous trials of pegylated IFN and ribavirin in children. The efficacy and tolerability of this combination is similar to that in adults. Current treatment options with DAAs are limited as there has been a delay in evaluating and approving these drugs for children. However, two clinical trials have shown high overall efficacy of DAA-based regimens in children and adolescents. In the first study, 100 HCV genotype 1-infected children were treated with sofosbuvir and ledipasvir for 12 weeks. The median age was 15 years (range 12–17). Only 1% were known to have cirrhosis; 80 patients were treatment-naïve. The SVR rate was 98% (98/100). The AUC and C_{max} for sofosbuvir, its metabolite GS-331007 and ledipasvir in adolescents were within the pharmacokinetic equivalence boundaries found in adults in clinical trials.[261] In the second study, the efficacy of sofosbuvir and ribavirin was assessed in 52 treatment-naïve and -experienced adolescents aged 12–17 years. The median age was 15 years; 26% were infected with genotype 2, 71% with genotype 3 and 2% with genotype 4. The SVR rate was 98% (51/52).[262]

In April 2017, the European Medicines Agency approved the fixed-dose combination of sofosbuvir and ledipasvir (for genotypes 1, 4, 5 and 6) and the combination of sofosbuvir and ribavirin (for genotypes 2 and 3) for adolescents aged 12–17 years, or weighing greater than 35 kg, with chronic hepatitis C. Thus, IFN-based treatment is no longer preferred. New trials of DAA combination regimens are ongoing in children 3–12 years.

Recommendations

- Adolescents aged 12 years and above infected with genotype 1, 4, 5 or 6 who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) for 12 weeks (**B1**).
- Adolescents aged 12 years and above infected with genotype 2 or 3 who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, can be treated with other regimens approved for adults, with caution pending more safety data in this population (**C2**).
- In children younger than 12 years, treatment should be deferred until DAAs, including pangenotypic regimens, are approved for this age group (**B1**).

Retreatment of non-sustained virological responders

Retreatment of patients who failed after a double combination of pegylated IFN-α and ribavirin, a triple combination of pegylated IFN-α, ribavirin and sofosbuvir, or a double combination of sofosbuvir and ribavirin

Treatment of patients who failed to achieve SVR after treatment with pegylated IFN-α and ribavirin, pegylated IFN-α, ribavirin and sofosbuvir, or sofosbuvir and ribavirin ("treatment-experienced" patients, as defined above) is described in the general recommendations (Tables 7 and 8).

Retreatment of patients who failed after a protease inhibitor- and/or NS5A inhibitor-containing regimen

Preliminary data suggest that retreatment can be optimised based on RAS testing.[263] The RASs that have been shown to confer reduced susceptibility to the corresponding drug class *in vitro* and/or that have been reported to be selected by DAA-containing therapies in patients who failed to achieve SVR are summarised (Table 9).[53,264] These many RASs and a number of alternative substitutions at the same positions can be present prior to retreatment in patients previously exposed to DAAs. Based on the current state of knowledge, no specific algorithms to guide retreatment decisions can be derived from these observations. Thus, retreatment must be guided either by the knowledge of which drugs were administered in previous treatment courses if no resistance test is available or, if resistance testing is performed, by probabilities of response according to the resistance profile observed and the treating team's experience.

Two phase III trials, POLARIS-1 and POLARIS-4, demonstrated the safety and efficacy of the triple combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks in patients who failed to achieve SVR with a DAA-based regimen, including patients exposed to protease and/or NS5A inhibitors.[265] In POLARIS-1, patients, including 46% with cirrhosis, previously failed a prior NS5A-containing treatment. The overall SVR rate was 96% (253/263) in patients receiving sofosbuvir, velpatasvir and voxilaprevir for 12 weeks. There was one viral breakthrough during treatment and 6 relapses post-retreatment. SVR was more frequent in patients without than in those with cirrhosis (99% and 93%, respectively). Neither the HCV genotype, nor the RAS profile at retreatment baseline had an influence on the response. Among the 7 patients with virological failure, NS3 RASs (Q80K) were present in 2 cases and NS5A RASs (at position 30 or 93) in 6 cases at retreatment baseline. Additional NS5A RASs were present at virological failure in only two of them.[265]

POLARIS-4 included patients who had previously failed to achieve SVR following a DAA-based treatment course not including an NS5A inhibitor, of whom 46% had cirrhosis. The overall SVR12 rate was 98% (178/182; one relapse) in patients randomized to receive sofosbuvir, velpatasvir and voxilaprevir for 12 weeks, compared to 90% (136/151; one virological breakthrough, 14 relapses) in similar patients treated with only sofosbuvir and velpatasvir for the same duration. Neither the HCV genotype, nor the RAS profile at retreatment baseline had an influence on the response in patients receiving the triple combination. Indeed, SVR was achieved in 98% (42/43) of patients without detectable RASs and in 97% (199/205) of patients with any NS3 and/or NS5A RASs. The patients who relapsed had no detectable RASs at baseline or at virological failure.[265]

Thus, the triple combination of sofosbuvir, velpatasvir and voxilaprevir appears as the treatment of choice for retreatment

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Table 9. Resistance-associated substitutions (RASs) conferring reduced susceptibility to the corresponding drug classes in *in vitro* assays and/or selected in patients who failed to achieve SVR on IFN-free, DAA-based regimens (excluding first-generation protease inhibitors telaprevir and boceprevir).

Drug class (genome region)	Amino acid position	Genotype/subtype						
		1a	1b	2	3	4	5	6
Nucleotide analogue (NS5B)								
	159	L159F	L159F	L159F	L159F			
	282	S282T/R	S282T	S282T	S282T	S282C/T	S282T	S282T
	316	C316F	C316N/F/H					
	320	L320I/F/V						
	321	V321A			V321A			
NS5A inhibitors (NS5A)								
	24	K24G/N/R		T24A/S	S24F*			Q24H
	26	K26E						
	28	M28A/G/T/-/V	L28M/T	L/F28C/S	M28T/K*	L28M/S/V	L28I	F28I/L/M/V
	29		P29S	P29S				
	30	Q30C/D/E/G/H/I/K/L/N/Q/R/S/T/Y	R30G/H/P/Q/R/S	L30H/S	A30K/S	L30G/H/R/S	Q30H	R30H
	31	L31I/F/M/P/V	L31F/I/M/V	L31I/M/V	L31F/I/M/V	M/L31I/V	L31F/I/V	L31M/V
	32	P32L/S	P32F/L/S				P32L	P32L/S
	38	S38F						
	58	H58D/L/R	P58D/S/R/T			T58P/S		T58A/N/S
	62		Q/E62D		S62L			
	92	A92K/T	A92K/T	C92R/S/T/W	E92K			
	93	Y93C/F/H/L/N/R/S/T/W	Y93C/H/N/S/T	Y93H	Y93H	Y93C/H/N/S/R/W	T93H	T93H/S
Protease inhibitors (NS3)								
	36	V36A/C/G/L/M	V36A/C/G/L/M					V36I
	41		Q41R					
	43		F43I/S/V					
	54	T54A/S	T54A/C/G/S					
	55		V55A					
	56	Y56H	Y56H/L/F	Y56H	Y56H	Y56H		Y56H
	80	Q80H/K/L/R	Q80H/K/L/R			Q80R		L80K/Q
	122	S122G/R	S122D/G/I/N/R/T					S122T
	155	R155G/I/K/M/S/T/W	R155C/G/I/K/L/Q/M/S/T/W			R155C/K		
	156*	A156G/P/S/T/V	A156G/P/S/T/V		A156G/P/T/V	A156G/H/K/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	D168E/H/T/V		D168A/E/H/Y
	170	I/V170F/T/V	I/V170A/L/T					I170V
	175		M175L					
Non-nucleoside palm-1 inhibitor (NS5B)								
	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/V	A553V					
	554	G554S	G554S					
	555	Y555H						
	556	S556G/N/R	S556G/R					
	557	G557R						
	558	G558R	G558R					
	559	D559G/N	D559G/N					
	561	Y561H/N						
	565	S565F						

These RASs and 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). However, differences exist between drugs belonging to the same class, so that the presence of a given RAS does not mean that all drugs from the class have reduced effectiveness. del: deletion. Adapted and updated from.[53] DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir; VOX: voxilaprevir.

* Genotype 3 NS5A S24F + M28K + A30K combined RASs confers >5,000-fold increase in pibrentasvir EC50 relative to wild-type *in vitro*.

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of patients who failed to achieve SVR after an IFN-free, DAA-based treatment course.

The MAGELLAN-1 trial showed that the combination of glecaprevir and pibrentasvir does not have a high enough barrier-to-resistance to achieve optimal SVR rates in patients previously exposed to an NS5A inhibitor.[266] Thus, this combination is not indicated in the retreatment of patients who failed a prior DAA-containing regimen, particularly if this regimen contained an NS5A inhibitor. Instead, a triple combination of sofosbuvir with an NS3 protease inhibitor and an NS5A inhibitor appears to be better suited to retreatment of DAA-exposed patients. Because pibrentasvir has a higher barrier-to-resistance than all other approved NS5A inhibitors *in vitro*,[105] the triple combination of sofosbuvir and the fixed-dose combination of glecaprevir and pibrentasvir could offer an interesting alternative for retreatment of difficult-to-cure patients, such as those with complex NS5A RAS patterns and/or those with advanced liver disease (excluding decompensated cirrhosis) who have experienced several unsuccessful courses of treatment. Individual cases of successful retreatment of such patients with the combination of sofosbuvir, glecaprevir and pibrentasvir have been observed. Preliminary results from an ongoing clinical trial have been recently reported. Twenty-three patients who failed to achieve SVR after 8, 12 or 16 weeks of the fixed-dose combination of glecaprevir and pibrentasvir in the phase II and III trials with this regimen were retreated with the combination of sofosbuvir, glecaprevir and pibrentasvir with ribavirin for 12 (n = 2) or 16 (n = 21) weeks. SVR was observed in 96% (22/23; one relapse) of cases. The combination was safe and well-tolerated.[267]

In particularly difficult-to-cure patients previously exposed to NS5A inhibitors, the triple combinations of sofosbuvir, velpatasvir and voxilaprevir, and of sofosbuvir, glecaprevir and pibrentasvir may theoretically benefit from the addition of weight-based ribavirin and/or extension of treatment duration to 16 to 24 weeks. However, there are no data to support these indications, which must be decided on an individual basis by expert multidisciplinary teams, taking into consideration the many parameters at retreatment baseline, including severity of liver disease and/or extra-hepatic manifestations, previous unsuccessful courses of treatment, RAS profiles, etc. The presence of decompensated cirrhosis will negate the use of protease inhibitor-based regimens, emphasizing the need to institute retreatment as soon as possible.

Recommendations

- Patients who failed after pegylated IFN-α and ribavirin, pegylated IFN-α, ribavirin and sofosbuvir, or sofosbuvir and ribavirin combination treatment must be retreated according to the above recommendations for "treatment-experienced" patients, by HCV genotype (**A1**).
- HCV resistance testing prior to retreatment in patients who failed after any of the DAA-containing treatment regimens is useful to guide retreatment by probabilities of response, according to the resistance profile observed in the context of a multidisciplinary team including experienced treaters and virologists (**B2**).
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis who failed after a DAA (protease inhibitor and/or NS5A inhibitor)-containing regimen should be retreated with the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks, ideally in the context of a multidisciplinary team including experienced treaters and virologists (**A1**).
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis who failed after a DAA (protease inhibitor and/or NS5A inhibitor)-containing regimen and have predictors of lower response (advanced liver disease, multiple courses of DAA-based treatment, complex NS5A RAS profile) can be retreated with the combination of sofosbuvir plus the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks, based on an individual decision in the context of a multidisciplinary team including experienced treaters and virologists (**B2**).
- In very difficult-to-cure patients (patients with NS5A RASs who failed twice to achieve SVR after a combination regimen including a protease and/or an NS5A inhibitor), the triple combination of sofosbuvir, velpatasvir and voxilaprevir, or the triple combination of sofosbuvir, glecaprevir and pibrentasvir can be administered for 12 weeks with weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) and/or treatment duration can be prolonged to 16 to 24 weeks, based on an individual decision in the context of a multidisciplinary team including experienced treaters and virologists (**C2**).
- Patients with decompensated (Child-Pugh B or C) cirrhosis who failed after a DAA (protease inhibitor and/or NS5A inhibitor)-containing regimen have a contraindication for the use of protease inhibitors, and should therefore be retreated with the fixed-dose combination of sofosbuvir and velpatasvir with weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) for 24 weeks, based on an individual decision in the context of a multidisciplinary team including experienced treaters and virologists (**B2**).

Treatment of acute hepatitis C

Most patients with acute hepatitis C are asymptomatic, but a high rate of chronicity is expected (50–90%). Symptomatic disease with jaundice, female gender, a young age, and genetic polymorphisms in the region upstream of the *IL28B* (recently renamed IFN lambda-3, *IFNL3*) gene have been associated with spontaneous viral clearance, but none of these parameters accurately predicts spontaneous resolution at the individual level.

Patients with acute hepatitis C should be considered for antiviral therapy in order to prevent progression to chronic hepatitis C. Indeed, immediate treatment of acute hepatitis C with DAAs improves clinical outcomes and was shown to be highly cost-effective compared with deferring treatment until the chronic phase of infection.[268] The ideal time point for starting therapy has not been firmly established.

High SVR rates (>90%) have been reported in a small number of patients with sofosbuvir-based IFN-free regimens. The ideal duration of treatment of acute hepatitis C with IFN-free regimens remains unknown. The combination of sofosbuvir and ribavirin for either 6 or 12 weeks was not sufficient to achieve high SVR rates in patients with acute or early chronic hepatitis

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C.[269,270] Three trials were performed with the fixed-dose combination of sofosbuvir and ledipasvir in patients infected with genotype 1. The SVR rates were: 93% (13/14) after 4 weeks of treatment in injection drug users,[271] 77% (20/26) after 6 weeks of treatment in HIV-positive individuals,[272] and 100% (20/20) after 6 weeks of treatment in HIV-negative, non-injection drug users.[273] The combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir administered for 8 weeks yielded a 97% (29/30; one non-virological failure) SVR rate in patients with acute or recent hepatitis C in the TARGET-3D study.[274]

Because of the small number of patients included in these trials, the differences in their results, and similarities with chronic hepatitis C for which at least 8 weeks of therapy are required to maximize SVR rates, patients with acute hepatitis C should be treated with DAA combinations for 8 weeks, pending additional data establishing the ideal treatment regimen and duration. Although the most recent DAA combinations have not been tested in patients with acute hepatitis C, there is no reason to believe that they would not be highly efficacious in these patients given their performance in patients with chronic hepatitis C.

There is currently no indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission.

Recommendations

- Patients with acute hepatitis C should be treated with a combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6) or a combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1b) for 8 weeks (**B1**).
- Based on similarities to chronic hepatitis C, patients with acute hepatitis C may be treated with a combination of sofosbuvir and velpatasvir (all genotypes), a combination of glecaprevir and pibrentasvir (all genotypes), or a combination of grazoprevir and elbasvir (genotypes 1b and 4) for 8 weeks (**C2**).
- 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**).

Treatment monitoring

Treatment monitoring includes monitoring of treatment efficacy, of safety and side effects and of drug-drug interactions.

Monitoring of treatment efficacy

Monitoring of treatment efficacy is based on measurements of HCV RNA levels in serum or plasma. The same assay, ideally from the same laboratory, should be used in each patient to measure HCV RNA at different time points, in order to assure consistency of results.[275–277] Measurements of HCV core antigen levels in serum or plasma by means of ELISA can be used as an alternative to HCV RNA level measurements in settings where HCV RNA assays are not available and/or not affordable.[23,24,26]

In order to monitor treatment efficacy, HCV RNA (or HCV core antigen) level measurements should be performed at specific time points, including baseline and 12 or 24 weeks after the end of therapy (to assess SVR12 or SVR24, respectively). In all cases, HCV RNA (or HCV core antigen) level monitoring indicates whether treatment has been successful.

Recommendations

- A sensitive molecular method with a lower limit of detection ≤15 IU/ml should be used to monitor HCV RNA levels in serum or plasma (**A1**).
- In low- or middle-income countries and in specific settings in high-income countries, a qualitative HCV RNA assay with a lower limit of detection ≤1,000 IU/ml (3.0 Log_{10} IU/ml) can be used to provide broad affordable access to HCV diagnosis and care (**B1**).
- Measurement of HCV core antigen levels in serum or plasma by EIA can be used as an alternative to HCV RNA level measurement to monitor treatment efficacy when HCV RNA assays are not available and/or not affordable (**A1**).
- In patients treated with an IFN-free regimen, HCV RNA or HCV core antigen levels should be measured at baseline and 12 or 24 weeks after the end of therapy (to assess SVR12 or SVR24, respectively) (**A1**).
- In some parts of the world, given the high SVR12 rates expected with DAA-based regimens, checking SVR may be dispensable, except in patients with high-risk behaviours and risk of reinfection (**B2**).

Monitoring of treatment safety

New DAA regimens are generally well tolerated. Frequencies of high grade or severe adverse events leading to discontinuation of IFN-free regimens are low. However, data in patients with decompensated cirrhosis or in liver transplant recipients are scarce.

Sofosbuvir and velpatasvir (without or with voxilaprevir)

The proportion of patients who permanently discontinued treatment because of adverse events during treatment was <1% for patients receiving sofosbuvir and velpatasvir for 12 weeks.

In clinical studies, no difference with placebo-containing arms was observed. Fatigue and headache were the most common adverse events in patients treated with sofosbuvir and velpatasvir. Renal function should be checked in patients receiving sofosbuvir.

The addition of voxilaprevir was associated with more frequent benign diarrhoea (18% and 15% in patients receiving the triple combination and 7% and 5% in those receiving sofosbuvir and velpatasvir only in the POLARIS-2 and POLARIS-3 trials, respectively).[71]

Glecaprevir and pibrentasvir

The proportion of patients who permanently discontinued treatment because of adverse events was <0.5% for patients receiving glecaprevir and pibrentasvir for 8 or 12 weeks.[278]

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In an integrated analysis of 2,265 patients treated with the combination of glecaprevir and pibrentasvir in phase II and III clinical trials, fatigue and headache were the most common adverse events.[278]

Sofosbuvir and ledipasvir

The proportion of patients who permanently discontinued treatment because of adverse events during treatment was 0%, <1% and 1% for patients receiving sofosbuvir and ledipasvir for 8, 12 and 24 weeks, respectively. In clinical studies, fatigue and headache were more common in patients treated with sofosbuvir and ledipasvir compared to placebo. Renal function should be checked before sofosbuvir is administered. A few cases of severe pulmonary arterial hypertension have been reported in patients receiving sofosbuvir-based regimens, but a causal link has not been firmly established.[279]

Grazoprevir and elbasvir

Severe adverse events were observed in 2.4% of patients receiving grazoprevir and elbasvir. They led to treatment interruptions in 0.1% of cases. The most frequent adverse events were fatigue, headache, and nausea, not more frequent than in placebo-containing arms. During the phase II and III trials, 0.8% (13/1690) of patients experienced asymptomatic ALT elevations up to >5 times the upper limit of normal, on average 10 weeks after the start of treatment. These events resolved spontaneously with continued therapy or end of treatment. Three patients (0.18%) discontinued because of ALT elevation.

Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir

Based on an integrated safety analysis, pruritus, fatigue, nausea, asthenia and insomnia were the most common adverse events encountered in clinical trials with this combination. However, the more frequent side effects were considered related to ribavirin, that was used in all patients infected with genotype 1a and in some patients infected with genotype 1b in these studies. Pruritus was considered related to the 3 DAA regimen. Severe adverse events occurred in <2.5% of cases. Treatment discontinuation because of adverse events occurred in 1–2% of patients per study.

Asymptomatic serum ALT elevations generally occurred within the first 4 weeks of treatment, but all resolved without intervention and with continued DAA treatment, none of them being synchronous with bilirubin elevations. Transient increases in indirect serum bilirubin were observed in patients with and without ribavirin, related to the inhibition of bilirubin transporters OATP1B1 and OATP1B3 by paritaprevir and associated haemolysis. A greater frequency of total bilirubin increases was observed in patients with cirrhosis. The use of oestrogen containing medications was associated with a greater risk of ALT elevations.

Recommendations

- The patients receiving a DAA-containing regimen should be assessed for clinical side effects at each visit (**A1**).
- ALT levels should be assessed at least at baseline and at 12 or 24 weeks post-treatment, and in case of suggestive symptoms (**B1**).
- Monitoring for indirect bilirubin increases should be performed in patients receiving the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (**A1**).
- Renal function should be checked monthly in patients with reduced eGFR receiving sofosbuvir (**A1**).
- Higher exposures have been observed with the protease inhibitors in patients with severe hepatic impairment and the use of protease inhibitor-containing regimens (glecaprevir and pibrentasvir; grazoprevir and elbasvir; ritonavir-boosted paritaprevir and ombitasvir with dasabuvir; sofosbuvir, velpatasvir and voxilaprevir) is contraindicated in patients with Child-Pugh B and C decompensated cirrhosis (**B1**).

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. It is important to review all the drugs taken by the patient, including over-the-counter preparations and recreational drugs. Also, the following series of questions should be asked: are all the co-administered drugs necessary during the period of HCV treatment (it may be possible to stop a drug, such as a statin, for a period of 8–12 weeks)? If not, is there an alternative in the same therapeutic class without a drug interaction? Finally, can a drug interaction be managed either by a change of dose or a clear monitoring plan? For specific drug-drug interactions and dose adjustments, see above. The patient needs to inform the treating team before starting any new medication during treatment.

Recommendations

- 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**).

Treatment dose reductions

No dose adjustments are required or recommended for any of the above-recommended DAA combination regimens, including protease inhibitor-based regimens for renal failure and sofosbuvir and ledipasvir for children >12 years of age. Treatment must be stopped in case of severe adverse events or in case of a hepatitis flare (ALT levels above 10 times normal, if not already present at the time of starting treatment).

If significant anaemia occurs (haemoglobin <10 g/dl) in patients receiving ribavirin (patients with decompensated [Child-Pugh B or C] cirrhosis), the dose of ribavirin should be adjusted downward by 200 mg in decrements. A more rapid reduction of dose may be required for patients with rapidly declining haemoglobin, particularly if the baseline haemoglobin

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was low. Ribavirin administration should be stopped if the haemoglobin level falls below 8.5 g/dl.[280–288]

Recommendations

- Treatment should be stopped in case of severe adverse events or in case of ALT flare >10 times the upper limit of normal values (**B1**).
- In patients who need ribavirin (patients with decompensated [Child-Pugh B or C] cirrhosis), the dose of ribavirin should be adjusted downward by 200 mg in 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**).

Measures to improve treatment adherence

Full adherence to all drugs is associated with high SVR rates. In contrast, suboptimal exposure to therapy is associated with a risk of virological breakthrough or post-treatment relapse and the selection of RASs. Simple measures to enhance adherence to treatment should thus be implemented.

Before starting antiviral therapy, patients must be instructed about the daily schedule and the rare side effects to be expected during treatment. Evidence exists for directly observed therapy for patients on OST with high treatment completion and SVR rates.[289,290]

The key element of effective HCV clinical management is access to a multidisciplinary team, generally including clinician and nursing clinical assessment and monitoring, virology, drug and alcohol services, HIV infection services, psychiatric support for selected cases, pharmacy and social work and other social support services (including peer support, if available). Measures to increase adherence are interdisciplinary. They include HCV education and monitoring services and, particularly, the help of a dedicated nurse.[291,292] For foreign patients, the language and comprehension difficulties should be addressed before starting treatment.

To maximize the likelihood of benefit for patients who begin new HCV treatment regimens, resources should be devoted to patient pre-treatment assessment and preparation, as well as to monitoring and supporting on-treatment adherence, which has become easy with the IFN-free regimens. Assessment tools utilised in chronic disease are available.[293]

Harmful alcohol consumption (Audit-C score >4) was associated with a slight reduction in SVR; however, SVR rates were good irrespective of Audit-C score, and excess alcohol should not preclude treatment.[294] Hepatitis C patients with ongoing alcohol consumption during treatment profit from additional support during antiviral therapy.[295–298] Pharmacists should advise on potential drug-drug interactions.

Recommendations

- 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 (**B1**).
- Peer-based support and patient activation assessment are recommended to improve HCV clinical management (**B2**).
- Patients with harmful alcohol consumption during treatment should receive additional support during antiviral therapy (**B1**).

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

In patients without cirrhosis who achieve an SVR, the HCV infection can be considered as definitively cured. Patients with pre-existing cofactors for liver disease (notably, history of excessive alcohol drinking, obesity and/or type 2 diabetes) should be carefully and periodically subjected to a thorough clinical assessment, as needed.

Patients with advanced fibrosis (METAVIR score F3) and patients with cirrhosis (F4) who achieve an SVR should remain under surveillance for HCC every 6 months by ultrasound, and for oesophageal varices by endoscopy if varices were present at pre-treatment endoscopy (though first variceal bleed is seldom observed after SVR). The presence of cofactors for liver disease, such as history of alcohol drinking, a metabolic syndrome possibly associated with obesity and/or type 2 diabetes, may determine that additional assessments are necessary. Long-term post-SVR follow-up studies showed that the risk of developing HCC remains in patients with cirrhosis who eliminate HCV, although it is significantly reduced compared to untreated patients or patients who did not achieve an SVR.[3,4,8,152,299] Thus, the duration of HCC surveillance in patients with advanced fibrosis or cirrhosis who achieve an SVR is indefinite.

Reported rates of reinfection following successful HCV treatment among patients at high risk, such as PWIDs or men who have sex with men, are of the order of 1–8% per year.[246–249,251,300–304] The ease of IFN-free therapy may increase the likelihood of reinfection, as recently suggested.[305] In order to maximize the benefit of therapy, the risks of reinfection should be emphasized to patients at risk, and behavioural modifications should be positively reinforced. Patients at risk should be monitored for reinfection and treatment should be offered to those patients who are reinfected, after 3 months to assess their ability to naturally cure infection.

Recommendations

- Patients with no to moderate fibrosis (METAVIR score F0-F2), with SVR and no ongoing risk behaviour should be discharged, provided that they have no other comorbidities (**A1**).
- Patients with advanced fibrosis (F3) or cirrhosis (F4) with SVR should undergo surveillance for HCC every 6 months by means of ultrasound (**A1**).
- In patients with cirrhosis, surveillance for oesophageal varices by endoscopy should be performed if varices were present at pre-treatment endoscopy, though index

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variceal bleed is seldom seen in low-risk patients after the achievement of SVR (unless additional causes for ongoing liver damage are present and persist) (**A1**).

- The risk of reinfection should be explained, to positively modify risk behaviour (**B1**).
- Following SVR, monitoring for HCV reinfection ideally through bi-annual, at least annual HCV RNA assessment should be undertaken in PWIDs or men who have sex with men with ongoing risk behaviour (**A1**).
- Retreatment should be made available, if reinfection is identified during post-SVR follow-up (**A1**).

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

Untreated patients with chronic hepatitis C and those who failed to respond to previous treatment should be regularly followed. The reason(s) for non-treatment and treatment failure should be clearly documented. Untreated patients should be assessed every 1 to 2 years with a non-invasive method.[41] Patients with advanced fibrosis (METAVIR score F3) and cirrhosis should undergo specific ultrasound surveillance every 6 months.

Recommendations

- 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 to follow-up assessment at intervals of 1 to two 2 (**A1**).
- HCC surveillance every 6 months must be continued indefinitely in patients with advanced fibrosis (F3) and cirrhosis (**A1**).

Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

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