Clinical Practice Guidelines

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EASL recommendations on treatment of hepatitis C: Final update of the series☆

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, as well as developments in diagnostic procedures and improvements in therapy and prevention. These therapies make it possible to eliminate hepatitis C as a major public health threat, as per the World Health Organization target, although the timeline and feasibility vary from region to region. These European Association for the Study of the Liver recommendations on treatment of hepatitis C describe the optimal management of patients with recently acquired and chronic HCV infections in 2020 and onwards.

Introduction

Background

In 2015 it was estimated that there were approximately 71 million individuals chronically infected with hepatitis C virus (HCV) worldwide,[1,2] many of whom were unaware of their infection.[3] HCV infection remains one of the main causes of chronic liver disease worldwide.[1,4] The long-term natural history of HCV infection is highly variable: the hepatic injury can range from minimal necro-inflammatory changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). Clinical care for patients with HCV-related liver disease has advanced considerably during the last couple of decades, thanks to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and radical 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 after treatment completion. An SVR corresponds to a cure of the HCV infection, as late relapse occurs in less than 0.2% of cases beyond 6 months of follow-up.[5] An SVR is generally associated with normalisation of liver enzymes and improvement or regression of liver necroinflammation and fibrosis, and improvement in liver function.[6–8] 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.[6,9–17] HCV is also associated with a number of extrahepatic manifestations, but viral elimination can reduce all-cause mortality.[18–25]

This final update of the EASL Recommendations on Treatment of Hepatitis C series started in 2014 is 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. The panel recognises the heterogeneity of per capita incomes, health insurance systems and drug prices in different regions, and therefore the constraints that apply to access to branded and generic drugs.

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. The evidence and recommendations have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[26] The strength of recommendations reflects the quality of underlying evidence. The quality of the evidence in the recommendations has been classified into 1 of 3 levels: high (A), moderate (B) or low (C). The GRADE system offers 2 grades of recommendation: strong (1) or weak (2) (Table 1). Thus, these 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.

Available drugs in Europe

The HCV drug combinations available in Europe are listed in this paragraph and in Table 2. Their known pharmacokinetic and safety profiles are presented.

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☆**Clinical Practice Guidelines Panel**: Chair: Jean-Michel Pawlotsky; EASL Governing Board representative: Francesco Negro; Panel members: Alessio Aghemo, Marina Berenguer, Olav Dalgard, Geoffrey Dusheiko, Fiona Marra, Massimo Puoti, Heiner Wedemeyer.

* Corresponding author: Address: European Association for the Study of the Liver (EASL), The EASL Building – Home of Hepatology, 7 rue Daubin, CH 1203 Geneva, Switzerland. Tel.: +41 (0) 22 807 03 60; Fax: +41 (0) 22 328 07 24.
E-mail address: easloffice@easloffice.eu.

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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

Sofosbuvir

Sofosbuvir should be administered at the dose of 400 mg (1 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. No dose adjustment of sofosbuvir is required for patients with mild to moderate renal impairment. Sofosbuvir-containing regimens were shown to be safe in patients with moderate to severe renal impairment, including those with estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 and those with end-stage renal disease requiring haemodialysis, with or without hepatic decompensation.[27] A recent study has confirmed the safety of sofosbuvir in patients with stage 4–5 kidney disease who were not on dialysis.[28]

Sofosbuvir exposure is not significantly changed in patients with mild liver impairment (Child-Pugh A cirrhosis), but it is increased 2.3-fold in those with moderate liver impairment (Child-Pugh B cirrhosis).

Sofosbuvir is well tolerated over 12 to 24 weeks of administration.

Sofosbuvir/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 1 tablet taken orally once daily with or without food.

Velpatasvir is metabolised *in vitro* by cytochrome P450 (CYP) 2B6, 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-glycoprotein (P-gp) and breast cancer resistance protein (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 hours.

Velpatasvir plasma exposure (area under curve, AUC) is similar in patients with moderate and severe hepatic impairment (Child-Pugh B and C cirrhosis, respectively) compared to those with normal hepatic function. Cirrhosis, including decompensated cirrhosis, had no clinically relevant effect on velpatasvir exposure in a population-level pharmacokinetic analysis in HCV-infected individuals.[29]

The pharmacokinetics of velpatasvir have been studied in HCV-negative patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2). Relative to individuals with normal renal function, the AUC of velpatasvir was 50% higher, which was not considered to be clinically relevant.[30] Treatment with sofosbuvir/velpatasvir for 12 weeks was reported to be safe in patients with end-stage renal disease undergoing haemodialysis.[31]

The safety assessment of sofosbuvir and velpatasvir was based on pooled phase III and real-world data.[32,33] Headache, fatigue and nausea were the most commonly reported adverse events, at a similar frequency to placebo-treated patients.

Sofosbuvir/velpatasvir/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 1 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.[34]

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 hours.

Population pharmacokinetic analysis of voxilaprevir in HCV-infected patients indicated that patients with compensated (Child-Pugh A) cirrhosis had 73% higher exposure to voxilaprevir than those without cirrhosis. Thus, no dose adjustment of sofosbuvir, velpatasvir and voxilaprevir is required for patients with compensated (Child-Pugh A) cirrhosis. The pharmacokinetics of single-dose voxilaprevir were also studied in patients with moderate and severe hepatic impairment (Child-Pugh B and C cirrhosis, respectively). Relative to patients with normal

Table 2. HCV DAAs approved in Europe recommended in this document and yet unapproved paediatric formulations (information provided by Abbvie and Gilead on request from the panel).

Product	Presentation	Posology
Sofosbuvir	Tablets containing 400 mg of sofosbuvir	One tablet once daily
	Half-strength tablets containing 200 mg of sofosbuvir[a]	One tablet once daily
Sofosbuvir/velpatasvir	Tablets containing 400 mg of sofosbuvir and 100 mg of velpatasvir	One tablet once daily
	Half-strength tablets containing 200 mg of sofosbuvir and 50 mg of velpatasvir[a,b]	One tablet once daily
	Granules containing 50 mg of sofosbuvir and 12.5 mg of velpatasvir[a,b]	Three or four granules once daily, according to body weight
Sofosbuvir/velpatasvir/voxilaprevir	Tablets containing 400 mg of sofosbuvir, 100 mg of velpatasvir and 100 mg of voxilaprevir	One tablet once daily with food
Glecaprevir/pibrentasvir	Tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir	Three tablets once daily with food
	Film-coated granules of glecaprevir and pibrentasvir in sachets containing 50 mg of glecaprevir and 20 mg of pibrentasvir mixed together in a small amount of food[a,b]	Three to five sachets once daily, according to body weight
Grazoprevir/elbasvir	Tablets containing 100 mg of grazoprevir and 50 mg of elbasvir	One tablet once daily

DAAs, direct-acting antivirals.
[a]Paediatric formulation.
[b]Approval pending.

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 should not be used in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

The pharmacokinetics of voxilaprevir have been studied in HCV-negative patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2). Relative to patients with normal renal function, the AUC of voxilaprevir was 71% higher in those 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 and real-world studies.[35–39] Headache, diarrhoea and nausea were the most commonly reported adverse events. The incidence of gastrointestinal side effects was greater than with the combination of sofosbuvir and velpatasvir alone.

Glecaprevir/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 3 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 both glecaprevir and pibrentasvir. Their half-lives are approximately 6 and 23 hours, respectively.

Population-level pharmacokinetic analysis in HCV-infected individuals showed that following administration of glecaprevir/pibrentasvir in HCV-infected patients with compensated (Child-Pugh A) cirrhosis, exposure to glecaprevir was approximately 2-fold higher whilst pibrentasvir exposure was similar to that in patients without cirrhosis. When compared to patients with normal hepatic function, the AUC of glecaprevir was 33% higher in patients with compensated (Child-Pugh A) cirrhosis, 100% higher in those with moderate hepatic impairment (Child-Pugh B cirrhosis), and increased to 11-fold in those with severe hepatic impairment (Child-Pugh C cirrhosis). Thus, glecaprevir/pibrentasvir should not be used in patients with Child-Pugh B or C cirrhosis.

Glecaprevir/pibrentasvir was studied in HCV-negative individuals with mild, moderate, severe, or end-stage renal impairment not on dialysis and compared to those with normal renal function. AUCs were increased by less than 56% in all patients with any stage of renal disease, which was not clinically significant. The AUC of glecaprevir/pibrentasvir was also similar in patients on dialysis; thus, this combination can be recommended in patients with mild, moderate, severe and end-stage renal impairment.[40]

The safety of pibrentasvir and glecaprevir was evaluated in phase II and III clinical trials and real-world studies.[41–44] Headache and fatigue were the most commonly reported adverse events.

Grazoprevir/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 1 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 hours, respectively.

Pharmacokinetic data from hepatic impairment studies in non-HCV-infected individuals have demonstrated a decrease in the AUC of elbasvir in patients with 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, elbasvir/grazoprevir should not be used in patients with decompensated (Child-Pugh B or C) cirrhosis.[45]

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 trials and real-world studies, with the most commonly reported adverse reactions being fatigue and headache.[46–51] Rare cases (0.8%) of substantial elevations in alanine aminotransferase (ALT) level were reported, slightly more frequently in female, Asian and elderly patients.

Diagnosis of recently acquired hepatitis C, chronic hepatitis C and HCV reinfection

Anti-HCV antibodies are detectable in serum or plasma by enzyme immunoassay (EIA) in the vast majority of patients with HCV infection, but may be undetectable in the early phase of acute infection and in patients with chronic hepatitis C who are profoundly immunosuppressed. Following spontaneous or treatment-induced viral clearance, anti-HCV antibodies persist in the absence of HCV RNA, but titres may wane and finally disappear in some individuals.[52–54] Anti-HCV antibody testing is not helpful to determine reinfection after treatment, as the antibodies are already present before reinfection in the vast majority of cases.

The diagnosis of recently acquired 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 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.[55] There is an important need for affordable (less than US$5–US$10) point-of-care or near-care nucleic acid testing assays to ascertain viraemia, which would be applicable for large-scale diagnosis where sensitive HCV RNA assays are not available and/or not affordable, *i.e.* in low-to middle-income areas, as well as in specific settings in high-income countries. For widespread population testing, a qualitative HCV RNA assay needs only to have a lower limit of detection ≤1,000 IU/ml (3.0 Log_{10} IU/ml). In such settings, the low incidence of a false-negative test for viraemia with these assays is outweighed by the benefit of scaling up access to diagnosis and care. 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.[56] In a report from the Swiss Hepatitis C Cohort, 88 out of 2,533 (3.5%) treatment-naïve patients with chronic hepatitis C and available quantitative HCV RNA testing results ever had an HCV RNA level less than or equal to 1,000 IU/ml.[57] Young age, excessive alcohol consumption and absence of intravenous drug use were independently associated with an HCV RNA level ≤1,000 IU/ml. Among patients from this study with a very low viral level who had another HCV RNA level measurement available more than 6 months after their initial very low viral level, the vast majority had an HCV RNA level >1,000 IU/ml.[57]

HCV core antigen in serum or plasma is a marker of HCV replication. Thus, HCV core antigen detection can be used to diagnose viraemia in recently acquired HCV infection, in chronic infection, or after HCV reinfection.[58] HCV core antigen assays are less sensitive than HCV RNA assays for the diagnosis of viraemia (lower limit of detection equivalent to approximately 500 to 3,000 HCV RNA IU/ml, depending on the HCV genotype[59–61]). They detect HCV core antigen in serum or plasma a few days after HCV RNA becomes detectable during acute HCV infection. In rare cases of chronic infection, HCV core antigen is undetectable in the presence of HCV RNA.[62]

The diagnosis of recently acquired hepatitis C can only be made confidently if recent seroconversion to anti-HCV antibodies can be documented. Not all patients with recently acquired hepatitis C test positive for anti-HCV antibodies at diagnosis. In these cases, recently acquired hepatitis C can be suspected if the clinical signs and symptoms are compatible with an acute hepatitis (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 concentrations may fluctuate with interludes (up to several weeks) of undetectable HCV RNA or HCV core antigen.[63,64] 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 when re-exposure to HCV has occurred in those with risk factors for infection. Reinfection is diagnosed based on the reappearance of HCV RNA or HCV core antigen after an SVR and the demonstration (by sequencing followed by phylogenetic analysis) that infection is caused by a different genotype or by a distantly related strain of the same genotype from the initial infection. Reinfection should be suspected in cases of a recurrence of HCV infection occurring more than 12 or 24 weeks post-SVR, if risk behaviours have continued.

Recommendations

- All patients with suspected *de novo* recently acquired HCV infection should be tested for anti-HCV antibodies and either HCV RNA or HCV core antigen in serum or plasma **(A1)**.
- Anti-HCV antibody-positive, HCV RNA-negative or HCV core antigen-negative patients with suspected *de novo* recently acquired HCV infection should be retested for HCV RNA 12 and 24 weeks later to confirm definitive clearance **(A1)**.
- All patients with suspected chronic HCV infection should be tested for anti-HCV antibodies in serum or plasma as first-line diagnostic test **(A1)**.
- If anti-HCV antibodies are detected in patients with suspected chronic HCV infection, either HCV RNA or HCV core antigen should be determined **(A1)**.
- HCV reinfection should be suspected in case of reappearance of HCV RNA or HCV core antigen after an SVR in individuals with risk factors for infection, and confirmed by the demonstration that infection is caused by a different genotype or, using sequencing followed by phylogenetic analysis, by a distantly related strain of the same genotype from the initial infection (A1).
- Anti-HCV antibodies should be determined in serum or plasma by enzyme immunoassay **(A1)**.
- HCV RNA should be determined in serum or plasma by a sensitive molecular method with a lower limit of detection ≤15 IU/ml **(A1)**.

- HCV core antigen in serum or plasma by enzyme immunoassay is a marker of HCV replication that can be used as an alternative to HCV RNA to diagnose HCV viraemia **(A1)**.
- Where sensitive HCV RNA assays are not available and/or not affordable, 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 broaden access to HCV diagnosis and care **(B1)**.

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.[65] Accurate HCV prevalence and incidence data are needed to analyse the epidemiology in different regions and to design apposite public health interventions. Thus, HCV screening is required to identify infected individuals and to engage them in care. The optimal regional or national screening approaches should be determined based on the local epidemiology.

Screening for HCV infection is based on the detection of anti-HCV antibodies. Either EIA or rapid diagnostic tests (RDTs) can be used to screen for anti-HCV antibodies. RDTs use various matrices, including serum and plasma, and can also utilise fingerstick capillary whole blood or oral (crevicular) fluid to facilitate screening without the need for venipuncture, sample centrifugation, freezing and skilled labour. RDTs for anti-HCV antibodies are simple to perform at room temperature without specific instrumentation or extensive training. They have been shown to have excellent sensitivity and specificity compared to EIAs.[66–71]

If anti-HCV antibodies are detected, the presence of HCV RNA by a molecular assay or, alternatively, HCV core antigen by EIA should be determined to identify patients with ongoing infection.

Currently, most laboratories use a two-step approach including an antibody test in step 1, followed by phlebotomy and a test for HCV RNA in step 2. This procedure lessens the prospect of a confirmatory HCV RNA test. Reflex testing, *i.e.* testing for HCV RNA in the sample obtained for anti-HCV antibody testing, has been shown to substantially increase the proportion of anti-HCV antibody-positive patients who are tested for viraemia and receive subsequent linkage to care.[72–76] Therefore, reflex testing should be applied whenever possible when anti-HCV antibodies are detected.

Dried blood spots (DBSs) can be used to collect and transport whole blood specimens for both detection of anti-HCV antibodies by EIA (on the first spot) and reflex HCV RNA testing (on a second spot) in a central laboratory.[77–82] The methodology is less sensitive than HCV RNA testing in serum or plasma, as quantitative HCV RNA is underestimated by approximately 1.6–1.8 Log_{10} IU/ml on average on DBSs.[78]

Confirmation of viraemia by testing for HCV core antigen from whole blood sampled on DBSs is not recommended, as DBSs are insufficiently sensitive for HCV core antigen detection. Indeed, false-negative tests occur in 7%–36% of viraemic patients with anti-HCV antibodies.[78,83–86]

A cartridge-based point-of-care HCV RNA assay has received World Health Organization (WHO) prequalification. This assay can be used with serum, plasma or fingerstick capillary whole blood, with equal performance.[87–89] The test can be used for reflex testing, but it is too expensive to be used instead of anti-HCV antibody testing for first-line screening.

Inexpensive direct tests for HCV RNA or HCV core antigen should be developed to replace screening based on anti-HCV antibody testing by a 1-step direct identification of viraemic individuals, in order to simplify testing algorithms and facilitate shorter pathways to treatment. These tests will require validation for sensitivity and specificity, as well as demonstrable cost-effectiveness, before replacing anti-HCV antibody testing in low-incidence populations.

Recommendations

- Screening strategies for HCV infection should be defined according to the local epidemiology of HCV infection, ideally within the framework of local, regional or national action plans **(A1)**.
- Anti-HCV antibody screening and diagnosis should be linked to prevention, care and treatment **(A1)**.
- Screening for HCV infection should be based on the detection of anti-HCV antibodies in serum or plasma by means of EIA **(A1)**.
- Whole blood sampled on DBSs 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 EIA will be performed **(A1)**.
- Rapid diagnostic tests using serum, plasma, fingerstick whole blood or crevicular fluid (saliva) as matrices can be used instead of classical EIAs as point-of-care tests to facilitate anti-HCV antibody screening and improve access to care **(A1)**.
- If anti-HCV antibodies are detected, the presence of HCV RNA by molecular assay or HCV core antigen by EIA in serum or plasma should be determined to identify patients with viraemia **(A1)**.
- Whole blood sampled on DBSs 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 **(A1)**.
- Whole blood sampled on DBSs should not be used as an alternative to serum or plasma obtained by venipuncture for HCV core antigen testing, as a substantial proportion of viraemic patients will be missed due to insufficient sensitivity **(B1)**.
- Reflex testing for HCV RNA or HCV core antigen in patients found to be anti-HCV antibody-positive should be applied to shorten pathways to care **(A1)**.
- Anti-HCV antibody screening for HCV infection can be replaced by low-cost point-of-care tests for viraemia with a lower limit of detection ≤1,000 IU/ml (3.0 Log_{10} IU/ml) or for HCV core antigen testing when such tests are available, if less costly than anti-HCV antibody testing in low-incidence populations **(C2)**.

Goal of HCV therapy

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

Recommendations

- The goal of therapy is to cure HCV infection, in order to: (i) prevent the complications of HCV-related liver and extrahepatic diseases, including hepatic necroinflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death; (ii) improve quality of life and remove stigma; (iii) prevent onward transmission of HCV through treatment as prevention **(A1)**.

Endpoint of HCV therapy

The endpoint of HCV 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 by regulators in Europe and the United States, given that their concordance is >99%.[90]

Undetectable HCV core antigen 12 or 24 weeks after the end of therapy can be used as an alternative to HCV RNA testing to define SVR12 and SVR24, respectively, in patients with detectable HCV core antigen before treatment.[59,60,62,91,92]

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 SVR12 or SVR24.

Long-term follow-up studies have shown that an SVR corresponds to a definitive cure of HCV infection in the vast majority of cases.[5,93] 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.[12] Thus, in these patients, surveillance for HCC must be continued.

Recommendations

- The endpoint of therapy is undetectable HCV RNA in serum or plasma by an assay with a 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 12 weeks (SVR12) or 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 **(A1)**.
- Undetectable HCV RNA in serum or plasma 12 weeks (SVR12) or 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 where sensitive HCV RNA assays are not available and/or not affordable **(B1)**.
- In patients with advanced fibrosis (METAVIR score F3) and cirrhosis (METAVIR score F4), surveillance for HCC must be continued because an SVR will reduce, but not abolish, the risk of HCC **(A1)**.

Indications for treatment: who should be treated?

All treatment-naïve and treatment-experienced patients with recently acquired or chronic HCV infection should be treated without delay.

Urgent treatment must be considered in patients with significant fibrosis (METAVIR score F2 or F3) or cirrhosis (METAVIR score F4), including decompensated cirrhosis; patients with clinically significant extrahepatic 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 and human immunodeficiency virus [HIV] coinfections, diabetes); and individuals at high risk of transmitting HCV (people who inject drugs [PWIDs], men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, patients on haemodialysis, incarcerated individuals). PWIDs and men who have sex with men with high-risk sexual practices should be made aware of the risk and routes of reinfection and transmission and should apply preventive measures after successful treatment.

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

Recommendations

- All treatment-naïve and treatment-experienced patients with recently acquired or chronic HCV infection must be offered treatment without delay **(A1)**.
- Urgent treatment should be considered: 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 extrahepatic 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 and HIV coinfections, diabetes); and in individuals at 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, patients on haemodialysis, incarcerated individuals) **(A1)**.
- Treatment is generally not recommended in patients with limited life expectancy due to non-liver-related comorbidities **(B2)**.

Contraindications to therapy

Few contraindications to treatment with HCV direct-acting antiviral (DAA) drug combinations exist. The use of certain CYP/P-gp-inducing agents (such as carbamazepine, phenytoin and phenobarbital) are contraindicated with all regimens, due to the risk of significantly reduced concentrations of DAAs and therefore the high risk of virological failure (see below). Patients on these anticonvulsants who cannot switch anticonvulsant therapy remain problematic and further data is required in the treatment of such patients with DAAs. Other concomitant medicine-related contraindications are discussed below.

Treatment regimens comprising an NS3-4A protease inhibitor, such as grazoprevir, glecaprevir or voxilaprevir, are contraindicated in patients with decompensated (Child-Pugh B or C) cirrhosis and in patients with previous episodes of decompensation, because of the substantially higher protease inhibitor concentrations in these patients and the related risk of toxicity.[94]

Recommendations

- There are few contraindications to current DAA-based treatments **(A1)**.
- The use of certain cytochrome P450/P-gp-inducing agents (such as carbamazepine, phenytoin and phenobarbital) contraindicates all HCV DAA regimens if they cannot be switched to other medications, due to the risk of significantly reduced concentrations of HCV DAAs **(A1)**.
- Treatment regimens comprising an HCV protease inhibitor, such as grazoprevir, glecaprevir or voxilaprevir, are contraindicated in patients with decompensated (Child-Pugh B or C) cirrhosis and in patients with previous episodes of decompensation **(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 liver comorbidities

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 past or current HBV infection (HBs antigen, anti-HBc antibodies and anti-HBs antibodies), for anti-HIV antibodies and for total antibody to hepatitis A virus (HAV). HBV and HAV vaccination should be proposed for patients who are not immune. Alcohol consumption and substance abuse should be assessed and quantified, and counselling given. In addition, HCV may cause a variety of extrahepatic manifestations which need to be considered in the work-up of HCV-infected patients. Renal function, the presence of diabetes mellitus, obesity and the possibility of drug-induced hepatotoxicity require assessment.

Recommendations

- The contribution of comorbidities to the progression of liver disease must be evaluated and appropriate corrective measures implemented **(A1)**.
- Alcohol consumption and substance abuse should be assessed and quantified, with specific counselling given **(A1)**.
- Extrahepatic manifestations of HCV infection should be identified **(A1)**.
- Renal function, including creatinine and eGFR, should be ascertained **(A1)**.
- All patients should be tested for past or current HBV infection, for HIV infection and for immunity to HAV **(A1)**.
- HBV and HAV vaccination should be proposed to patients who are not immune **(A1)**.

Assessment of liver disease severity

Assessment of liver disease severity is necessary prior to therapy. Diagnosing clinically inapparent cirrhosis (METAVIR score F4) or advanced (bridging) fibrosis (METAVIR score F3) is required, as the choice of treatment regimen and the post-treatment prognosis and surveillance for HCC every 6 months depend on the stage of fibrosis. Patients with cirrhosis need to be assessed for portal hypertension, including oesophageal varices.

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 liver stiffness measurement, such as obesity, high ALT levels, or post-prandial testing. Well established panels of fibrosis biomarkers can also be applied. Among them, aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4) are generally available, simple and inexpensive, and the information they provide is reliable, but they may lack sensitivity in African populations. Both liver stiffness measurement and biomarkers perform well in the identification of cirrhosis *vs.* no fibrosis, but they perform less well in resolving intermediate degrees of fibrosis.[95] 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 3.[96–101] The combination of blood biomarkers or the combination of liver stiffness measurement and a blood test improve accuracy.[102,103] Notably, non-invasive tools should not be used to assess fibrosis stage after therapy, as they are unreliable in this setting.

Liver biopsy may be required in cases of known or suspected mixed aetiologies (*e.g.* metabolic syndrome, alcoholism or autoimmunity).

Table 3. Non-invasive markers cut-offs for prediction of stages of fibrosis, including F3 (advanced fibrosis) and F4 (cirrhosis).

Test	Stage of fibrosis	Number of patients	Cut-off(s)	AUROC	Sensitivity	Specificity	Positive predictive value	Negative predictive value	References
FibroScan®	F3	560 HCV-positive	10 kPa[a]	0.83	72%	80%	62%	89%	96
	F4	1,855 HCV-positive	13 kPa[a]	0.90–0.93	72–77%	85–90%	42–56%	95–98%	96,98,101
ARFI (VTQ®)	F3	2,691 (including 1,428 HCV-positive)	1.60–2.17 m/sec	0.94 (95% CI 0.91–0.95)	84% (95% CI 80–88%)	90% (95% CI 86–92%)	n.a.	n.a.	100
	F4	2,691 (including 1,428 HCV-positive)	2.19–2.67 m/sec	0.91 (95% CI 0.89–0.94)	86% (95% CI 80–91%)	84% (95% CI 80–88%)	n.a.	n.a.	100
Aixplorer®	F3	379 HCV-positive	9 kPa[a]	0.91	90% (95% CI 72–100%)	77% (95% CI 78–92%)	n.a.	n.a.	99
	F4	379 HCV-positive	13 kPa[a]	0.93	86% (95% CI 74–95%)	88% (95% CI 72–98%)	n.a.	n.a.	99
Fibrotest®	F4	1,579 (including 1,295 HCV-positive)	0.74	0.82–0.87	63–71%	81–84%	39–40	93–94	96,98,101
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.	97
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.	97

n.a., not applicable.
[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).

Recommendations

- Liver disease severity must be assessed prior to therapy **(A1)**.
- Cirrhosis must be identified, as some treatment regimens 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)**.
- Fibrosis stage must initially be assessed by non-invasive methods, including liver stiffness measurement or serum biomarkers, including APRI and FIB-4 that are inexpensive and reliable biomarker panels **(A1)**.
- Liver biopsy should be reserved for cases where there is uncertainty or potential additional aetiologies **(A1)**.
- Non-invasive methods should not be used to assess fibrosis stage after therapy, as they are unreliable in this setting **(B1)**.

Recommendations

- The presence of viraemia, reflected by the presence of HCV RNA or HCV core antigen, must be demonstrated prior to initiating therapy **(A1)**.
- 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)**.
- HCV core antigen detection and quantification should be made by EIA **(A1)**.
- HCV RNA detection can be made by a low-cost point-of-care test with a lower limit of detection ≤1,000 IU/ml (3.0 Log_{10} IU/ml) where sensitive HCV RNA assays are not available and/or not affordable **(B1)**.

HCV RNA or HCV core antigen detection/quantification

Detection or detection/quantification of HCV RNA or HCV core antigen in serum or plasma must be available prior to initiating therapy. HCV RNA assessment should be performed with a reliable and sensitive assay, and HCV RNA levels should be expressed in IU/ml. HCV core antigen quantification should be carried out with a reliable EIA assay and core antigen levels should be expressed in fmol/L.

HCV genotype determination

Pan-genotypic HCV drug regimens, including sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, can be used to treat individuals without identifying their HCV genotype and subtype, simplifying therapy.

Nevertheless, identifying certain genotypes before starting first-line therapy remains useful and may be required where drug procurement or pricing dictates genotype-specific treatment, or to optimise treatment regimens. 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.[104] The most widely used, CE-IVD-marked method is based on reverse hybridisation with the second-generation line probe assay.[105] A commercial CE-IVD-marked assay based on deep sequencing is also available.[106,107]

Recently, distinct subtypes of genotypes 1 to 8 that are infrequent in Europe, North America, Japan and Australia (defined as genotype 1 non-1a/1b, genotype 2 non-2a/2b, genotype 3 non-3a, genotype 4 non-4a/4d, and subtypes of genotypes 5 to 8) have been shown to be highly prevalent in certain regions of Africa and Asia and in migrants from these regions.[108–111] Some (for instance genotypes 1l, 4r, 3b, 3g, 6u, 6v among others) harbour natural polymorphisms that confer

inherent resistance to NS5A inhibitors, resulting in unacceptably frequent virological failures in both the resident populations as well as in migrants from these regions.[108,110–115] Thus, HCV genotype and subtype should ideally be determined before treatment in regions where these HCV subtypes are present in substantial proportions, or in migrants from these regions, to optimise treatment regimens. Reverse hybridisation with the line probe assay accurately identifies only genotypes 1 to 6 and subtypes 1a and 1b, but misclassifies most of these infrequent, less treatment-susceptible subtypes.[105] Their accurate determination requires sequence analysis of the NS5B or another coding region of the HCV genome followed by phylogenetic analysis. A commercial CE-IVD-marked assay based on deep sequencing can be used for this purpose, but it requires specific equipment and skills.[106,107] If this assay is not available and/or not affordable, only in-house population sequencing (Sanger sequencing) or deep sequencing technologies can be used. These technologies are not available in low- and middle-income settings where these subtypes are prevalent. Virological studies are required in countries in Africa, Asia and South America to determine the epidemiology, distribution and prevalence of HCV subtypes inherently resistant to NS5A inhibitors and thus to optimise treatment decisions without the need for individual HCV genotype and subtype determination.[111]

Recommendations

- Treatment with pangenotypic regimens, including sofosbuvir/velpatasvir or glecaprevir/pibrentasvir, can be initiated without knowledge of the genotype and subtype with a high probability of success **(A1)**.
- It is still useful to determine the HCV genotype and subtype where such determination is available and does not limit access to care, to identify patients who may benefit from treatment tailoring **(A1)**.
- Migrants from countries where distinct, less treatment-susceptible HCV subtypes are known to be prevalent may benefit from determination of genotype and subtype by means of population or deep sequencing of the NS5B or another coding region followed by phylogenetic analysis, to identify HCV subtypes inherently resistant to NS5A inhibitors (such as subtypes 1l, 4r, 3b, 3g, 6u, 6v and other undetermined subtypes) in order to avoid treatment failure **(B1)**.
- In geographical areas or settings where HCV subtypes inherently resistant to NS5A inhibitors (such as subtypes 1l, 4r, 3b, 3g, 6u, 6v and other undetermined subtypes) are present, the HCV genotype and subtype should be determined whenever possible by means of population or deep sequencing of the NS5B or another coding region followed by phylogenetic analysis (but population or deep sequencing methods are not available for patients in most low- and middle-income countries where these HCV subtypes are present) **(B2)**.

HCV resistance testing

Only 1 standardised semi-automated, deep sequencing-based test for HCV resistance to approved DAAs is available as a purchasable kit. This test is CE-IVD-marked for resistance testing in the NS3 (protease), NS5A and NS5B (polymerase) regions of HCV genotypes 1a, 1b and 3a; sequence information is also generated and interpretable for most of the other HCV genotypes and subtypes.[116,117] Alternatively, resistance testing relies on in-house techniques based on population sequencing (Sanger sequencing) or deep sequencing.[118] A limited number of laboratories have made such tests available in Europe and elsewhere. HCV resistance testing may be technically difficult, particularly for genotypes other than 1 and 4, and the performance of the available in-house assays varies widely.

Access to 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 that are effective in patients with detectable pre-existing resistance-associated substitutions (RAS) at baseline. Thus, systematic testing for HCV resistance prior to treatment in DAA-naïve individuals is not recommended.[119]

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 2016 EASL Recommendations on Treatment of Hepatitis C.[120]

Recommendations

- Testing for HCV resistance prior to first-line treatment is not recommended **(A1)**.
- 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 2016 version of the EASL Recommendations on Treatment of Hepatitis C **(B2)**.

Assessment of drug-drug interactions prior to starting therapy

Prior to starting treatment with a DAA, a full and detailed drug history should be taken including all prescribed medications, over-the-counter drugs, herbal and vitamin preparations and any illicit drug use discussed and documented. The pre-treatment appointment can be used to rationalise prescribing.

The pharmacokinetic profiles and how HCV drugs impact key drug-drug interactions is presented below. For a more comprehensive listing of drug-drug interactions, see Tables 4A to 4H, and www.hep-druginteractions.org for a list of 800 co-medications. For additional information on the disposition of individual DAAs, refer to the Summary of Product Characteristics.

Sofosbuvir

Sofosbuvir is not metabolised by CYP, but is transported by P-gp. Drugs that are potent P-gp inducers significantly decrease sofosbuvir plasma concentrations and may lead to a reduced

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

		SOF	SOF/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
NRTIs	Abacavir	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆
	Tenofovir disoproxil fumarate (TDF)	◆	■*	■*	◆	◆
	Tenofovir alafenamide (TAF)	◆	◆	◆	◆	◆
NNRTIs	Doravirine	◆	◆	◆	◆	◆
	Efavirenz	◆	●	●	●	●
	Etravirine	◆	●	●	●	●
	Nevirapine	◆	●	●	●	●
	Rilpivirine	◆	◆	◆	◆	◆
Protease inhibitors	Atazanavir/ritonavir	◆	◆*	●	●	●
	Atazanavir/cobicistat	◆	◆*	●	●	●
	Darunavir/ritonavir	◆	◆*	■*	●	●
	Darunavir/cobicistat	◆	◆*	◆*	●	●
	Lopinavir/ritonavir	◆	◆*	●	●	●
Entry/Integrase inhibitors	Bictegravir/emtricitabine/tenofovir alafenamide (TAF)	◆	◆	◆	◆	◆
	Cabotegravir	◆	◆	◆	◆	◆
	Dolutegravir	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (TDF)	◆	■*	■*	◆	●
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (TAF)	◆	◆	◆	◆	●
	Maraviroc	◆	◆	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆

DAAs, direct-acting antivirals; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PIB, pibrentasvir; 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 co-administered.

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.

therapeutic effect. Thus, sofosbuvir should not be administered with known inducers of P-gp, such as rifampicin, carbamazepine, phenobarbital, phenytoin or St John's wort. Other potential interactions may occur with moderate inducers such as rifabutin, oxcarbazepine, rifapentine 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 antiretroviral drugs.[121]

Sofosbuvir-based regimens are contraindicated in patients treated with the anti-arrhythmic amiodarone because of the risk of life-threatening arrhythmias. 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. 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 anti-arrhythmics other than amiodarone.[122]

Sofosbuvir/velpatasvir

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 a 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.

There is an increase in exposure of co-medications that are substrates for P-gp and/or BCRP with velpatasvir. The sofosbuvir and velpatasvir combination may be co-administered with P-gp, BCRP, OATP and CYP substrates.[123] Caution is required with co-medications that have a narrow therapeutic window, as reflected by the colour coding for sofosbuvir/velpatasvir in Tables 4A to 4H (*e.g.* for digoxin, dabigatran and ticagrelor).

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

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

	SOF	SOF/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
Amphetamine	◆	◆	◆	◆	◆
Cannabis	◆	◆	◆	◆	◆
Cocaine	◆	◆	◆	◆	◆
Diamorphine	◆	◆	◆	◆	◆
Diazepam	◆	◆	◆	◆	◆
Fentanyl	◆	◆	◆	■	■
Gamma -hydroxybutyrate	◆	◆	◆	■	■
Ketamine	◆	◆	◆	◆	◆
MDMA (ecstasy)	◆	◆	◆	◆	◆
Mephedrone	◆	◆	◆	◆	◆
Methadone	◆	◆	◆	◆	◆
Methamphetamine	◆	◆	◆	◆	◆
Oxycodone	◆	◆	◆	■	■
Phencyclidine (PCP)	◆	◆	◆	◆	◆
Temazepam	◆	◆	◆	◆	◆

DAAs, direct-acting antivirals; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; PIB, pibrentasvir; 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 co-administered.

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/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
Atorvastatin	◆	■	●	●	■
Bezafibrate	◆	◆	◆	◆	◆
Ezetimibe	◆	◆	■	■	◆
Fenofibrate	◆	◆	◆	◆	◆
Fluvastatin	◆	■	●	■	■
Gemfibrozil	◆	◆	◆	■	■
Lovastatin	◆	■	●	●	■
Pitavastatin	◆	■	●	■	◆
Pravastatin	◆	◆	■	■	◆
Rosuvastatin	◆	■	●	■	■
Simvastatin	◆	■	●	●	■

DAAs, direct-acting antivirals; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; PIB, pibrentasvir; 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 co-administered.

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

		SOF	SOF/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
Anti-depressants	Amitriptyline	◆	◆	◆	◆	◆
	Citalopram	◆	◆	◆	◆	◆
	Duloxetine	◆	◆	◆	◆	◆
	Escitalopram	◆	◆	◆	◆	◆
	Fluoxetine	◆	◆	◆	◆	◆
	Paroxetine	◆	◆	◆	◆	◆
	Sertraline	◆	◆	◆	◆	◆
	Trazodone	◆	◆	◆	◆	◆
	Venlafaxine	◆	◆	◆	◆	◆
Anti-psychotics	Amisulpride	◆	◆	◆	◆	◆
	Aripiprazole	◆	◆	◆	■	■
	Chlorpromazine	◆	◆	◆	◆	◆
	Clozapine	◆	◆	◆	■	◆
	Flupentixol	◆	◆	◆	◆	◆
	Haloperidol	◆	◆	◆	◆	◆
	Olanzapine	◆	◆	◆	◆	◆
	Paliperidone	◆	◆	■	■	◆
	Quetiapine	◆	◆	◆	■	■
	Risperidone	◆	◆	◆	◆	◆
	Zuclopentixol	◆	◆	◆	◆	◆

DAAs, direct-acting antivirals; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; PIB, pibrentasvir; 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 co-administered.

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

		SOF	SOF/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
Antiarrhythmics	Amiodarone	●	●	●	■	■
	Digoxin	◆	■	■	■	◆
	Vernakalant	◆	◆	◆	◆	◆
	Flecainide	◆	◆	◆	◆	◆
Beta-blockers	Atenolol	◆	◆	◆	◆	◆
	Bisoprolol	◆	◆	◆	◆	◆
	Carvedilol	◆	■	■	■	◆
	Propranolol	◆	◆	◆	◆	◆
Calcium channel blockers	Amlodipine	◆	◆	◆	◆	◆
	Diltiazem	◆	■	■	■	◆
	Nifedipine	◆	◆	◆	◆	◆
Hypertension and heart failure agents	Losartan	◆	◆	◆	◆	◆
	Doxazosin	◆	◆	◆	◆	◆
	Enalapril	◆	◆	■	■	◆

DAAs, direct-acting antivirals; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; PIB, pibrentasvir; 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 co-administered.

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.*

inhibitor, at a maximum dose comparable to omeprazole 20 mg (Table 5).

Sofosbuvir/velpatasvir may be given with most antiretroviral drugs, 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. Patients on a regimen containing tenofovir disoproxil fumarate (TDF), particularly if prescribed with the pharmacokinetic enhancers ritonavir or cobicistat, require monitoring of renal function.[124]

Sofosbuvir/velpatasvir/voxilaprevir

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 exposure to these co-medications.[125] Dose adjustment or additional monitoring is required. 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 BCRP substrates, 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 and carvedilol. 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 exposure to 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. Moderate P-gp or CYP inducers (such as modafinil, efavirenz, oxcarbazepine and others) which can also reduce exposure of this DAA 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

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

	SOF	SOF/VEL	SOF/VEL /VOX	GLE/PIB	GZR/EBR
Azathioprine	◆	◆	◆	◆	◆
Cyclosporine	◆	◆	●	■	●
Etanercept	◆	◆	◆	◆	◆
Mycophenolate	◆	◆	◆	◆	◆
Sirolimus	◆	◆	■	■	■
Tacrolimus	◆	◆	■	■	■

DAAs, direct-acting antivirals; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; PIB, pibrentasvir; 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 co-administered.

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/VEL	SOF/VEL /VOX	GLE/PIB	GZR/EBR
Clopidogrel	◆	◆	◆	◆	◆
Dabigatran	◆	■	●	●	■
Ticagrelor	◆	■	■	■	■
Rivaroxaban	◆	■	■	■	■
Apixaban	◆	■	■	■	■
Edoxaban	◆	■	●	■	■
Warfarin	■	■	■	■	■

DAAs, direct-acting antivirals; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; PIB, pibrentasvir; 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 co-administered.

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.*

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.

Sofosbuvir/velpatasvir/voxilaprevir is not recommended with the inducing HIV 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, and renal function should be monitored in patients on an antiretroviral regimen containing TDF.

Glecaprevir/pibrentasvir

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, particularly in narrow therapeutic index drugs.

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. Prescription of moderate inducers, such as

Table 4H. Drug-drug interactions between HCV DAAs and anticonvulsants.

	SOF	SOF/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
Carbamazepine	●	●	●	●	●
Clonazepam	◆	◆	◆	◆	◆
Eslicarbazepine	◆	●	●	●	●
Ethosuximide	◆	◆	◆	◆	◆
Gabapentin	◆	◆	◆	◆	◆
Lacosamide	◆	◆	◆	◆	◆
Lamotrigine	◆	◆	◆	◆	◆
Levetiracetam	◆	◆	◆	◆	◆
Lorazepam	◆	◆	◆	◆	◆
Oxcarbazepine	●	●	●	●	●
Phenobarbital	●	●	●	●	●
Phenytoin	●	●	●	●	●
Primidone	●	●	●	●	●
Topiramate	◆	◆	◆	◆	◆
Valproate	◆	◆	◆	◆	◆
Zonisamide	◆	◆	◆	◆	◆

DAAs, direct-acting antivirals; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; PIB, pibrentasvir; 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 co-administered.

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.*

oxcarbazepine and eslicarbazepine, is not recommended. Co-medications that inhibit P-gp and BCRP may increase plasma exposure of glecaprevir/pibrentasvir. Similarly, OATP1B1/3

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.

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 metabolised by CYP3A with a narrow therapeutic index (*e.g.* tacrolimus) or drugs with large dose ranges such as quetiapine, whereas patients on higher doses may need additional monitoring, dose reduction and/or an electrocardiogram.

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. The C_{max} of glecaprevir decreases on average by 64% when co-administered with omeprazole 40 mg. Data indicate that this does not affect SVR and 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 have not been studied and may lead to a greater decrease in glecaprevir concentrations. As with any DAA, reviewing the need for proton pump inhibitor in the first instance must be considered.

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 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 the integrase inhibitor elvitegravir.[126]

Grazoprevir/elbasvir

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 to 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 (34% increase in midazolam exposure) and elbasvir a weak inhibitor of P-gp. Caution is required when co-administering drugs metabolised by CYP3A and P-gp, especially with a narrow therapeutic index (*e.g.* tacrolimus, some statins, dabigatran, ticagrelor), or drugs with large ranges such as quetiapine.

There are limitations on which antiretrovirals can be co-administered with elbasvir/grazoprevir. The nucleotide reverse transcriptase inhibitors abacavir, lamivudine, tenofovir (either as TDF or as tenofovir alafenamide [TAF]), emtricitabine, along with rilpivirine, raltegravir, dolutegravir, maraviroc, doravirine, bictegravir and cabotegravir can be used (Table 4A).

Recommendations

- A thorough drug-drug interaction risk assessment prior to starting HCV 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 4H 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-retroviral 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)**.

Virological results of clinical trials and real-world studies that support the present recommendations on treatment of chronic hepatitis C in patients without cirrhosis and in patients with compensated (Child-Pugh A) cirrhosis

Sofosbuvir/velpatasvir

The below recommendations are based on the results of the phase III ASTRAL-1, ASTRAL-2, ASTRAL-3 and ASTRAL-5 trials, additional phase III or IV trials and post-approval real-world studies.

Patients infected with HCV genotypes 1, 2, 4, 5 and 6

In ASTRAL-1, in patients with HCV genotype 1 infection (22% with cirrhosis; 66% treatment-naïve; 34% treatment-experienced, of whom 44% were exposed to previous DAAs) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, an SVR12 was observed in 98% (206/210; 1 relapse) of patients infected with genotype 1a and in 99% (117/118; 1 relapse) of those infected with genotype 1b.[127] The SVR12 rate was 100% (104/104) in treatment-naïve (approximately two-thirds) and treatment-experienced (one-third) patients infected with HCV genotype 2, of whom approximately 30% had cirrhosis.[127] In the phase III ASTRAL-2 trial in patients with HCV genotype 2 infection (14% with compensated cirrhosis, 86% treatment-naïve, 14% treatment-experienced) receiving sofosbuvir/velpatasvir for 12 weeks, the SVR12 rate was 99% (133/134; no virological failure).[128] In ASTRAL-1, patients with HCV genotype 4 infection (23% with cirrhosis, 55% treatment-naïve, 45% treatment-experienced) treated with the same regimen for 12 weeks achieved SVR12 in 100% (116/116) of cases, those with HCV genotype 5 (14% with cirrhosis, 69% treatment-naïve, 31% treatment-experienced) in 97% (34/35) of cases, and those with HCV genotype 6 (15% with cirrhosis, 93% treatment-naïve, 17% treatment-experienced) in 100% (41/41) of cases.[127] The latter results were confirmed by a 97% (35/36; 1 relapse) SVR12 rate in a phase III trial in patients infected with genotype 6 from Singapore, Malaysia, Thailand and Vietnam.[129] In the ASTRAL-1 trial, 1 patient subsequently found to be infected with HCV genotype 7 achieved SVR12 after 12 weeks of sofosbuvir/velpatasvir.[130]

Patients infected with HCV genotype 3

Patients with HCV genotype 3 infection were studied in the phase III ASTRAL-3 trial (29% with compensated cirrhosis, 74% treatment-naïve, 26% treatment-experienced). After treatment with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, the SVR12 rate was 98% (160/163; 1 relapse) in treatment-naïve patients without cirrhosis. An overall 90% (104/116; 10 virological failures) SVR12 rate was observed in patients who were treatment-experienced or had cirrhosis with this regimen, including 93% (40/43; 3 relapses) in treatment-naïve patients with compensated cirrhosis, 91% (31/34; 3 relapses) in treatment-experienced patients without cirrhosis and 89% (33/37; 4 relapses) in treatment-experienced patients with compensated cirrhosis.[128] The SVR12 rates after 12 weeks of sofosbuvir/velpatasvir were 97% (225/231) in patients without NS5A RASs at baseline *vs.* 88% (38/43) in those with detectable NS5A RASs at baseline in this study. Treatment failures associated with NS5A RASs were observed in both treatment-experienced patients without cirrhosis and treatment-naïve and treatment-experienced patients with compensated cirrhosis.[128] In the POLARIS-3 trial, which assessed the safety and efficacy of the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir in patients infected with HCV genotype 3, the SVR rate was 96% (105/109) after 12 weeks of sofosbuvir/velpatasvir in the control arm. There were only 4 patients with the NS5A Y93H RAS (who all achieved SVR) in this arm.[36]

In a randomised controlled trial, genotype 3-infected patients with compensated cirrhosis were assigned to receive sofosbuvir and velpatasvir for 12 weeks, or sofosbuvir and velpatasvir plus ribavirin for 12 weeks.[131] Although the study was not powered to show a significant difference, there were 6/101 (6%) virological failures in the no ribavirin arm *vs.* 2/103 (2%) in the ribavirin-containing arm. In the sofosbuvir and velpatasvir without ribavirin arm, the proportion of patients with baseline NS5A RASs who achieved an SVR was lower than that of patients without NS5A RASs (84% *vs.* 96%, respectively). In the sofosbuvir and velpatasvir plus ribavirin arm, baseline NS5A RASs had less effect on the proportion of patients with an SVR (96% *vs.* 99%, respectively).[131] When pooling the results of ASTRAL-3, POLARIS-3 and the randomised controlled trial in patients with cirrhosis, the SVR rates after sofosbuvir/velpatasvir without ribavirin were 73/81 (90%) in patients with any NS5A RAS, but only 27/33 (82%) in patients with the Y93H RAS.[36,128,131]

Patients coinfected with HIV

In the ASTRAL-5 trial in treatment-naïve or treatment-experienced patients with or without cirrhosis coinfected with HCV and HIV, the SVR12 rates with the fixed-dose combination of sofosbuvir and velpatasvir were 95% (63/66; 2 relapses) in patients with genotype 1a, 92% (11/12; no virological failure) in patients with genotype 1b, 100% (11/11) in patients with genotype 2, 92% (11/12; no virological failure) in patients with genotype 3, and 100% (4/4) in patients with genotype 4.[132]

Pooled resistance analysis

In a pooled resistance analysis from phase III trials with sofosbuvir/velpatasvir, virological failure was observed in 20/1,778 patients (1.1%), including 7/694 (1.0%) infected with genotype 1, 0/316 infected with genotype 2, 12/478 (2.5%) infected with genotype 3, 1/197 (0.5%) infected with genotype 4 and 0/93 infected with genotypes 5 to 7.[133]

Real-world studies

The high SVR rates achieved with sofosbuvir/velpatasvir have been confirmed in a large number of real-world studies. In particular, the real-world efficacy of the fixed-dose combination of sofosbuvir and velpatasvir administered for 12 weeks has been reported in a very large and heterogeneous population from 12 cohorts originating from 7 countries across the European Union and North America.[33] The intent-to-treat SVR12/24 rate was 93% (5,134/5,541), while the per protocol SVR12/24 rate was 98% (5,134/5,214) due to a 6% non-virological failure rate (lost-to-follow-up, early discontinuation, death, *etc*). Overall, the virological failure rate was 1.4% (80/5,541). Per protocol, the SVR12/24 rates were 99% (1,595/1,615) for genotype 1, 99% (1,535/1,553) for genotype 2, 98% (1,646/1,686) for genotype 3, 99% (238/239) for genotype 4, 98% (67/68) for genotypes 5 and 6, and 100% (36/36) for mixed/unknown genotypes, with no difference according to the stage of fibrosis or the presence of cirrhosis. The results for populations known to be more "difficult-to-cure" were 98% (753/766) for treatment-experienced patients, 98% (678/693) for historic or current intravenous drug users, 96% (297/308) for patients infected with genotype 3 with compensated cirrhosis, 98% (263/268) for patients using proton pump inhibitors at baseline, 99% (443/447) for patients aged more than 70 years, and 96% (181/188) for patients coinfected with HIV.[33]

In another large, non-selective real-world cohort study based on the English HCV Treatment Registry, SVR12 rates with

sofosbuvir/velpatasvir plus ribavirin were significantly higher than those with sofosbuvir/velpatasvir without ribavirin in patients infected with HCV genotype 3 with compensated cirrhosis (98.0% [192/196] *vs.* 92% [200/218], $p = 0.005$). The addition of ribavirin did not make a significant difference in genotype 3 patients with no, mild or moderate fibrosis (F0–F3).[134]

Patients infected with "unusual" HCV subtypes inherently resistant to NS5A inhibitors

Limited data are available on the efficacy of the fixed-dose combination of sofosbuvir and velpatasvir in patients with so-called "unusual" (denoting less common in Western countries) HCV subtypes that are inherently resistant to NS5A inhibitors. However, the intrinsic presence of several polymorphisms in the NS5A region of the genome of these viruses is likely to impact SVR rates, as suggested by *in vitro* studies.[114,115,135] In a single-arm, open-label phase III study performed in Asia (China, Thailand, Vietnam, Singapore and Malaysia) in patients infected with HCV genotypes 1 to 6, an overall SVR12 rate of 96% (362/375) was achieved. Notably, 42 of the 375 patients included (11%) were infected with HCV subtype 3b and had baseline RASs in the NS5A region, generally A30K + L31M. Among patients with subtype 3b infection, 89% (25/28) of those without cirrhosis and only 50% (7/14) of those with cirrhosis achieved SVR12.[110] Data is required on other "unusual" subtypes inherently resistant to NS5A inhibitors, including subtypes 1l, 4r, 3g, 6u, 6v and others that remain to be determined. From 114 patients who failed to achieve SVR after a course of sofosbuvir/velpatasvir sent to the French National Reference Center for Viral Hepatitis B, C and D for subtyping and resistance analysis, 6 were infected with a non-1a/1b genotype 1 subtype, 16 with a non-2a/2c subtype and 6 with a non-4a/4d subtype (Slim Fourati and Jean-Michel Pawlotsky, personal communication to the panel).

Glecaprevir/pibrentasvir

The below recommendations are based on the phase II SURVEYOR-2 trial, on phase III studies (ENDURANCE-1, ENDURANCE-3, ENDURANCE-4, EXPEDITION-1, EXPEDITION-2, EXPEDITION-8, CERTAIN-1, CERTAIN-2, VOYAGE-1, and VOYAGE-2), on integrated analyses of phase II and III trials and on real-world data.

Patients infected with HCV genotypes 1 to 6 without cirrhosis

In the ENDURANCE-1 phase III trial, the SVR12 rate was 99% (150/152; 1 virological breakthrough) in genotype 1a-infected and 100% (198/198) in genotype 1b-infected treatment-naïve or treatment-experienced patients without cirrhosis receiving 8 weeks of glecaprevir/pibrentasvir, including 13 and 2 patients who were HIV-coinfected, respectively.[136] These results were confirmed in the CERTAIN-1 phase III trial, showing an SVR rate of 99% (128/129, no virological failure) in Japanese patients infected with genotype 1 (97% of whom were infected with genotype 1b) receiving the same treatment regimen for 8 weeks.[137]

In the phase II SURVEYOR-2 study, the SVR12 rate was 98% (53/54; no virological failure) in treatment-naïve and treatment-experienced patients infected with HCV genotype 2 without cirrhosis after 8 weeks of glecaprevir/pibrentasvir.[138] These results were confirmed in the CERTAIN-2 trial, showing an SVR rate of 98% (88/90, no virological failure) in Japanese patients infected with genotype 2 without cirrhosis receiving the same treatment regimen for 8 weeks.[139]

In the phase III ENDURANCE-3 trial, SVR12 was achieved in 95% (149/157; 5 relapses, 1 virological breakthrough) of treatment-naïve patients, infected with HCV genotype 3 without cirrhosis, receiving glecaprevir/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).[140] 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.[141] In the SURVEYOR-2 study, the SVR12 rates were 91% (20/22; 2 relapses) and 95% (21/22; 1 relapse) in treatment-experienced patients with HCV genotype 3 without cirrhosis treated for 12 or 16 weeks, respectively.[138] 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 and 90% (44/49) in treatment-experienced patients without cirrhosis treated for 12 weeks with glecaprevir/pibrentasvir.[142]

In the phase II SURVEYOR-2 trial, the SVR12 rate was 93% (43/46; no virological failure) in treatment-naïve and treatment-experienced patients infected with HCV genotype 4 without cirrhosis receiving glecaprevir/pibrentasvir for 8 weeks,[138] while in ENDURANCE-4, similar patients achieved SVR12 in 99% (75/76; no virological failures) of cases after 12 weeks of treatment.[143] Two out of 2 patients without cirrhosis infected with HCV genotype 5 achieved SVR12 after 8 weeks of treatment in SURVEYOR-2,[138] while in ENDURANCE-4, genotype 5 patients without cirrhosis treated for 12 weeks achieved SVR in 100% (26/26) of cases.[143] In patients infected with genotype 6, 90% (9/10; no virological failure) of treatment-naïve and treatment-experienced individuals without cirrhosis achieved SVR12 after 8 weeks of treatment in SURVEYOR-2,[138] and 100% (19/19) achieved SVR12 after 12 weeks of treatment in ENDURANCE-4.[143]

In the VOYAGE-1 phase III trial, 362 Asian patients without cirrhosis, infected with HCV genotypes 1 to 6 (genotype 1a: 5%; genotype 1b: 45%; genotype 2: 38%; genotype 3a: 4%; genotype 3b: 3%; genotype 6: 5%) were treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks.[144] The global SVR12 rate was 97% (352/362; 2 on-treatment virological failures and 6 relapses), including 99.4% (178/179; no virological failure) in patients infected with genotype 1 and 98% (136/139) in patients infected with genotype 2. All 8 patients who experienced virological failure were from China: the 2 patients who had on-treatment virological failure were infected with genotype 3b; among the 6 patients who experienced post-treatment relapse, 3 were infected with genotype 3b, 2 with genotype 2 and 1 with genotype 3a.[144]

Patients infected with HCV genotypes 1 to 6 with compensated (Child-Pugh A) cirrhosis

The phase III EXPEDITION-1 trial included treatment-naïve and treatment-experienced patients infected with HCV genotypes 1, 2, 4, 5 or 6 with compensated (Child-Pugh A) cirrhosis who received glecaprevir/pibrentasvir for 12 weeks. The SVR12 rates were 98% (47/48; 1 relapse) in genotype 1a patients, 100% (39/39) in genotype 1b patients, 100% (31/31) in genotype 2 patients, 100% (16/16) in genotype 4 patients, 100% (2/2) in genotype 5 patients and 100% (7/7) in genotype 6 patients.[145] These results were confirmed in Japanese patients in the phase III CERTAIN-1

and CERTAIN-2 trials for genotypes 1 and 2, with SVR12 rates of 100% (38/38) and 100% (18/18), respectively.[137,139]

In an integrated analysis of phase II and III trials, the SVR12 rate after 12 weeks of glecaprevir/pibrentasvir in treatment-naïve patients, infected with genotype 3 with compensated cirrhosis, was 97% (67/69; 1 virological breakthrough).[141] In the SURVEYOR-2 study, the SVR12 rates were 97% (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.[146] A pooled analysis of phase II and III clinical trials in patients infected with genotype 3 showed SVR12 rates of 98% (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.[142] No data have been generated on 12 weeks of treatment with glecaprevir and pibrentasvir in treatment-experienced patients with compensated cirrhosis.

In the phase III EXPEDITION-8 trial, 343 treatment-naïve patients (95 with genotype 1a, 136 with genotype 1b, 26 with genotype 2, 63 with genotype 3, 13 with genotype 4, 1 with genotype 5 and 9 with genotype 6) with compensated cirrhosis (median Fibroscan score in 295 patients: 20.2 [16.4–26.6]) have been treated with 8 weeks of glecaprevir/pibrentasvir. Among them, 171 (50%) had a platelet count <150 × 10^9/L and 63 (18%) a platelet count <100 × 10^9/L. The global SVR rate was 98% (335/343). The SVR12 rates by genotype were: 98% (226/231; no virological failure) for genotype 1, 100% (26/26) for genotype 2, 95% (60/63; 1 relapse) for genotype 3, 100% (13/13) for genotype 4, 100% (1/1) for genotype 5 and 100% (9/9) for genotype 6.[147]

In the VOYAGE-2 phase III trial, 160 Asian patients with compensated (Child-Pugh A) cirrhosis, infected with HCV genotypes 1 to 6 (genotype 1a: <1%; genotype 1b: 53%; genotype 2: 33%; genotype 3a: 4%; genotype 3b: 5%; genotype 4: <1%; genotype 6: 4%), were treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks, except treatment-experienced patients infected with genotype 6 who received treatment for 16 weeks.[144] The SVR12 rate was 99% (159/160; 1 relapse). The patient who relapsed was from China and infected with genotype 3b.[144]

Patients coinfected with HIV

One hundred and fifty-three patients coinfected with HIV, including 16 (10%) with compensated cirrhosis, were enrolled in the phase III EXPEDITION-2 study. The 137 patients without cirrhosis (66 with genotype 1a, 21 with genotype 1b, 9 with genotype 2, 22 with genotype 3, 16 with genotype 4 and 3 with genotype 6) received 8 weeks of glecaprevir/pibrentasvir, while the 16 patients with cirrhosis (5 with genotype 1a, 5 with genotype 1b, 1 with genotype 2, 4 with genotype 3, 1 with genotype 4) were treated for 12 weeks. The SVR12 rate was 98% (150/153; no virological failures) in 137 patients treated for 8 weeks. One genotype 3-infected patient with cirrhosis had on-treatment virological failure.[126]

Pooled resistance analysis

In a pooled resistance analysis from phase II and III trials with glecaprevir/pibrentasvir, virological failure was observed in 22/2,256 patients (1.0%), including 2/889 (0.2%) infected with genotype 1, 2/466 (0.4%) infected with genotype 2, 18/643 (2.8%) infected with genotype 3, and 0/258 infected with genotypes 4 to 6.[148] The higher frequency of glecaprevir/pibrentasvir failure in patients infected with genotype 3 was confirmed in a meta-analysis including 3,302 patients from 17 studies.[149] Among 50 patients with a virological failure, 48% were infected with genotype 3 *vs.* 44% with genotype 1. Baseline RASs were present in 44/50 patients (88%). The presence of NS5A RASs Y93H and A30K at baseline significantly impacted SVR12 rates in patients infected with genotype 3; in contrast, the presence of NS5A RASs at baseline had no effect in those infected with genotype 1.[149]

Real-world studies

The high SVR rates achieved with glecaprevir/pibrentasvir have been confirmed in a large number of real-world studies. One of the reports included 16 real-world cohorts including 11,101 adults treated with glecaprevir/pibrentasvir for 8 or 12 weeks. The global intent-to-treat and modified intent-to-treat (mITT: excluding non-virological failures) SVR rates were 97% (7,808/8,082 from 14 cohorts) and 98% (5,757/5,863 from 12 cohorts), with a 2.4% rate of virological failure (143/5,863 mITT patients).[150] The intent-to-treat and mITT SVR12 rates by genotype were, respectively: 95% (1,609/1,685 from 6 cohorts) and 98% (2,288/2,335 from 5 cohorts) for genotype 1; 96% (361/375 from 6 cohorts) and 98% (359/368 from 5 cohorts) for genotype 2; 95% (1,032/1,084 from 6 cohorts) and 96% (651/679 from 7 cohorts) for genotype 3; and 99% (212/214 from 4 cohorts) and 98% (194/197 from 3 cohorts) for genotype 4. There was no difference in SVR12 rates according to the presence or absence of cirrhosis (intent-to-treat: 98% *vs.* 97%; mITT: 98% *vs.* 98%, respectively) or to the duration of treatment of 8 or 12 weeks (intent-to-treat: 96% *vs.* 96%; mITT: 98% *vs.* 97%, respectively). mITT SVR12 was achieved in more than 99% (3,267/3,280 from 8 cohorts) of treatment-naïve patients without cirrhosis who underwent 8 weeks of treatment and in 99% (295/298 from 7 cohorts) of treatment-naïve patients with compensated cirrhosis who underwent 12 weeks of treatment. The mITT results for populations known to be more “difficult-to-cure” were 98% for patients with F3 fibrosis (180/183 from 4 cohorts), 96% for patients with alcohol abuse or dependence (111/115 from 2 cohorts), 99% in patients with chronic kidney disease stage 4 or 5 (58/59 from 2 cohorts), 97% in patients using drugs or on opioid substitution (227/233 from 3 cohorts), 98% in patients with psychiatric disorders (103/105 from 2 cohorts) and 98% in patients using proton pump inhibitors (179/183 from 3 cohorts).[150]

Patients infected with HCV subtypes inherently resistant to NS5A inhibitors

Few data are available on the efficacy of the fixed-dose combination of glecaprevir and pibrentasvir in patients with “unusual” HCV subtypes inherently resistant to NS5A inhibitors. Pibrentasvir has a higher barrier to resistance than other NS5A inhibitors against several NS5A RASs intrinsically present in the genome of these viruses.[114,115,135] From 24 patients who failed to achieve SVR after a course of glecaprevir/pibrentasvir sent to the French National Reference Center for Viral Hepatitis B, C and D for subtyping and resistance analysis (the introduction of glecaprevir/pibrentasvir is more recent in France than that of sofosbuvir/velpatasvir, at least partly explaining the small number of cases observed thus far), 1 was infected with a non-1a/1b genotype 1 subtype, 2 with a non-2a/2c subtype, 6 with a non-4a/4d subtype and 1 with a non-6a subtype (Slim Fourati

and Jean-Michel Pawlotsky, personal communication to the panel). Among the 20 patients infected with HCV genotype 3b included in the VOYAGE-1 and VOYAGE-2 Asian phase III trials, 6 patients (30%) experienced a virological failure (out of a total of 9 with virological failure among 522 patients treated with glecaprevir and pibrentasvir).[144]

Grazoprevir/elbasvir for genotype 1b

In the phase III C-EDGE-TN trial, in treatment-naïve patients infected with genotype 1b receiving grazoprevir and elbasvir for 12 weeks, the SVR12 rate was 98% (129/131; 1 relapse).[151] In the C-CORAL trial, performed in Russia and the Asia-Pacific region, the SVR12 rate was 98% with the same regimen (382/389; 5 relapses).[152] In treatment-experienced patients included in the C-EDGE-TE phase III trial, in which approximately one-third of patients had compensated cirrhosis, the SVR12 rate in genotype 1b patients was 100% (34/34) after 12 weeks of grazoprevir/elbasvir.[153] A pooled analysis of all phase II and III trials showed an SVR rate of 97% (1,040/1,070; 15 relapses and 15 non-virological failures) in patients infected with genotype 1b treated for 12 weeks with this regimen.[47]

In the open-label C-EDGE-COINFECTION trial, the SVR12 rate was 95% (42/44) in genotype 1b-infected treatment-naïve patients coinfected with HIV, with or without compensated cirrhosis, treated with grazoprevir and elbasvir for 12 weeks.[154]

In the STREAGER study, treatment-naïve genotype 1b-infected patients with F0–F2 fibrosis (excluding patients with advanced fibrosis or cirrhosis) treated with grazoprevir/elbasvir for 8 weeks achieved an SVR12 in 97% (109/112; 3 relapses) and an SVR24 in 95% (106/111; 5 relapses) of cases.[155] In the Chinese EGALITE study, 8 weeks and 12 weeks of treatment yielded SVR12 rates of 88% (36/41, 4 relapses) and 100% (41/41), respectively, in treatment-naïve patients infected with genotype 1b with mild fibrosis.[156]

Sofosbuvir/velpatasvir/voxilaprevir for genotype 3a

Patients infected with HCV genotype 3 have been treated with sofosbuvir/velpatasvir/voxilaprevir in 2 phase III trials: POLARIS-2 and POLARIS-3. In POLARIS-2, in which approximately three-quarters of patients were treatment-naïve and one-quarter treatment-experienced and approximately 20% of individuals had cirrhosis, the SVR12 rate was 99% (91/92; no virological failure) after 8 weeks of the triple combination of sofosbuvir, velpatasvir and voxilaprevir in genotype 3-infected patients.[36] 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.[36] No data with 12 weeks of therapy have been generated in these phase III trials.

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

General principles of treatment of chronic hepatitis C in patients without cirrhosis and in patients with compensated (Child-Pugh A) cirrhosis

Because of their virological efficacy, ease of use, safety and tolerability, interferon (IFN)-free, ribavirin-free, pangenotypic DAA-based regimens (including sofosbuvir/velpatasvir, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir) are the recommended options in HCV-infected patients without cirrhosis and in those 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).

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).

Generic drugs and their combinations produced by companies under the license of the Medicines Patent Pool and prequalified by WHO and/or other regulatory authorities have been shown to generate similar results to the original compounds, with similar safety and tolerability.[157–167]

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 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.[120,168–171] In particular, in many low- and middle-income countries where the pangenotypic DAA combinations recommended in the present document are not available and/or not affordable, the combination of generic sofosbuvir and daclatasvir is safe and well tolerated and provides high SVR rates at a very low price. This combination should be used according to the 2016 EASL Recommendations on Treatment of Hepatitis C.[120]

Recommendations

- Because of their virological efficacy, ease of use, safety and tolerability, IFN-free, ribavirin-free, pangenotypic DAA-based regimens are preferred 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) **(A1)**.
- The following pangenotypic regimens are recommended for the treatment of patients infected with HCV, 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 3 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.

- The non-pangenotypic fixed-dose combination of grazoprevir (100 mg) and elbasvir (50 mg) in a single tablet administered once daily can also be used in patients infected with HCV genotype 1b **(A1)**.
- The same IFN-free, ribavirin-free treatment regimens should be used in HIV-coinfected patients as in patients without HIV infection, because the virological results of therapy are identical **(A1)**.
- In HIV-coinfected patients, treatment alterations or dose adjustments should be performed in case of interactions with antiretroviral drugs **(A1)**.
- 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 pangenotypic DAA regimens become available and affordable **(A1)**.
- Generic drugs can be used, provided that quality controls are met and guaranteed by the provider **(A1)**.
- In low- and middle-income countries where the IFN-free, ribavirin-free options proposed in this document are not available and/or not affordable, the pangenotypic combination of generic sofosbuvir and generic daclatasvir is safe, highly efficacious and affordable, and should be used according to the 2016 EASL Recommendations on Treatment of Hepatitis C **(A1)**.
- In patients with advanced fibrosis (F3) or compensated (Child-Pugh A) cirrhosis (F4), post-SVR surveillance for the diagnosis of HCC and linkage to care must be provided when treatment for HCC is available **(A1)**.

Simplified, genotyping/subtyping-free treatment of chronic hepatitis C with pangenotypic drug regimens in patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis

Improving access to anti-HCV therapy has become a worldwide priority. Many obstacles remain that reduce the global benefit of HCV treatment, including the numbers of infected individuals, the cost of diagnostic tests, the amount of information needed to inform treatment decisions, and the relative complexity of treatment strategies based on genotype. Thus, wherever genotype/subtype determination is not available, not affordable and/or limits access to HCV care, simplified treatment without knowledge of the HCV genotype and subtype should be used to facilitate the cascade of care. Populations who are historically less engaged in healthcare, such as PWIDs, prisoners, homeless individuals, migrants, people living in rural communities with poor access to care, patients struggling with mental health or substance use disorders, men who have sex with men, sex workers, or indigenous populations are those who will benefit more from a streamlined care pathway.

The only information needed to start treatment with either sofosbuvir/velpatasvir or glecaprevir/pibrentasvir in patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, including treatment-naïve or treatment-experienced patients (as defined above), 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 the duration of treatment (8 or 12 weeks) with certain HCV genotypes and regimens, and 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 Table 3). If this information is not available, a universal duration of 12 weeks is recommended, regardless of the treatment regimen used. Lower SVR12 rates may be achieved in patients infected with HCV genotype 3 and compensated (Child-Pugh A) cirrhosis than in other patients, but efficacious retreatment strategies exist in individuals with virological failure.

The following simplified treatment recommendations are summarised in Table 6A.

Recommendations

- Simplified, genotyping/subtyping-free, pangenotypic anti-HCV treatment must be used to improve access to HCV treatment and increase the global infection cure rates in any setting where genotype and subtype determination is not available, not affordable and/or would limit access to therapy **(A1)**.
- Pre-treatment assessment can be limited to proof of HCV viraemia (presence of HCV RNA or HCV core antigen) and determination of the presence or absence of cirrhosis by a non-invasive method **(A1)**.
- Possible drug-drug interactions should be carefully checked and dose modifications implemented when necessary **(A1)**.
- Treatment-naïve patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis and treatment-experienced patients without cirrhosis should be treated without testing genotype/subtype with either: (i) the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, or (ii) the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks **(B1)**.
- Treatment-experienced patients with compensated (Child-Pugh A) cirrhosis should be treated without testing genotype/subtype with either: (i) the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, or (ii) the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks **(B1)**.
- Given the high SVR12 rates expected with these regimens across all groups of patients if adherent, testing for SVR can be omitted (except in patients with high-risk behaviours and risk of reinfection who require SVR testing 12 weeks after the end of treatment and yearly thereafter whenever possible) **(B1)**.

Genotype/subtype-based treatment of chronic hepatitis C in patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis

In settings where HCV genotype and subtype determination are available and affordable and would not limit access to care, this information remains useful to optimise the results of anti-HCV therapy. Identifying genotype 3a patients with compensated

Table 6A. Recommendations for simplified, genotyping/subtyping-free treatment of HCV-monoinfected or HCV-HIV coinfected adult (≥18 years) and adolescent (12–17 years) patients with chronic hepatitis C 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; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin).

Type of treatment	Genotype	Cirrhosis status	Prior treatment experience	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Simplified treatment, no genotype/subtype determination[a]	All genotypes	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced		12 weeks		

IFN, interferon.
[a]Whenever HCV genotype and subtype determination is not available, not affordable and/or limits access to care.

cirrhosis enables reinforced treatment, while identifying patients infected with HCV genotype 1b allows treatment with the less expensive non-pangenotypic combination of grazoprevir and elbasvir.

The combination of sofosbuvir and velpatasvir without ribavirin is suboptimal in patients with compensated cirrhosis infected with HCV genotype 3a carrying the Y93H RAS in the NS5A region of the viral genome. The clinical data are supported by *in vitro* resistance studies in cell culture indicating intermediate-level resistance to velpatasvir conferred by the Y93H RAS alone and high-level resistance when Y93H is combined with other NS5A RASs, in particular at position L31.[135] These *in vitro* data have been verified in clinical reports, as detailed above.[36,128,131,134] Thus, if the sofosbuvir/velpatasvir option is chosen, patients infected with genotype 3a with compensated cirrhosis should be treated with either 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) or 12 weeks of the triple fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir. If NS5A resistance testing is available and performed, only patients carrying the Y93H RAS on their genome should be treated with either 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) or 12 weeks of the triple fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir, whereas patients without Y93H can be treated with 12 weeks of sofosbuvir/velpatasvir alone.

A small number of patients infected with HCV genotype 3a with compensated (Child-Pugh A) cirrhosis have been included in clinical trials with the fixed-dose combination of glecaprevir and pibrentasvir (see above). It is still unclear whether 16 weeks of treatment is superior to 12 weeks in treatment-experienced individuals,[142] and real-world studies have been inconclusive. In the phase III EXPEDITION-8 trial, the efficacy of an 8-week treatment regimen in treatment-naïve patients with genotype 3a and cirrhosis is supported by the inclusion of only 63 patients,

Table 6B. Recommendations for genotype/subtype-based treatment of HCV-monoinfected or HCV-HIV coinfected adult (≥18 years) and adolescent (12-17 years) patients with chronic hepatitis C 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; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin).

Type of treatment	Genotype	Cirrhosis status	Prior treatment experience	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Genotype/subtype determination-based treatment	Genotype 1a, 1b, 2, 4, 5 and 6	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	12 weeks (genotype 1b only)
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced		12 weeks		
	Genotype 3	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced		12 weeks		No
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve	12 weeks with weight-based ribavirin[a]	8-12 weeks[b]	12 weeks[a]	No
			Treatment-experienced		16 weeks		No
	Subtype 1l, 4r, 3b, 3g, 6u, 6v or any other subtype naturally harbouring one or several NS5A RASs[c]	No cirrhosis	Treatment-naïve	Unknown	Unknown	12 weeks	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced				

IFN, interferon; RASs, resistance-associated substitutions.
[a]If resistance testing is performed, only patients with the NS5A Y93H RAS at baseline should be treated with sofosbuvir/velpatasvir plus ribavirin or with sofosbuvir/velpatasvir/voxilaprevir, whereas patients without the Y93H RAS should be treated with sofosbuvir/velpatasvir alone.
[b]In treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis, treatment with glecaprevir/pibrentasvir can be shortened to 8 weeks, but more data are needed to consolidate this recommendation.
[c]As determined by sequence analysis of the NS5A region by means of population sequencing or deep sequencing (cutoff 15%).

with 1 post-treatment relapse.[147] In a real-world study including 11,101 adults treated with glecaprevir/pibrentasvir for 8 or 12 weeks, the modified intent-to-treat SVR12 was smaller in the 679 patients infected with genotype 3 (95.8%) than in the 2,900 patients infected with genotypes 1, 2 and 4 (97.6% to 98.5%), but no predictive factors of virological failure have been identified.[150] Thus, recommendations on treatment duration in patients infected with genotype 3a and compensated cirrhosis are based on moderate-quality evidence. Whatever the HCV genotype, whether 8 weeks of treatment with glecaprevir/pibrentasvir is sufficient in treatment-naïve patients with compensated (Child-Pugh A) cirrhosis and signs of portal hypertension, *i.e.* a liver stiffness >20 kPa with a platelet count <150 × 10^9/L (according to the Baveno VI classification), remains to be determined.

The fixed-dose combination of grazoprevir/elbasvir yields high SVR12 rates in patients infected with genotype 1b, but 8 weeks of treatment appears to be suboptimal in treatment-naïve patients with F0–F2 fibrosis.[155,156] Thus, 12 weeks is the recommended duration for this combination, regardless of the fibrosis score.

In settings where sequence analysis of the NS5A region by means of population sequencing or deep sequencing (cut-off 15%) is available and affordable, it should be performed in patients born in sub-Saharan Africa, China or South-East Asia in order to: (i) identify infrequent HCV subtypes not detected by the line probe assay (defined as genotype 1 non-1a/1b, genotype 2 non-2a/2b, genotype 3 non-3a, genotype 4 non-4a/4d, and subtypes of genotypes 5 to 8) by means of phylogenetic analysis of the sequences generated, and (ii) characterize the NS5A RAS profile to identify patients harbouring viruses inherently resistant to NS5A inhibitors. In the absence of clinical trial or real-world data, patients infected with subtypes 1l, 4r, 3b, 3g, 6u and 6v and patients infected with other infrequent subtypes harbouring ≥1 RAS(s) known to confer resistance to NS5A inhibitors (see below) should be treated first-line with the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir, pending data with dual pangenotypic regimens.

The following genotype/subtype-dependent treatment recommendations are summarised in Table 6B.

Recommendations

- In settings where HCV genotype and subtype determination are available and affordable and would not limit access to care, this information remains useful to optimise the virological results of HCV therapy **(A1)**.
- Treatment-naïve and treatment-experienced patients infected with HCV genotypes 1a, 1b, 2, 4, 5 or 6 without cirrhosis should be treated with: (i) the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, or (ii) the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks **(A1)**.
- Treatment-naïve patients infected with HCV genotypes 1a, 1b, 2, 4, 5 or 6 with compensated (Child-Pugh A) cirrhosis should be treated with: (i) the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, or (ii) the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks **(A1)**.
- Treatment-experienced patients infected with HCV genotypes 1a, 1b, 2, 4, 5 or 6 with compensated (Child-Pugh A) cirrhosis should be treated with: (i) the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, or (ii) the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks **(A1)**.
- Treatment-naïve patients infected with genotype 3 without cirrhosis should be treated with: (i) the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, or (ii) the fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks **(A1)**.
- Treatment-experienced patients infected with genotype 3 without cirrhosis should be treated with: (i) the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, or (ii) the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks **(A1)**.
- Treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis should be treated with: (i) 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 12 weeks, or (ii) the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks, or (iii) the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks **(A1)**.
- In treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis, treatment with glecaprevir/pibrentasvir can be shortened to 8 weeks, but more data are needed to consolidate this recommendation **(B1)**.
- Treatment-experienced patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis should be treated with: (i) 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 12 weeks, or (ii) the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks, or (iii) the fixed-dose combination of glecaprevir and pibrentasvir for 16 weeks **(A1)**.
- If resistance testing is performed at baseline in treatment-naïve and treatment-experienced patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis, only patients with the NS5A Y93H RAS at baseline should be treated with sofosbuvir/velpatasvir plus ribavirin or with sofosbuvir/velpatasvir/voxilaprevir for 12 weeks, whereas patients without the Y93H RAS should be treated with sofosbuvir/velpatasvir alone for 12 weeks **(B1)**.
- Treatment-naïve and treatment-experienced patients infected with genotype 1b, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, can be treated with the fixed-dose combination of grazoprevir and elbasvir for 12 weeks **(A1)**.
- In settings where sequence analysis of the NS5A region by means of population or deep sequencing is available and affordable, patients infected with subtypes 1l, 4r, 3b, 3g, 6u and 6v and patients infected with other infrequent subtypes harbouring ≥1 RAS(s) known to confer resistance to NS5A inhibitors should be considered for

treatment with the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks, pending data with dual pangenotypic regimens **(B2)**.

Treatment of chronic hepatitis C in patients with decompensated (Child-Pugh B or C) cirrhosis with or without an indication for liver transplantation

General principles of treatment of chronic hepatitis C in patients with decompensated (Child-Pugh B or C) cirrhosis or with compensated (Child-Pugh A) cirrhosis with prior episodes of decompensation

IFN-free, DAA-based pangenotypic regimens are the most suitable options for patients with decompensated (Child-Pugh B or C) cirrhosis. However, the use of protease inhibitors is contraindicated in patients with decompensated cirrhosis or with prior episodes of decompensation, because of substantially higher drug exposure and risk of toxicity.[172] Thus, the fixed-dose combination of sofosbuvir and velpatasvir is the treatment of choice for patients with decompensated (Child-Pugh B or C) cirrhosis or with compensated (Child-Pugh A) cirrhosis with prior episodes of decompensation.

In the ASTRAL-4 study, patients with Child-Pugh B decompensated cirrhosis infected with genotypes 1 to 4 were randomised 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.[173] The SVR12 rates with these 3 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 87% (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; and 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.[173] The benefit of adding ribavirin to DAA treatment has been confirmed in patients with decompensated cirrhosis from the United States Chronic Hepatitis Cohort Study.[174]

Recommendations

- Patients with decompensated (Child-Pugh B or C) cirrhosis should be treated in experienced centres with easy access to liver transplantation **(A1)**.
- Close monitoring of patients with decompensated (Child-Pugh B or C) cirrhosis during therapy is required, with the possibility of stopping therapy if there is evidence of worsening decompensation during treatment **(A1)**.
- Protease inhibitor-containing regimens are contraindicated in patients with decompensated (Child-Pugh B or C) cirrhosis and in patients with compensated (Child-Pugh A) cirrhosis with previous episodes of decompensation **(A1)**.
- Patients with decompensated (Child-Pugh B or C) cirrhosis and patients with compensated (Child-Pugh A) cirrhosis with previous episodes of decompensation should be treated 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 12 weeks **(A1)**.
- In patients with decompensated (Child-Pugh B or C) cirrhosis, 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 and patients with compensated (Child-Pugh A) cirrhosis with previous episodes of decompensation with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and velpatasvir for 24 weeks without ribavirin **(A1)**.

Treatment of patients with decompensated (Child-Pugh B or C) cirrhosis with or 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 with DAA combinations containing sofosbuvir and an NS5A inhibitor have demonstrated high SVR rates, equivalent in Child-Pugh B and C patients, in individuals with decompensated cirrhosis, together with a beneficial effect of viral clearance on liver function, with significant improvements in bilirubin, albumin and international normalised ratio values and, as a result, in model for end-stage liver disease (MELD) and Child-Pugh scores in one-third to half of patients.[173,175–178] Similar results have been reported in real-world studies.[179–184] 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.[179]

Treatment of HCV infection pre-transplant in patients awaiting liver transplantation has 2 complementary goals: preventing liver graft infection after transplantation 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 management. Improvement of liver function indicates delisting of some patients.[185] However, with the exception of living-donor grafts, the time of transplantation is variable and unpredictable, so a 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.

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 142 patients – followed for a median duration of 34.9 months (IQR 29.0–39.5 months) – receiving IFN-free, DAA-based therapy on the waiting list, 7 patients died on the waiting list, 49% (69/142) were transplanted, and 31% (44/142) were delisted.

Thirteen patients were still on the waiting list and 9 were delisted for reasons unrelated to clinical improvement. Four delisted patients were relisted because of HCC in 1 case and ascites in 3 cases.[186] 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.[180] 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.[187] A retrospective analysis of data from 4 trials on the effects of sofosbuvir-based therapy in patients with decompensated cirrhosis (502 with a Child-Pugh B and 120 with a Child-Pugh C score) identified 5 baseline factors associated with a reduction of Child-Pugh score to A (compensated), including body mass index, encephalopathy, ascites, and serum ALT and albumin levels.[188]

In the ASTRAL-4 trial, of the patients with a baseline MELD score <15 treated with sofosbuvir and velpatasvir, with or without ribavirin, 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.[173] In these studies, the median MELD score improvement was 2 points (range: 1–17), but was not always followed by clinical improvement. 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. Long-term clinical follow-up data are lacking.

Overall, the short-term benefits observed must be balanced with the respective risks of death on the waiting list and likelihood of transplantation. A 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 1 year, arguing for transplanting individuals with very severe disease prior to HCV therapy.[189] 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.[190]

Recommendations

- Patients with decompensated (Child-Pugh B or C) cirrhosis not on the waiting list for liver transplantation and without concomitant comorbidities that could impact their survival should be treated urgently **(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 **(A1)**.
- Patients with decompensated (Child-Pugh B or C) cirrhosis with an indication for treatment should be treated with the fixed-dose combination of sofosbuvir and velpatasvir plus daily weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) for 12 weeks. Ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance **(A1)**.
- Patients with decompensated (Child-Pugh B or C) cirrhosis with an indication for treatment with contraindications for ribavirin, or with poor tolerance to ribavirin on treatment, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 24 weeks without ribavirin **(B1)**.
- Patients with decompensated (Child-Pugh B or C) cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18–20 should be transplanted first, without antiviral treatment, and HCV infection should be treated after liver transplantation **(B1)**.
- If the waiting time on the transplant list exceeds 6 months, patients with decompensated (Child-Pugh B or C) cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18–20 should be treated before transplantation, depending on the local circumstances **(B1)**.

Treatment of hepatitis C in solid organ (including liver) transplant recipients

Treatment of hepatitis C in HCV-positive liver transplant recipients with post-transplantation HCV recurrence

Recurrence of HCV infection is universal in patients with detectable HCV RNA at the time of liver transplantation.[191] The course of HCV-related liver disease is accelerated in liver transplant recipients, of whom approximately one-third develop cirrhosis within 5 years following transplantation in the absence of antiviral treatment.[192–195] Overall, graft survival is 30% lower in HCV-infected compared to non-HCV-infected liver transplant recipients, because of recurrent HCV disease, but also extrahepatic manifestations of HCV infection, management issues and complications of immunosuppression.

Cure of HCV infection following liver transplantation has significantly improved post-transplant survival.[196,197] Patients with fibrosing cholestatic hepatitis and patients with moderate to extensive fibrosis or portal hypertension 1 year after transplantation are at high risk of graft loss, and require urgent antiviral therapy.[198,199]

Liver transplant recipients with HCV recurrence have been 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 1 genotype 3 patient out of 35 relapsed.[200] No clinically significant drug-drug interactions are expected between this combination and common immunosuppressive agents used post-liver transplantation, such as tacrolimus, cyclosporine, corticosteroids, mycophenolate mofetil or everolimus (see drug-drug interactions above). Ribavirin should be added to sofosbuvir/velpatasvir in case of decompensated cirrhosis.

In the MAGELLAN-2 study, 80 liver transplant recipients without graft cirrhosis on a stable immunosuppressive regimen have been treated 3 months or more after transplantation with the fixed-dose combination of glecaprevir and pibrentasvir. Prednisone/prednisolone was permitted at ≤10 mg/day and cyclosporine A at ≤100 mg/day at the time of screening. All but 1

patient achieved SVR12.[201] Because of possible drug-drug interactions between the protease inhibitor glecaprevir and immunosuppressant drugs, the latter need to be carefully monitored in order for drug dose adjustments to be made if necessary. Because protease inhibitors are contraindicated in patients with decompensated cirrhosis, glecaprevir/pibrentasvir should not be used in patients with decompensated cirrhosis post-liver transplantation.

Recommendations

- All patients with post-transplant recurrence of HCV infection must be treated **(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 necessitate urgent antiviral treatment **(A1)**.
- Patients with post-transplant HCV recurrence without cirrhosis or with compensated (Child-Pugh A) cirrhosis should be treated with either: (i) the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (without the need for immunosuppressant drug dose adjustments), or (ii) the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (with the need to monitor immunosuppressant drug levels and adjust 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 velpatasvir with daily weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) for 12 weeks **(B1)**.
- In patients with post-transplant HCV recurrence with decompensated (Child-Pugh B or C) cirrhosis, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance **(B1)**.
- Patients with post-transplant HCV recurrence and 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 velpatasvir for 24 weeks without ribavirin **(B1)**.

Treatment of hepatitis C in HCV-positive 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.[202] 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.[185] 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.[203]

Reports demonstrate that DAA therapies effectively cured HCV in 97% (406/418) of kidney transplant recipients, of whom the majority were treated with sofosbuvir-based regimens.[204] In the MAGELLAN-2 study, 100% (20/20) of kidney transplant recipients achieved SVR12 after 12 weeks of the fixed-dose combination of glecaprevir and pibrentasvir. A few patients required immunosuppressant drug dosage adjustments during therapy.[201]

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, sofosbuvir-based treatments were safe and effective in 12 patients with chronic HCV infection.[164] 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.[205] 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 solid organ recipients can be treated with the expectation of high SVR rates and acceptable safety. The combination of sofosbuvir and velpatasvir is the preferred choice because it does not require immunosuppressant drug dose adjustments. The fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks can also be used, but immunosuppressant drug levels need to be adjusted as needed during and after the end of treatment.

Recommendations

- Non-hepatic solid organ transplant recipients, including kidney, heart, lung, pancreas or small bowel recipients, should be treated for their HCV infection before or after transplantation **(A1)**.
- Before kidney, heart, lung, pancreas or small bowel transplantation, patients on the waiting list can be treated for their HCV infection according to the general recommendations above **(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 velpatasvir for 12 weeks without the need for immunosuppressant drug dose adjustments **(B1)**.
- After transplantation, solid organ transplant recipients, including kidney, heart, lung, pancreas or small bowel recipients, can be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks, but immunosuppressant drug levels need to be monitored and adjusted as needed during and after the end of treatment **(B1)**.

Treatment of hepatitis C in HCV-negative 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. In some European countries, the waiting list mortality rate for orthotopic liver transplantation ranges from 15% to 30%.[206] Thus, accepting grafts from anti-HCV antibody-positive, including HCV RNA-positive, donors increases access to organ transplantation and is cost-effective.[207]

The number of anti-HCV antibody-positive donors that are HCV RNA-negative could increase substantially with the advent of highly efficacious DAA-based antiviral therapies. Rare cases of transmission after liver transplantation have been reported from anti-HCV-positive but HCV RNA-negative donors, possibly because of acute infection during the "window" period.[206,208]

In contrast, the risk of HCV transmission is very high in solid organ transplantation recipients of HCV RNA-positive donors. Post-transplant treatment with HCV DAAs yields very high rates of SVR in these patients. However, transplanting solid organs from HCV viraemic donors to uninfected recipients has been complicated by acute HCV infection in a few patients, with consequent fibrosing cholestatic hepatitis and *de novo* glomerular disease.[209,210]

Assessing liver graft quality, through visual inspection and histological examination, is crucial when accepting anti-HCV antibody-positive grafts. New techniques, such as elastography or liquid biopsy, will soon become available for this purpose. Grafts with advanced fibrosis (F3) must be 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 HCV DAAs 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.[207,211] Some centres, particularly in areas with high HCV positivity rates as a result of the "opioid epidemic" and high rates of mortality on the waiting list, have started using HCV RNA-positive livers for non-infected liver and kidney graft recipients, with good preliminary results.[207,212] In a recent study, early liver graft outcomes were similar in recipients of HCV RNA-positive and -negative donors.[213] In another study, a life expectancy benefit was observed in liver recipients with MELD scores ≥20, with the maximum benefit observed in those with a MELD score ≥28.[189] 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.

The transplantation of HCV-negative recipients with HCV-positive kidneys is now also possible with the availability of all-oral DAA-based therapies. In a trial including 10 kidney transplant candidates receiving HCV genotype 1-infected kidneys, the median time on the waiting list before entering the trial once eligible was very short (58 days, IQR: 53–100) and all recipients achieved SVR after DAA-based treatment, with acceptable graft function at 6 months of follow-up.[214] Other data indicate very high SVR rates after DAA treatment of HCV-negative recipients of HCV-positive kidneys treated with DAAs post-transplant.[209,215] A study from the Organ Procurement Transplant Network compared the short-term outcomes of renal transplantation from 196 HCV RNA-positive donors with 352 anti-HCV antibody-positive, HCV RNA-negative donors and 36,934 donors without HCV markers. Compared to the latter group, delayed graft function was less frequent in transplants performed using HCV-seropositive, non-viraemic and viraemic donors. The recipients of HCV RNA-positive grafts had better allograft function at 6 months post-transplant, while there was no statistical difference in the overall graft failure risk at 12 months between the different groups.[216]

Whether a prophylactic or preemptive approach (starting DAAs prior to or on the day of transplant) or a delayed approach (starting treatment after confirmation of recipient viraemia) is best remains to be determined. The efficacy of ultra-short-term perioperative DAA prophylaxis was tested in HCV-negative recipients of HCV RNA-positive kidney transplants in a single-centre pilot trial. Three of 10 patients (30%) receiving 1 dose of sofusbuvir/velpatasvir pre-transplant followed by 1 dose at day 1 post-transplant were infected. Three of another 40 patients (7.5%) receiving additional sofosbuvir/velpatasvir doses at days 2 and 3 post-transplant (total: 4 doses) were infected. Five of the 6 infected patients cleared HCV after another course of DAA treatment.[217] These results are encouraging, but longer preemptive therapy is probably required to achieve 100% prevention of infection.

Positive results have also been reported in heart transplant recipients grafted with an HCV RNA-positive organ.[215,218–220] In an open-label study, preemptive administration of glecaprevir/pibrentasvir resulted in expedited organ transplantation, rapid HCV suppression, prevention of chronic HCV infection and excellent early allograft function in patients receiving HCV-infected donor hearts.[221] In another study, 36 patients received lung transplantation and 8 received heart transplantation from HCV-infected donors. Sofosbuvir-velpatasvir was preemptively administered to the recipients for 4 weeks, beginning within a few hours after transplantation. All of the first 35 patients who had completed 6 months of follow-up achieved an SVR, with excellent graft function.[222] In a recent phase III, single-centre, open-label study, 30 transplant recipients (lung, kidney-heart and kidney-pancreas) received both glecaprevir/pibrentasvir and ezetimibe, an unapproved HCV entry blocker, once prior to transplantation and daily for 7 days post-transplant. All of them had undetectable HCV RNA 12 weeks after transplantation.[223] Larger studies are required to evaluate the optimal duration of antiviral therapy in recipients of HCV RNA-positive organs.

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 HCV RNA-positive organs for HCV RNA-negative recipients is possible, provided that it is allowed by local regulations, rigorous informed consent is obtained, and rapid post-transplant DAA therapy is guaranteed **(B1)**.
- The use of HCV RNA-positive liver grafts with moderate (F2) or advanced (F3) fibrosis is not recommended **(B2)**.
- Treatment of HCV infection in HCV RNA-negative recipients of HCV RNA-positive organs is identical to the

treatment of chronic hepatitis C in HCV-infected solid organ transplant recipients (B1).
- Prophylactic/preemptive treatment of HCV infection in HCV RNA-negative recipients of HCV RNA-positive organs beginning just before transplantation is an option, but further studies are needed to determine the ideal regimen and duration pre- and post-transplant **(C2)**.

Treatment of chronic hepatitis C in patients with HCC

HCV is a leading cause of HCC worldwide and the morbidity and mortality from HCV-associated HCC is increasing. 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.

Treatment of chronic hepatitis C in patients with HCC without cirrhosis or with compensated (Child-Pugh A) cirrhosis with an indication for curative therapy, including liver transplantation

In patients with HCC, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, who have an indication for curative therapy (including liver transplantation), the ideal timing for antiviral therapy (before or after HCC treatment) is still debated. Lower SVR rates have been reported with various DAA regimens in patients with HCC.[224] In a systematic review with meta-analysis including 5,522 patients with HCC from 56 studies, the overall SVR rate was 88%. In the 27 studies also including patients without HCC, SVR was achieved in 88% of patients with HCC and in 92% of those without HCC (p <0.001). A higher SVR rate was observed in patients who received curative HCC therapy than in those who received non-curative therapy or were not treated.[225]

In a retrospective cohort study of 149 liver transplantation candidates with HCV infection and HCC at a single centre, patients treated with DAAs for their HCV infection had lower risk of waitlist dropout due to tumour progression or death compared to the patients who had not been treated.[226]

Post-liver transplantation treatment of HCV was reported to be cost-effective in patients with HCC.[190] In patients with HCC, without cirrhosis or with compensated cirrhosis, with an indication for liver transplantation, pre- or post-liver transplant antiviral treatment indications are similar to those in patients who do not have HCC (see general recommendations).

Recommendations

- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis with HCC who are eligible for potentially curative therapy with liver resection or ablation should defer DAA therapy until after HCC treatment is completed **(A1)**.
- In patients with HCC awaiting liver transplantation with an HCV infection, the timing of antiviral treatment (pre- or post-transplant) should not interfere with the management of the patient on the waiting list and must be decided on a case-by-case basis through a multidisciplinary discussion **(B1)**.
- In patients with HCC awaiting liver transplantation with an HCV infection in centres with long waiting times, HCV treatment should be initiated before liver transplantation in order to facilitate locoregional therapies to reduce waiting list dropouts due to tumour progression **(B2)**.
- Patients with HCC without cirrhosis or with compensated (Child-Pugh A) cirrhosis awaiting liver transplantation should be treated for their HCV infection, prior to or after liver transplantation, according to the general recommendations **(A1)**.

Treatment of chronic hepatitis C in patients with treated HCC without an indication for liver transplantation

Several large cohort studies and meta-analyses have examined the relationship between SVR and reduction in the risk of HCC in patients infected with HCV. They show that DAA-induced SVR is associated with a substantial reduction in the incidence of *de novo* HCC, of all-cause mortality and of liver-related mortality in the mid- to long-term.[12,16,227,228] However, the risk of HCC is not abolished by an SVR. A large-scale study from the Veterans Administration has shown that an increased risk for HCC persists up to 10 years after HCV eradication in patients with cirrhosis or a high FIB-4 score at HCV treatment baseline, justifying post-SVR surveillance in these patients.[229]

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 a beneficial or deleterious effect on the risk of recurrence following resection or ablation of HCC has been debated, following publication of a large number of generally small-scale, retrospective studies with contradictory results.[226,230–249] A systematic review, meta-analysis and meta-regression including 13,875 patients from 41 studies (26 studies on HCC occurrence and 17 on HCC recurrence) concluded that there is no evidence for a difference in the incidence of *de novo* HCC occurrence or recurrence following an SVR after DAA- or IFN-based therapy.[250] In addition, a retrospective US cohort study including 797 patients with HCV-related HCC who achieved a complete response to resection, local ablation, transarterial chemo- or radio-embolisation or radiation therapy has shown that DAA treatment of HCV infection was associated with a significant reduction in the overall risk of death.[251]

An expert review was produced by the American Gastroenterological Association Institute.[252] After an exhaustive review of the literature, the experts concluded that DAA treatment of HCV infection is associated with a reduction in the risk of incident *de novo* HCC, with a similar relative risk reduction in patients with and without cirrhosis. The presence of active HCC is associated with a small but statistically significant decrease in SVR rates with DAA therapy. There are no conclusive data that DAA therapy is associated with increased or decreased risk, differential time to recurrence, or aggressiveness of recurrent HCC in patients with a complete response to HCC therapy. Thus, DAA therapy should not be withheld from such patients. DAA therapy can conveniently be deferred 4–6 months in patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, to consolidate treatment and confirm a response to HCC therapy in patients treated with curative intent.[252]

Recommendations

- Patients with complete response to HCC therapy should be treated for their HCV infection according to the general recommendations in patients without HCC **(A1)**.
- Patients with complete response to HCC therapy who achieve SVR have a continued risk of HCC recurrence and require indefinite post-SVR HCC surveillance by means of ultrasound every 6 months **(A1)**.
- Patients palliated for HCC may be treated for HCV depending on the overall prognosis and potential benefit **(B2)**.

Treatment of chronic hepatitis C in special epidemiological groups

Treatment of chronic hepatitis C in adolescents and children

It is thought that approximately 3.5 million (0.15%) adolescents and children globally, aged 1–19 years, are chronically infected with HCV.[253,254] Mother-to-infant transmission is the major route of infection with an estimated rate of transmission of 4%–8%. The transmission rates are higher from HIV-HCV-coinfected mothers, with an estimated rate of perinatal transmission of 8%–15%.[255] The opioid epidemic in the United States is also associated with an increasing ongoing risk of HCV transmission from mothers to their children.[256] As a result, all children born to HCV-infected women should be tested for HCV infection from the age of 18 months. The status of at-risk children should be checked. Other sources of acquisition, including nosocomial transmission, occur in children and adolescents. Adolescents are at risk via injecting drug use.

Symptoms of chronic HCV infection in the paediatric population are usually absent. Cirrhosis and HCC are rare in children.[254,257] However, liver disease may progress during early life.[258] 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.[259] Childhood obesity, alcohol use and/or viral coinfections may contribute to advancing liver disease.[254]

Dose-finding and safety have been assessed in an international trial of the fixed-dose combination of sofosbuvir and velpatasvir in patients aged 6–17 years infected with HCV genotypes 1 to 4.[260] Adolescents between 12 and 17 years received 400 mg of sofosbuvir and 100 mg of velpatasvir for 12 weeks, either as a single 400 mg/100 mg tablet or as two 200 mg/50 mg tablets each day. Children between 6 and 11 years received half of the adult/adolescent dose for 12 weeks, *i.e.* 200 mg of sofosbuvir and 50 mg of velpatasvir each day, either as a single 200 mg/50 mg tablet or as 4 oral granules containing 50 mg of sofosbuvir and 12.5 mg of velpatasvir. Plasma concentrations of sofosbuvir, its metabolite GS-331007 and velpatasvir measured at several time points during the first 12–24 hours of administration were comparable to those observed in adult populations receiving the full-dose combination of sofosbuvir and velpatasvir. SVR12 was achieved in 95% (97/102; 1 virological failure) of adolescents aged 12–17 years and in 93% (68/73; 1 virological failure) of children aged 6–11 years. Eight patients were lost-to-follow-up and 2 additional patients discontinued treatment due to spitting up or an inability to swallow the drug. Equivalent safety was reported compared to the adult population.[260] Children aged 3–5 years received 200 mg/50 mg or 150 mg/37.5 mg of sofosbuvir/velpatasvir according to body weight ≥17 kg or <17 kg, respectively, either as a single 200 mg/50 mg tablet or as 4 or 3 oral granules containing 50 mg of sofosbuvir and 12.5 mg of velpatasvir, respectively. The SVR12 rate was 83% (34/41). There was no virological failure, failures being related to loss to follow-up or early treatment discontinuation (data on file communicated to the panel by Gilead). The most common adverse events were headache, fatigue, and nausea in adolescents; vomiting, cough and headache in 6- to 11-year-old children; and vomiting in 3- to 5-year-old children.

The DORA clinical trial was performed in children and adolescents infected with HCV genotype 1, 2, 3 or 4 who received the fixed-dose combination of glecaprevir and pibrentasvir for 8 to 16 weeks.[261] In the first part of the study, all 47 adolescents aged 12–17 years were treated with glecaprevir/pibrentasvir and 100% of them achieved SVR12. The safety profile and exposure were consistent with that in adults, while pharmacokinetics exposures of glecaprevir and pibrentasvir were comparable to exposures in adults.[261] In the second part of the DORA study, 80 children aged 3–11 years received film-coated granules of glecaprevir and pibrentasvir mixed together in a small amount of food for daily administration in sachets containing 50 mg of glecaprevir and 20 mg of pibrentasvir: 250 mg/100 mg (5 sachets) of glecaprevir and pibrentasvir, respectively, for children aged 9–11 years weighing 30–44 kg; 200 mg/80 mg (4 sachets) for children aged 6–8 years weighing 20–29 kg; 150 mg/60 mg (3 sachets) for children aged 3–5 years weighing 12–19 kg. This formulation has not yet received regulatory approval. Pharmacokinetic exposures were within those reported for adult and adolescent patients receiving the approved dose of glecaprevir/pibrentasvir. The most common adverse events were headache (14%) and vomiting (14%). The SVR12 rate was 96% (77/80; 1 relapse in a 9-year-old Asian patient infected with HCV subtype 3b who received 8 weeks of treatment) (data on file communicated to the panel by Abbvie).

Recommendations

- All children born to HCV-infected women should be tested for HCV infection from the age of 18 months **(A1)**.
- Adolescents aged 12–17 years who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated according to the general recommendations in adult patients with either: (i) the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily; or (ii) the fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in 3 tablets (100 mg/40 mg) administered once daily with food **(A1)**.
- Children aged 3–11 years who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, can be treated with the fixed-dose combination of sofosbuvir and velpatasvir administered once daily for 12 weeks, according to their body weight: (i) for those weighing ≥17 kg, the fixed-dose combination of sofosbuvir (200 mg) and velpatasvir (50 mg), either in a single tablet (200 mg/50 mg) or as 4 oral granules containing 50 mg of sofosbuvir and 12.5 mg of velpatasvir, pending approval of these formulations; (ii) for

those weighing <17 kg, the fixed-dose combination of sofosbuvir (150 mg) and velpatasvir (37.5 mg) as 3 oral granules containing 50 mg of sofosbuvir and 12.5 mg of velpatasvir, pending approval of this formulation **(B2)**.
- Children aged 3–11 years who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, can be treated with the fixed-dose combination of glecaprevir and pibrentasvir administered once daily for 12 weeks in the form of sachets containing 50 mg of glecaprevir and 20 mg of pibrentasvir as film-coated granules mixed together in a small amount of food, according to their body weight, pending approval of this formulation: (i) for those weighing 30–44 kg, the fixed-dose combination of glecaprevir (250 mg) and pibrentasvir (100 mg) as 5 sachets containing 50 mg of glecaprevir and 20 mg of pibrentasvir; (ii) for those weighing 20–29 kg, the fixed-dose combination of glecaprevir (200 mg) and pibrentasvir (80 mg) as 4 sachets containing 50 mg of glecaprevir and 20 mg of pibrentasvir; (iii) for those weighing 12–19 kg, the fixed-dose combination of glecaprevir (250 mg) and pibrentasvir (100 mg) as 3 sachets containing 50 mg of glecaprevir and 20 mg of pibrentasvir **(B2)**.

Treatment of chronic hepatitis C in pregnant women

In women of reproductive age, HCV prevalence continues to increase.[256] Data in some parts of the world showed a doubling of incidence between 2006 and 2014,[262] but the true global incidence is difficult to identify as many cases remain undiagnosed. In most regions, universal screening of HCV in pregnant females is not performed.

Models have shown that universal prenatal HCV screening improves health outcomes in women with HCV infection, improves identification of HCV in at-risk neonates, and is cost-effective.[263] Screening remained cost-effective at a prevalence of 0.07%, which is translatable to a European population.[264] Universal HCV testing in pregnant women is therefore recommended as part of the strategy for global elimination. Testing is recommended at early stages of the pregnancy alongside other prenatal tests to allow for appropriate referral, but it can be carried out at any stage.

HCV infection may influence the outcome of pregnancy, leading to a higher incidence of preterm births and a higher incidence of intrauterine foetal death, preterm delivery and small-for-gestational age. Higher rates of antepartum and postpartum haemorrhage, gestational diabetes, or premature rupture of membranes have been reported. Chronic HCV infection has also been linked with higher rates of intrahepatic cholestasis of pregnancy. Women identified with HCV infection when pregnant should, where possible, be looked after by a multidisciplinary team involving hepatology, obstetric and paediatric input.

Currently there are no large-scale published data on the safety and efficacy of HCV DAAs in pregnant women and none are licensed for use in pregnancy. A phase I study looking at the safety and virological response to the fixed-dose combination of sofosbuvir and ledipasvir in 9 pregnant women showed that all achieved SVR with a low incidence of adverse events.[265] A case series of 15 women in India was also presented, as well as incidences of accidental conception during treatment, both with positive outcomes.[266,267]

Whilst antivirals are used in HIV and HBV infection for the prevention of mother-to-child transmission, there is currently no data on the use of DAAs to prevent mother-to-child transmission of HCV. As a result, HCV treatment during pregnancy cannot currently be recommended. Treatment can be considered during pregnancy, or in the case of accidental conception during treatment, only on a case-by-case basis after a thorough discussion with the patient about the potential risks and benefits and in a joined-up approach with liver and obstetric services.

An ongoing, open-label, prospective study is being conducted at 2 maternity hospitals in Australia in pregnant women who will be treated with a 12-week course of sofosbuvir and velpatasvir. The primary outcome of this study is to determine whether the pharmacokinetic profiles of sofosbuvir and velpatasvir are similar between pregnant and non-pregnant women. Secondary endpoints will include SVR12, maternal and neonatal safety, neonatal HCV transmission, and maternal preferences and acceptability of HCV treatment.

Breastfeeding is not contraindicated in women with HCV as available data show that it does not increase the risk of mother-to-child transmission.[268] In the case of bleeding or cracked nipples, due to the risk of HCV transmission from blood exposure, consideration should be given to stopping and specialist input should be provided for these women.

Recommendations

- HCV treatment during pregnancy is not recommended in the absence of safety and efficacy data **(C2)**.
- Treatment can be considered during pregnancy, or in the case of accidental conception during treatment, only on a case-by-case basis after a thorough discussion with the patient about the potential risks and benefits and in a joined-up approach with hepatology and obstetric services **(C2)**.
- Breastfeeding is not contraindicated in women with HCV, except in the case of bleeding or cracked nipples for which specialist advice should be sought **(B1)**.

Treatment of chronic hepatitis C in PWIDs 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 on opioid substitution therapy (OST).[269] In Europe, two-thirds of the HCV burden is attributable to injecting drug use.[270] The prevalence of chronic HCV infection among people who recently injected drugs is approximately 40%.[271]

Recommendations for HCV testing in this population are based on the high prevalence of infection,[272,273] the demonstration that awareness of their HCV status induces sustained protective behavioural changes,[274,275] the potential public health benefit of reducing transmission by treating current drug users,[276–280] and the proven benefits of care and treatment in reducing HCV-related morbidity and mortality.[10,281] Because of the high incidence of HCV infection in PWIDs[273,282,283] 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. This effect is increased to 74% by the concomitant use of clean drug injecting equipment.[284] However, global coverage of OST and needle and syringe programme interventions is low.[285] 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.[286,287]

The goals of HCV treatment in PWIDs are to prevent the complications of chronic hepatic and extrahepatic HCV-associated disease, but also to prevent onward transmission of HCV. Among patients receiving OST and those with recent injecting drug use, pangenotypic 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.[288,289]

In an integrated analysis of the 3 ASTRAL-1 to 3 trials, OST did not impact completion, adherence, safety or the SVR rate (96% [49/51] in patients on OST *vs.* 98% [966/984] in patients not on OST).[290] The lack of difference between patients on or not on OST was confirmed in an extension of the previous study in which patients treated with sofosbuvir/ledipasvir in the phase III ION trials and with sofosbuvir/velpatasvir/voxilaprevir in the phase III POLARIS trials were added.[291] The SIMPLIFY study included only patients with recent (last 6 months) injecting drug use receiving or not receiving OST and treated with sofosbuvir and velpatasvir for 12 weeks. Adherence was 94% and SVR12 was obtained in 94% (97/103; no virological breakthrough, 1 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 and mortality risk in this population.[292–294]

In an integrated analysis, data were pooled from 7 phase III trials of 8 or 12 weeks of glecaprevir/pibrentasvir in patients chronically infected with HCV genotypes 1 to 6.[295] Among 1,819 patients, 5% and 34% were recent or former drug users, respectively, whereas the remaining 61% were non-drug users. Treatment adherence and completion were ≥96%, regardless of drug use status. SVR12 was achieved by 93% (91/98), 97% (591/610) and >99% (1,106/1,111) of recent, former, and non-drug users, respectively. No HCV re-infections were reported among recent drug users.[295] Another integrated analysis included 2,256 patients from 8 phase II and III clinical trials with glecaprevir/pibrentasvir, of whom 157 patients (7%) were receiving OST. SVR12 rates in OST and non-OST patients were 96% (151/157; 1 relapse) and 98% (2055/2099; 22 relapses), respectively.[296] In the C-EDGE CO-STAR trial in patients on OST, treatment with grazoprevir and elbasvir also yielded a high SVR rate in patients infected with genotype 1b.[288]

These results were confirmed in several real-world cohort studies. In the British Columbia Hepatitis Testers Cohort, PWIDs and patients on OST achieved high SVR rates on sofosbuvir/velpatasvir, although slightly lower than people not injecting drugs. This study also highlighted the need for additional measures to prevent loss-to-follow-up and overdose-related deaths among PWIDs.[297] Meanwhile, a pooled analysis of ongoing post-marketing real-world studies showed high SVR rates with glecaprevir/pibrentasvir in recent drug users (98%, 98/100; no virological failure), former drug users (98%, 317/324; 1 breakthrough and 3 relapses) and non-drug users (99%, 1,010/1,022; 5 breakthroughs and 6 relapses).[298] 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. Per protocol SVR was similar in both groups (96% and 95%, respectively).[299] A systematic review and meta-analysis of both observational studies and clinical trials, including 3,634 patients from 38 studies, showed high SVR rates in PWIDs with recent drug use, including those who still inject, and in individuals on OST.[300]

Altogether, these studies suggest that pangenotypic regimens are efficacious and well tolerated in patients with active or recent drug use, including those on OST. However, it is 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. Injecting drug use and risk behaviours appear to remain stable or decrease during and following DAA-based HCV treatment.[301]

Successful models have been multidisciplinary and often peer-supported in community-based clinics, drug treatment clinics, correctional facilities, needle-syringe programmes, supervised consumption rooms, specialised hospital-based clinics and primary care.[302]

Reinfection may occur after successful antiviral treatment in active drug users. A recent meta-analysis of 36 studies reported a follow-up of 6,311 person-years.[303] The overall rate of HCV reinfection was 5.9/100 person-years among people with recent injecting or non-injecting drug use, 6.2/100 person-years among people recently injecting drugs, and 3.8/100 person-years among those receiving OST. Reinfection rates were comparable following IFN-based and DAA-based therapy (5.4/100 person-years *vs.* 3.9/100 person-years, respectively). Higher reinfection rates were observed in people with recent drug use receiving or not OST than in people receiving OST with no recent drug use. In meta-regression analysis, longer follow-up was associated with a lower reinfection rate, suggesting higher reinfection risk early post-treatment.[303] 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 risk behaviour. Retreatment should be offered in case of positivity to avoid continued transmission.

Aiming at eliminating HCV is crucial in PWIDs. Modelling suggests that such elimination can be achieved by scaling up treatment in this population.[304] The prevention benefits of treatment will be greatest when delivered in combination with OST and needle and syringe programmes.[305]

Recommendations

- PWIDs should be routinely tested for anti-HCV antibodies and HCV RNA **(A1)**.
- 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 programmes, including in correctional facilities **(A1)**.
- All PWIDs who are infected with HCV, including those receiving OST, those with a history of injecting drug use and those who recently injected drugs, should be treated according to the general recommendations **(A1)**.
- Pre-therapeutic education should include discussion and counselling about HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk and harm reduction strategies **(A1)**.
- In patients on OST, DAA-based anti-HCV therapy does not require methadone or buprenorphine dose adjustment **(A1)**.
- Following SVR, monitoring for HCV reinfection through bi-annual or, 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)**.
- HCV treatment should be scaled-up in PWIDs to increase the likelihood of achieving the goals of HCV elimination in this group of patients, including treatment as prevention **(A1)**.

Treatment of chronic hepatitis C in prisoners

PWIDs are often incarcerated due to criminalisation of drug possession in most countries and to the high frequency of crime supporting drug use. As a result, HCV is common in correctional facilities.[306] In addition, harm reduction is not available to most prisoners. Therefore, the incidence of HCV infection among prisoners who use drugs during incarceration can be very high. Drug use in prisons is increasing. Recent drug use has been reported by 30% of those who are incarcerated in Europe. The incidence of HCV infection has been estimated to be of the order of 16 per 100 person-years (range 1–34) among prisoners with a history of drug use.[306] Despite this high incidence and prevalence, access to HCV testing and treatment in prisons is generally limited, but it is improving in countries with dedicated test-and-treat programmes.

Opt-in testing is commonly provided in European prisons. However, mathematical modelling in US prisons has suggested that opt-out testing is the most cost-effective approach, as opposed to risk-based testing.[307] Short prison stays and frequent transfers are important barriers to treatment in prison.[308] Shorter treatment durations with current DAAs have made HCV treatment during incarceration more feasible than it was during the IFN era. Nevertheless, ensuring the care continuum in prison is a challenge.

The feasibility of treating HCV in prison has been demonstrated in a study from Australia in which a nurse-led model of care was provided.[309] HCV RNA was detected in 562 patients and 416 commenced treatment with DAAs. SVR12 in the intent-to-treat analysis was 72% (301/416). However, most failures were due to loss of follow-up after release. Thus, among 313 persons treated and followed, per protocol SVR12 was achieved in 96% of cases (301/313; 11 relapses and 1 reinfection).[309]

In a study performed in English prisons, DBS testing, nurse-led inreach and consultations delivered by telemedicine were offered.[310] HCV RNA was found in 374 prisoners, of whom 266 started DAA treatment. Among 128 individuals with follow-up data, 87% (111/128; 6 relapses, 11 incomplete treatments) achieved SVR12. Among 48 persons with long-term follow-up, 21 (44%) were reinfected.[310]

In many countries, OST is available only for individuals who started treatment before their incarceration, while needle-syringe exchange programmes are available in a limited number of prisons in Europe.[311] Prison employees are often opposed to needle-syringe exchange programmes in prison, due to a perceived risk introduced by providing sharp utensils in a prison. Even when needle-syringe exchange programmes are in place, prisoners may be unwilling to use this programme if participation requires disclosure of drug use.

Recommendations

- Opt-out screening for HCV infection should be offered to all incarcerated individuals **(A1)**.
- HCV treatment should be offered to all incarcerated individuals with chronic hepatitis C, following the above general recommendations **(A1)**.
- OST should be made available to all opiate-dependent incarcerated individuals **(B1)**.
- Needle-syringe exchange programmes acceptable to incarcerated individuals and prison staff should be available in prisons **(B1)**.

Treatment of chronic hepatitis C in patients with comorbidities

Treatment of chronic hepatitis C in patients with immune complex-mediated manifestations of HCV infection

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 because of vascular deposition of immune complexes. Rituximab, an anti-CD20 monoclonal antibody, has been used for both skin and organ involvement.

In a prospective international multicentre cohort study, an SVR rate of 87% was achieved in 148 patients with cryoglobulin-associated vasculitis; DAA therapy induced a complete clinical response (improvement of all organs involved at baseline and absence of clinical relapse) in 73% (106/148) of cases, a partial response (improvement in some but not all organs involved at baseline) in 23% (33/148) of cases, and no response in 5% (7/148) of cases. Cryoglobulins were no longer detected in 53% of patients. Symptoms of purpura were cleared from 97% of patients, renal involvement from 91% of patients, arthralgias from 86% of patients, and neuropathy from 77% of patients. Factors associated

with no or partial response were a severe form of cryoglobulin-associated vasculitis and peripheral neuropathy.[312]

There is a significant association between persistent hepatitis C and B cell non-Hodgkin lymphoma. Low-grade lymphomas are treated with rituximab with or without corticosteroids, whereas high-grade lymphomas receive standard-of-care R-CHOP regimens. The outcome of the latter appears to be enhanced with rituximab, although rituximab may increase viral replication. Several cases of remission of B cell non-Hodgkin lymphoma have been reported after successful antiviral therapy. In an Italian observational study, antiviral treatment with DAAs was associated with remission of aggressive lymphomas in HCV-infected patients and was found to be an independent predictor of disease-free survival when combined with specific chemotherapy.[313] The relationship between successful DAA-based antiviral treatment and regression of B cell non-Hodgkin lymphoma was confirmed in a systematic review and meta-analysis pooling 13 studies.[314]

The association of chronic HCV infection and chronic renal disease is well established.[315] A spectrum of histopathological lesions has been reported. 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, corticosteroids and cyclophosphamide.[316] In a retrospective cohort study in 45,260 US Veterans treated for their HCV infection with DAAs, the risk of glomerulonephritis was significantly reduced following an SVR.[317] Although the data are scarce with the most recent DAA combinations, remissions from glomerular disease have been reported in patients with SVR.[318]

Recommendations

- Mixed cryoglobulinemia and renal disease associated with chronic HCV infection should be treated with pangenotypic DAA combinations, according to the general recommendations **(B1)**.
- Careful monitoring for adverse events is mandatory when treating mixed cryoglobulinemia and renal disease associated with chronic HCV infection with pangenotypic DAA combinations **(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 pangenotypic DAA regimens, according to the general recommendations, in combination with specific chemotherapy, taking into account possible drug-drug interactions **(B1)**.

Treatment of chronic hepatitis C in patients with renal impairment, including patients on haemodialysis

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.[316] 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 can potentially improve with antiviral treatment. However, organ recovery may be delayed after an SVR in patients with cryoglobulinemia.[319] 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 patients on dialysis, irrespective of HCV status.

In patients with renal impairment, including those with CKD stage 4 or 5 and patients with end-stage renal disease on haemodialysis, 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.

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, 2 virological failures).[320] An integrated analysis 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).[321] In a Japanese prospective multicentre study assessing 8 or 12 weeks of glecaprevir and pibrentasvir, SVR was achieved in 100% (32/32) of patients with CKD stage 4, 99% (108/109) of patients with CKD stage 5 and 99% (99/100) of patients on haemodialysis.[322] In a meta-analysis of real-world studies assessing the safety and efficacy of glecaprevir/pibrentasvir in adult patients with chronic hepatitis C, the SVR12 rate was 99% (58/59) in those with CKD stage 4 or 5.[150] Thus, the fixed-dose combination of glecaprevir and pibrentasvir is the treatment of choice for patients with chronic hepatitis C and stage 4 or 5 CKD (including those on haemodialysis).

The safety of sofosbuvir-based regimens has been questioned in patients with severe renal dysfunction (eGFR <30 ml/min/1.73 m^2), as sofosbuvir is eliminated mainly by the renal route.[323] However, sofosbuvir-based regimens have been reported to be safe and effective in patients with severe CKD, including patients on haemodialysis, in several studies.[28,31,324–326] Based on pharmacokinetic data obtained from studies involving HCV-infected patients with end-stage renal disease requiring dialysis, the current product licence indicates that, although safety data are limited in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) and end-stage renal disease requiring haemodialysis, sofosbuvir and velpatasvir can be used in these patients with no dose adjustment when no other relevant treatment

options are available. The safety of the sofosbuvir/velpatasvir combination has been evaluated in a 12-week non-controlled study including 59 patients with end-stage renal disease requiring haemodialysis. In this setting, exposure of sofosbuvir metabolite GS-331007 was increased 20-fold, exceeding levels where adverse reactions have been observed in preclinical trials. In this limited clinical safety data set, the rate of adverse events and deaths was not higher than expected in patients with end-stage renal disease.[31]

Voxilaprevir exposure is not expected to be meaningfully altered in patients with end-stage renal disease requiring dialysis. Thus, it can be used in patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis. Protease inhibitors are contraindicated in patients with decompensated (Child-Pugh B and C) cirrhosis and CKD; thus, these patients should be treated with the fixed-dose combination of sofosbuvir and velpatasvir. Ribavirin can be used in patients with mild to moderate (eGFR ≥30 ml/min/1.73 m^2) renal impairment, whereas patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) should be treated for 24 weeks without ribavirin.

In the C-SURFER trial, 55 patients infected with HCV genotype 1b with stage 4 or 5 CKD, including 75% on haemodialysis, were treated with grazoprevir and elbasvir for 12 weeks. The SVR12 rate was 92% (54/59; 1 relapse). The frequencies of renal system adverse events were comparable between treatment groups.[327] A real-world study using the same regimen in American patients with various stages of CKD showed similarly high SVR rates in patients infected with genotype 1b, regardless of the severity of renal disease.[48]

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. HCV-associated liver damage may be accelerated by immunosuppression. Antiviral therapy should be considered for all patients on haemodialysis. Studies showing high efficacy and safety of IFN-free anti-HCV regimens in kidney transplant recipients suggest that these patients can also be transplanted and treated for their HCV infection after kidney transplantation with a high probability of cure.[328–332] 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 regarding the use of 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.[210,214]

Recommendations

- 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 on- and post-treatment monitoring by a multidisciplinary team **(B1)**.
- Patients with HCV infection and mild to moderate (eGFR ≥30 ml/min/1.73 m^2) or severe (eGFR <30 ml/min/1.73 m^2) renal impairment, including those with end-stage renal disease on haemodialysis, should be treated for their HCV infection according to the general recommendations, with no need for dose adjustments of HCV DAAs **(A1)**.
- The fixed-dose combination of glecaprevir and pibrentasvir and, for patients infected with HCV genotype 1b only, the fixed-dose of grazoprevir and elbasvir are the preferred choices in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) and in those with end-stage renal disease requiring haemodialysis **(B1)**.
- Patients with decompensated (Child-Pugh B or C) cirrhosis and mild to moderate renal impairment (eGFR ≥30 ml/min/1.73 m^2) should be treated with the fixed-dose combination of sofosbuvir and velpatasvir with ribavirin for 12 weeks. Ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance and haemoglobin levels **(B1)**.
- Patients with decompensated (Child-Pugh B or C) cirrhosis and severe renal impairment (eGFR <30 ml/min/1.73 m^2) should be treated with the fixed-dose combination of sofosbuvir and velpatasvir without ribavirin for 24 weeks **(B1)**.
- 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)**.

Treatment of chronic hepatitis C in patients with 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 characterised 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.[333,334] 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 2 times the upper limit of normal and HBV treatment had to be initiated in 2 cases.[335]

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.

Recommendations

- Patients coinfected with HCV and HBV should be tested for HIV if their HIV status is unknown **(A1)**.
- Patients coinfected with HCV and HBV should be treated with the same anti-HCV regimens, following the same rules as HCV-monoinfected patients **(A1)**.
- 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 to detect possible reactivation **(B1)**.

Treatment of chronic hepatitis C in patients with 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.[336]

Haemophilia is an inherited bleeding disorder caused by a deficiency of either factor VIII or IX in haemophilia A and B, respectively. 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 numerous 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 that in HCV-positive individuals in the general population. 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 was among the commonest causes of death in patients with inherited bleeding disorders. The management of chronic hepatitis C in haemophilia is the same as in the non-haemophilic population.

Trials with antiviral therapy have been published in patients with inherited blood disorders.[337–342] In a Lebanese study, 7 patients with transfusion-dependent thalassemia and HCV infection were treated with the fixed-dose combination of sofosbuvir and velpatasvir. All of them achieved SVR and treatment was well tolerated.[343] In the C-EDGE IBLD study, the fixed-dose combination of grazoprevir and elbasvir was administered for 12 weeks in patients infected with genotype 1b with haemoglobinopathies including sickle cell anaemia, β-thalassemia, haemophilia A/B or von Willebrand disease. One patient out of 4 had cirrhosis and patients with a haemoglobin level <7 g/dl were excluded. SVR12 was achieved in 96% (44/46; 1 relapse) of cases, while haemoglobin levels were maintained on treatment.[344] In a recent Italian multicentre study, SVR was achieved in 99% (193/195) of patients with haemophilia and chronic HCV reinfection receiving treatment with various DAA regimens following the EASL recommendations. No serious adverse events were observed.[345]

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 hours, 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)**.
- Patients with haemoglobinopathies or bleeding disorders should be treated with the same anti-HCV regimens, following the same rules as HCV-monoinfected patients **(B1)**.

Retreatment of DAA failures

With currently available highly efficacious pangenotypic DAA regimens, treatment failure, *i.e.* the failure to achieve SVR, is rare.[346] Retreatment of patients who failed can be optimised based on RAS testing.[346–348] Therefore, specialist advice can improve outcomes after retreatment for DAA failures.

The RASs that have been shown to confer reduced susceptibility to the corresponding drug classes *in vitro* and/or that have been reported to be selected by DAA-containing therapies in patients who failed to achieve SVR are summarised in Table 7.[119,346,348,349] These many RASs and several 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.[35] POLARIS-1

Table 7. 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), *e.g.* sofosbuvir								
	150				A150V			
	159	L159F	L159F	L159F	L159F			
	206				K206E			
	282	S282G/R/T	S282G/R/T	S282G/R/T	S282G/R/T	S282C/G/R/T	S282G/R/T	S282G/R/T
	316	C316H/R	C316F/H/N					
	320	L320I/F/V						
	321	V321A	V321I		V321A	V321A		
NS5A inhibitors (NS5A)								
	24	K24E/QR/T	Q24K	T24A/S	S24F			Q24H
	26	K26E						
	28	M28A/G/S/T/V	L28A/M/T	L/F28C/S	M28T/K	L28M/S/T/V	L28I	F/L28A/I/L/M/T/V
	29	P29R	P29S, del29	P29S				
	30	Q30C/D/E/G/H/K/L/N/R/T/Y, del30	R30G/H/P/Q/S	L30H/S	A30D/E/K/S	L30F/G/H/R/S	Q30H	R30E/H/N/S
	31	L31I/F/M/P/V	L31F/I/M/V/W	L31I/M/V	L31F/I/M/P/V	M/L31I/V	L31F/I/V	L31I/M/V
	32	P32L/S, del32	P32F/L/S, del32				P32L	P32A/L/Q/R/S
	38	S38F						
	58	H58C/D/L/P/R	P58A/D/L/S/R/T			T58A/P/S		T58A/G/H/N/S
	62		Q/E62D		S62L			
	92	A92K/T	A92E/K/T/V	C92R/S/T/W	E92K			E92T
	93	Y93C/F/H/L/N/R/S/T/W	Y93C/H/N/R/S/T	Y93F/N/H	Y93H/N/S	Y93C/H/N/S/R/W		T93A/H/N/S
Protease inhibitors (NS3)								
	36	V36A/C/F/G/L/M	V36A/C/G/L/M					V36I
	41	Q41R	Q41R		Q41K	Q41R		Q41K/R
	43	F43I/L/S/V	F43I/S/V	F43V				
	54	T54A/S	T54A/C/G/S					
	55	V55I	V55A	V55A/I				
	56	Y56H	Y56H/L/F	Y56H/F	Y56H	Y56H		Y56H
	80	Q80K/L/R	Q80H/K/L/R		Q80K/R	Q80R		L80K/Q
	122	S122G/N/R	S122A/D/G/I/N/R/T					S122T
	155	R155G/I/K/M/Q/S/T/V/W	R155C/G/I/K/L/Q/M/S/T/W		R155K	R155C/K	R155K	
	156	A156G/P/S/T/V	A156G/P/S/T/V	A156L/M/T/V	A156G/P/T/V	A156G/H/K/L/S/T/V	A156T/V	A156T/V
	158	V158I	V158I					
	166				A166S/T/Y			
	168	D168A/C/E/F/G/H/I/K/L/N/Q/R/T/V/Y	D168A/C/E/F/G/H/I/K/L/N/Q/T/V/Y	D168A/E/F/G/H/N/S/T/V/Y	Q168H/K/L/R	D168A/E/G/H/T/V	D168A/E/H/K/R/V/Y	D168A/E/G/H/V/Y
	170	I/V170T/V	I/V170A/L/T					I170V
	175		M175L					
Non-nucleoside palm-1 inhibitor (NS5B), *e.g.* dasabuvir								
	314	L314H						
316	C316Y	C316H/N/Y/W						
	368		S368T					
	395	A395G						
	411		N411S					
	414	M414I/T/V	M414I/T/V					
	445		C445F/Y					
	446	E446K/Q						
	448	Y448C/H	Y448C/H					
	553	A553T/V	A553V					
	554	G554S	G554S					
	555	Y555H						

(*continued on next page*)

Table 7. (*continued*)

Drug class (genome region)	Amino acid position	Genotype/subtype						
		1a	1b	2	3	4	5	6
	556	S556G/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. Adapted and updated from.[119]
DAAs, direct-acting antivirals; del, deletion; IFN, interferon; RAS(s), resistance-associated substitution(s); SVR, sustained virological response.

included patients who failed a prior NS5A-containing treatment, of whom 46% had cirrhosis. The overall retreatment SVR rate was 96% (253/263; 1 virological breakthrough and 6 relapses) in patients receiving sofosbuvir, velpatasvir and voxilaprevir for 12 weeks. SVR was more frequent in patients without than in those with cirrhosis (99% *vs.* 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 in only 2 of them at virological failure.[35]

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 retreatment SVR12 rate was 98% (178/182; 1 relapse) in patients randomised to receive sofosbuvir, velpatasvir and voxilaprevir for 12 weeks, compared to 90% (136/151; 1 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 after retreatment had no detectable RASs at baseline or at virological failure.[35]

Several real-world studies assessing the efficacy of the triple combination of sofosbuvir, velpatasvir and voxilaprevir in the retreatment of DAA-containing regimen failures confirmed the high SVR rates achieved with this regimen, regardless of patient gender, body mass index, HCV genotype and baseline HCV RNA.[350–352] The only pre-treatment parameter associated with a slightly lower SVR rate was cirrhosis.[350] Thus, the triple combination of sofosbuvir, velpatasvir and voxilaprevir appears as the treatment of choice for retreatment of patients who failed to achieve SVR after an IFN-free, DAA-based treatment course. Retreatment studies are ongoing with the triple combination of sofosbuvir, velpatasvir and voxilaprevir in patients aged 12–17 years. No formulation will be available for younger children.

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.[353] In a randomised study of 177 patients with chronic HCV genotype 1 infection who received previous treatment with sofosbuvir plus an NS5A inhibitor, 16 weeks treatment with glecaprevir/pibrentasvir induced SVR12 in 86–97% of patients. Treatment failed in 7.3% of patients with genotype 1a infection. Treatment-selected RASs in the NS3 and NS5A regions were observed in 9 and 10 patients with treatment failure, respectively.[354] Overall, the combination of glecaprevir and pibrentasvir 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*,[115,135,142] 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. In a phase II trial, patients who failed to achieve SVR after a 12-week course of glecaprevir/pibrentasvir were retreated with the triple combination of sofosbuvir plus glecaprevir/pibrentasvir for 12 or 16 weeks. Only 1 out of the 23 patients, who received 12 weeks of therapy, failed to achieve SVR.[355]

In particularly difficult-to-cure patients previously exposed to NS5A inhibitors, the triple combinations of sofosbuvir, velpatasvir and voxilaprevir, and of sofosbuvir plus 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 extrahepatic manifestations, previous unsuccessful courses of treatment, RAS profiles, etc. The presence of decompensated cirrhosis will negate the use of protease inhibitor-based regimens, emphasising the need to institute retreatment as soon as possible.

Recommendations

- Patients who failed after any of the DAA-containing treatment regimens should be retreated in the context of a multidisciplinary team including experienced treaters and virologists **(B1)**.
- 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 **(B1)**.
- 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 **(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 multidisciplinary decision **(B1)**.
- In very difficult-to-cure patients (patients with NS5A RASs who failed twice or more 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 multidisciplinary decision **(B1)**.
- In patients who failed to achieve SVR after retreatment with the triple combination of sofosbuvir, velpatasvir and voxilaprevir, the triple combination of sofosbuvir, glecaprevir and pibrentasvir can be administered for 24 weeks with weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) **(B1)**.
- 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 multidisciplinary decision **(B1)**.

Treatment of recently acquired hepatitis C

Historically, HCV infection has been classified as either acute or chronic. By convention, acute hepatitis C was defined as the first 6 months of infection, followed by chronic infection in the absence of spontaneous clearance. These definitions are challenged by recent insights into the natural history of HCV persistence, emerging trends in transmission patterns and the evolution of HCV therapy.

Acute hepatitis C is generally benign and often asymptomatic.[356] In most cases, the diagnosis of HCV infection is based on elevated serum ALT levels, testing of high-risk populations or routine HCV screening.[357] Precise timing of infection is therefore difficult to establish. Several funding authorities have denied treatment reimbursement in patients considered to have acute hepatitis C, because the licensing of HCV DAAs was based on studies performed in patients with chronic infection. Given the high efficacy and safety of current HCV DAAs, such classification is a barrier to HCV elimination.

In this context, the term "recently acquired" hepatitis C is more appropriate than acute hepatitis C. Recently acquired *de novo* HCV infection is defined by the presence of anti-HCV antibodies, HCV RNA and/or HCV core antigen that were not detectable in previous samples up to 12 months. If such historical samples are unavailable, the diagnosis of recently acquired hepatitis C is based on the presence of HCV RNA or HCV core antigen, in the presence or absence of anti-HCV antibodies, associated with a 3-fold or greater rise in ALT levels above baseline in an individual who had a risk behaviour in the preceding 6 months and in the absence of other causes of acute liver injury. Recently acquired HCV reinfection uses the same criteria following spontaneous or DAA-induced viral clearance. In this case, demonstration of a different strain by means of genome sequence analysis confirms reinfection.

Recent data indicate that DAA treatment in the early phase of HCV infection is cost-effective and useful to achieve micro-elimination in specific groups of patients,[358] whereas postponing therapy to meet the criteria for chronic infection increases the risk of HCV transmission. In HIV-infected patients, the lack of a 2-log drop of HCV RNA level 4 weeks after the initial presentation predicts a low-likelihood (negative predictive value <1%) of spontaneous clearance.[359] Thus, at least in individuals living with HIV, early chronic HCV infection can be defined as an estimated duration of infection <12 months and a lack of a 2-log reduction of HCV RNA levels 4 weeks after initial presentation with recently acquired hepatitis C.

High SVR rates have been reported in a small number of patients with recently acquired hepatitis C receiving DAA-based regimens. The ideal duration of treatment remains unknown. 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,[360] 77% (20/26) after 6 weeks of treatment in HIV-positive individuals,[361] and 100% (20/20) after 6 weeks of treatment in HIV-negative, non-injection drug users.[362] The combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir administered for 8 weeks yielded a 97% (29/30; 1 non-virological failure) SVR rate in patients with recently acquired hepatitis C in the TARGET-3D study.[363] Finally, 6 weeks of treatment with glecaprevir/pibrentasvir yielded a 90% SVR12 rate (27/30; 1 virological failure) in patients with recently acquired hepatitis C.[364]

In a multicentre international, open-label trial, patients with recently acquired hepatitis C were randomised into 2 groups to receive either 6 or 12 weeks of the fixed-dose combination of sofosbuvir and velpatasvir. Interim analysis results were presented from 127 of the planned 250 inclusions. The SVR12 rates were 79% (53/67; 6 relapses) in the 6-week arm and 95% (57/60; no virological failure) in the 12-week arm. The high relapse rate

in the short-duration arm led to early termination of the trial.[365] In an open-label, single-arm, multicentre, international pilot study, 30 adults with recently acquired HCV infection (mean age 43 years, 90% men who have sex with men, 77% HIV-coinfected) were treated with the fixed-dose combination of glecaprevir and pibrentasvir. They were infected with genotypes 1, 4 and 3 in 83%, 10% and 7% of cases, respectively. The SVR12 rate was 90% (27/30; 1 relapse).[366]

Because at least 8 weeks of therapy are required to maximize SVR rates in patients with chronic hepatitis C, patients with recently acquired hepatitis C should be treated with DAA combinations for 8 weeks, pending additional data on the ideal treatment duration in this group.

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

Recommendations

- Patients with recently acquired *de novo* hepatitis C should be treated with the combination of sofosbuvir and velpatasvir or with the combination of glecaprevir and pibrentasvir for 8 weeks **(B1)**.
- SVR should be assessed 12 and 24 weeks after 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.

Assessment of treatment efficacy

Minimal monitoring is now required to assess treatment efficacy, except in populations at risk of poor adherence to treatment. In all cases, HCV RNA or HCV core antigen assessment at week 12 or 24 indicates whether treatment has been successful.

Recommendations

- HCV RNA or HCV core antigen detection should be performed at week 12 (SVR12) or 24 (SVR24) post-treatment to assess whether treatment has been successful **(A1)**.
- Given the high SVR12 rates expected with pangenotypic DAA-based regimens, checking SVR is dispensable, except in patients with high-risk behaviours and in patients at risk of reinfection **(B1)**.

Monitoring of treatment safety

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

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 these patients. 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).[36]

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.[367] In an integrated analysis of 2,265 patients treated with this combination in phase II and III clinical trials, fatigue and headache were the most common adverse events.[367]

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% (13/1,690) 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.

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)**.
- Renal function should be checked monthly in patients with reduced eGFR **(A1)**.

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. It is necessary to check whether all the co-administered drugs are 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, an alternative in the same therapeutic class without a drug interaction should be found. A drug interaction can also be managed either by a change of dose or a clear monitoring plan. The introduction of new medications during HCV treatment requires monitoring.

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. Treatment must be stopped in case of severe adverse events or in case of a hepatitis flare (ALT levels above 10 times the upper limit of normal, if not already present at the time of starting treatment).

If significant anaemia occurs (haemoglobin <10 g/dl) in patients with decompensated (Child-Pugh B or C) cirrhosis receiving ribavirin, 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 their baseline haemoglobin was low. Ribavirin administration should be stopped if the haemoglobin level falls below 8.5 g/dl.[368–376]

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 with decompensated (Child-Pugh B or C) cirrhosis who need ribavirin, the dose of ribavirin should be adjusted downward by 200 mg in decrements if the haemoglobin level drops below 10 g/dl **(A1)**.
- In patients with decompensated (Child-Pugh B or C) cirrhosis who need ribavirin, ribavirin administration should be stopped if the haemoglobin level drops below 8.5 g/dl **(A1)**.

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 unless additional causes for ongoing liver damage are present and persist). In patients without varices at baseline, annual monitoring of platelet counts and transient elastography assessment allows for individualised monitoring with endoscopy. If platelet counts remain above 150,000 and elastography values <20 kPa, there is no need to perform endoscopy.[377] The presence of cofactors for liver disease, such as a history of alcohol drinking or a metabolic syndrome associated with obesity and/or type 2 diabetes, may make additional assessments 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.[6,9,10,12–17,250,378] 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 with high-risk behaviour, are of the order of 1–8% per year.[303,379–388] The ease of pangenotypic DAA-based therapy may increase the likelihood of reinfection, as recently suggested.[389] To maximize the benefit of therapy, the risks of reinfection should be emphasised to patients at risk, and behavioural modifications should be positively reinforced. Patients at-risk should be monitored for reinfection and treatment should be offered without stigma or delay to those patients who are reinfected.

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, because the risk of *de novo* or incident HCC is reduced but not abolished by SVR **(A1)**.
- In patients with cirrhosis, surveillance for oesophageal varices by endoscopy should be performed if varices were present at pre-treatment endoscopy, or if the platelet count falls below 150,000 and elastography increases to more than 20 kPa **(A1)**.
- The risk of reinfection should be explained to positively modify risk behaviour in at-risk populations **(B1)**.
- Following SVR, monitoring for HCV reinfection through bi-annual or, at least, annual HCV RNA assessments should be undertaken in PWIDs or men who have sex with men with ongoing risk behaviour **(A1)**.
- Retreatment should be offered without stigma or delay to those patients who are reinfected **(A1)**.

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

Untreated patients with chronic hepatitis C and those who failed to respond to several courses of appropriate treatment (incurable patients) 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.[95] Patients with advanced fibrosis (METAVIR score F3) and cirrhosis (METAVIR score F4) should undergo specific ultrasound surveillance every 6 months.

Recommendations

- Untreated patients with chronic hepatitis C and those who definitively failed several prior treatment courses (incurable patients) should be regularly followed **(A1)**.
- Non-invasive methods for staging fibrosis are best suited to follow-up assessment at intervals of 1 to 2 years **(A1)**.
- HCC surveillance every 6 months must be continued indefinitely in patients with advanced fibrosis (F3) and cirrhosis (F4) **(A1)**.

Conflict of interest

Jean-Michel Pawlotsky: Grant and research support: Abbott, Vela Diagnostics. Advisory Boards: Abbvie, Arbutus, Gilead, GlaxoSmithKline, Merck, Regulus and Siemens Healthcare. Speaking and teaching: Abbvie and Gilead. Alessio Aghemo: Grant and research support: Abbvie and Gilead. Advisory Boards: Abbvie, Alfasigma, Gilead, Intercept, Merck and Mylan. Speaking and teaching: Abbvie, Alfasigma, Gilead, Intercept, Merck and Mylan.

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

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Supplementary data

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