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REVIEW

Current and future challenges in HCV: insights from an Italian experts panel

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Abstract

Background   The recent availability of direct acting antiviral drugs (DAAs) has drastically changed hepatitis C virus (HCV) treatment scenarios, due to the exceedingly high rates of sustained virological response (SVR) and excellent tolerability allowing for treatment at all disease stages.

Methods   A panel of Italian experts was convened twice, in November 2016 and January 2017, to provide further support on some open issues and provide guidance for personalized HCV care, also in light of forthcoming regimens.

Results and conclusions   Treatment recommendations issued by international and national liver societies to guide clinicians in the management of HCV infection are constantly updated due to accumulating new data. Such recommendations may not be applicable to all healthcare settings for a variety of reasons. Moreover, some gaps still remain and the spectrum of patients to be treated is also evolving.

Keywords   HCV · Treatment · DAAs · Comorbidities

Introduction

Hepatitis C virus (HCV) remains a major problem worldwide, and is responsible for a large number of deaths related to HCV-associated hepatocellular carcinoma (HCC) and cirrhosis [1]. About 3% of the world's population, or around 80 million people, are infected with HCV [2]. While its prevalence varies by geographic region, reliable epidemiological data are not available [3–5]. In addition, many HCV-infected individuals are unaware of being infected, but frequently progress to advanced fibrosis, cirrhosis, and HCC [1]. In addition to the liver, extra hepatic manifestations of HCV infection also cause significant negative impact and a substantial number of deaths [6, 7].

The availability of direct acting antiviral drugs (DAAs) has significantly changed management of HCV by providing clinicians with tools to modify the natural history of HCV infection, transmission and/or re-infection.

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Considering the rapidly accumulating data on the use of DAAs, treatment guidelines have been issued by the American (AASLD), European (EASL) and Italian (AISF) liver societies to guide clinicians in routine management of HCV infection [8–10], even if some gaps remain. With the aim of providing further support for clinicians, a panel of Italian experts was convened twice in November 2016 and January 2017, the first via web conference and the second a face-to-face meeting in Rome, to discuss relevant aspects. Herein, the expert's opinion on some of these open issues has been summarized, and relative statements made to provide guidance for clinicians on selected issues in the management of HCV infections.

Treatment perspectives with new drugs

In 2016, two novel DAAs combinations, elbasvir/grazoprevir and sofosbuvir/velpatasvir, have been registered for use in USA and Europe. The glecaprevir/pibrentasvir combination has recently been licensed by EMA and will become available by the end of 2017, while the triple combination of sofosbuvir/velpatasvir/voxilaprevir has recently been approved by the FDA [11]. Still other combinations such as elbasvir/ruzasvir/uprifosbuvir are currently under evaluation in phase III trials [12]. Of note, at least in Italy, sofosbuvir and sofosbuvir/ledipasvir are no longer reimbursed by the national healthcare system since May 2017.

The new combination of sofosbuvir/velpatasvir is available for treatment of genotypes 1, 2, 3, 4, 5 and 6; [13].

The NS3/4A protease inhibitor grazoprevir combined with the NS5A inhibitors elbasvir is able to eradicate HCV in patients with genotype 1 and 4 [14]. It is now considered that this new combination offers an opportunity to cure HCV infection with short interferon (IFN)-free therapy, even in difficult to treat patients such as those with cirrhosis, HIV co-infection, patients with CKD stages 4–5 and/or on dialysis, as well as those who have failed previous therapy [15].

The upcoming pangenotypic combination of glecaprevir/pibrentasvir can be administered to all patients regardless of genotype, allowing treatment for 8 weeks in patients with low viral load (< 6 million IU/mL) or in patients without cirrhosis and naive to DAAs. Indeed, the results of the phase 3 study Endurance 1 concluded that 8 weeks of treatment are not less effective than 12 weeks in patients with HCV genotype 1 even if co-infected with HIV [16]. A regimen of 12 weeks should be chosen for patients with genotypes 4, 5, or 6 [17], previous failure to peg-IFN and ribavirin, and in experienced or cirrhotic patients with genotype 3 [18].

Patients with mild disease are easiest to treat. In fact, even if the new antiviral drugs are much less influenced by host parameters, severe disease is associated with lower SVR rates on both IFN-containing and IFN-free combination regimens. This is related to a slower, second-phase HCV-RNA decline in cirrhotic vs. non-cirrhotic patients, even if the molecular mechanisms underlying the infected cell clearance in cirrhotic patients are still unclear. To overcome the low rate of viral response, patients with advanced disease should be treated with long regimens, and ribavirin is strongly recommended in some cases [19]. Conversely, in patients with mild disease, the efficacy of antiviral treatment is higher.

Relevant points

- Elbasvir/grazoprevir can eradicate HCV in most patients with genotype 1 and 4, both treatment naïve and treatment experienced, with compensated cirrhosis (Child–Pugh A) and without cirrhosis.
- Sofosbuvir/velpatasvir is available and effective for patients with genotypes 1, 2, 3, 4, 5 and 6.
- Early treatment of comorbidities is needed even in the absence of advanced liver disease.
- Patients with advanced liver disease should be treated with long regimens, and ribavirin is strongly recommended in some cases.

Pharmacology of new DAAs

Two new STRs have completed their development phase and were approved in 2016, namely elbasvir/grazoprevir (NS5A inhibitor + NS3/4A inhibitor) and sofosbuvir/velpatasvir (NS5B inhibitor + NS5A inhibitor). Glecaprevir/pibrentasvir (GCV/PBV, NS3/4A inhibitor + NS5A inhibitor) is at the end of its clinical development and in an earlier phase of development, there are three DAAs that are classifiable, respectively, as a NS5B inhibitor (uprifosbuvir, MK-3682), NS3/4 inhibitor (voxilaprevir), and NS5A inhibitor (ruzasvir, MK-8408).

Metabolism and drug–drug interactions

Elbasvir/grazoprevir

These drugs are both substrates of the cytochrome P450 isoenzyme CYP3A4 and membrane transporter P-glycoprotein (Pgp), making them candidate victims of molecules acting on CYP3A4 and/or Pgp as inducers (e.g. rifampicin, efavirenz) or inhibitors (e.g. anti-HIV boosted protease inhibitors), while their potential as perpetrators of drug–drug interactions appears to be low, and possibly mediated by BCRP inhibition (both) or weak inhibition of CYP3A4 (grazoprevir) or Pgp (elbasvir). No significant drug–drug interactions have been observed when the combination is co-administered with buprenorphine,

naloxone, famotidine, pantoprazole, tacrolimus, mycophenolate moetil, prednisone, montelukast, digoxin, or the phosphate binder sevelamer. An increase in grazoprevir exposure was observed in case of co-administration with cyclosporin, while co-administration led to overexposure of both atorvastatin and rosuvastatin. Concomitant use of a proton pump inhibitor use does not reduce the efficacy of elbasvir/grazoprevir. Elbasvir and grazoprevir have elimination half-lives of 31 and 24 h, respectively, which allows for QD administration [20–22].

Velpatasvir

This drug is marketed in co-formulation with the well-established NS5B inhibitor sofosbuvir. Velpatasvir is metabolized by CYP3A4, CYP2C8, and CYP2B6, and is a substrate of the transporters Pgp, BCRP, OAT1B1 and OAT1B3 on which it exerts mild inhibitory action [23, 24]. Thus, velpatasvir is more a candidate victim of cytochrome P450 enzymes rather than a relevant perpetrator of drug–drug interactions. Expectedly, the pharmacokinetic exposure of velpatasvir is reduced in case of co-administration with efavirenz, and, vice versa, tends to minor increases in exposure when given with a boosted anti-HIV protease inhibitor. The solubility of elpatasvir decreases as the pH increases. Thus, drugs that increase gastric pH are expected to decrease the levels of velpatasvir. Co-administration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to co-administer a proton-pump inhibitor, velpatasvir should be taken with food 4 h before omeprazole 20 mg. Use with other proton-pump inhibitors has not been studied. Velpatasvir was found to increase exposure of both rosuvastatin and tenofovir, probably as a result of transporter inhibition; its elimination half-life is around 15 h, which is compatible with QD administration [25].

Glecaprevir/pibrentasvir

A relevant feature of this combination consists of the significant increase of pibrentasvir attributable to glecaprevir, with a rise in C_{max} and C_{trough} of almost five- and sevenfold, respectively [26]. Drug–drug interactions have been assessed with some antiretrovirals, resulting in an increase in rilpivirine by around twofold (all pharmacokinetic parameters) and an increase in the C_{trough} of raltegravir by almost threefold, with no variations for glecaprevir/pibrentasvir. The plasma elimination half-life is around 3 h for glecaprevir and 4 h for pibrentasvir, with a subsequent multiexponential subsequent phase; QD administration is successful in the clinical conditions tested [27].

Uprifosbuvir (MK-3682), ruzasvir (MK-8408), voxilaprevir (GS-9857)

Uprifosbuvir has a plasma elimination half-life < 3 h, dose proportional pharmacokinetics, and no tendency to accumulate. No clinico-pharmacological information is available for ruzasvir; voxilaprevir is substrate of both CYP3A4 and CYP2C8 as well as substrate and inhibitor of the transporters Pgp, BCRP, and several OATPs. As a perpetrator, voxilaprevir was found to increase the AUC of both rosuvastatin and pravastatin by approximately eight- and twofold, respectively, possibly as a result of both BCRP and OAT inhibition [11, 23].

Pharmacokinetics in advanced liver disease

As is also seen with first and second generation DAAs, NS3/4 inhibitors display an overt tendency to increase their pharmacokinetic exposure when a certain degree of advanced impairment of liver vasculature and metabolic capacity is present. Grazoprevir and glecaprevir show a log magnitude of pharmacokinetic exposure increase in decompensated cirrhotic patients, while this is not the case for velpatasvir and elbasvir, although the latter is only available in combination with grazoprevir. It is thus apparent that NS5A inhibitors can be administered in case of decompensated cirrhosis, while protease inhibitors are not recommended or contraindicated in case of Child–Pugh stage B and C [28].

Relevant points

- Close scrutiny of the pharmacology of the new DAAs is warranted due to limited data available.
- NS5A inhibitors can be used in patients with decompensated cirrhosis, while protease inhibitors are not recommended or contraindicated beyond Child–Pugh stage B7.
- PPI use with EBR/GZR has no significant effect on SVR12 rates in GT1/4-infected patients with and without cirrhosis.
- Co-administration of sofosbuvir/velpatasvir with PPI is not recommended.

HCV resistance associated variants: problems and solutions

HCV resistance involves both natural and selected resistance associated substitutions (RASs). Globally, natural resistance to NS5A inhibitors is found with highly variable prevalence according to HCV-genotype and geographic region, ranging from 13 to 30% [29, 30]. In DAA-naïve patients, resistance testing, therefore, can confirm the presence of pre-existent NS5As RASs that confer high-level resistance, thus allowing

the addition of ribavirin and/or increasing the duration of treatment to individualize therapy [19, 31]. At the same time, clinicians should be aware that HCV sequencing is not only useful to identify RASs, but also to confirm the "correct" genotype.

Studies evaluating the effects of natural HCV NS5A RASs in response to the combination of ledipasvir and sofosbuvir in patients with HCV genotype 1 infection, with or without ribavirin, have shown that baseline RASs in NS5A-naïve patients have minimal effects on responses to ledipasvir/sofosbuvir [32]. However, when these RASs do have effects, they can be largely overcome by extending treatment duration or through treatment intensification. The 2016 recommendations of the EASL highlight that treatment of NS5A-naïve GT-1a patients can be modulated by the presence of NS5A RASs.

In HCV genotype 3 NS5A-naive patients treated with velpatasvir/sofosbuvir, SVR12 was 84% in patients with natural Y93H; moreover, the addition of ribavirin greatly enhances the efficacy of the combination, from 50 to 85% [33]. Similarly, the 2016 recommendations of the EASL have provided guidance for HCV genotype 3.

HCV resistance to DAAs also plays an important role in the failure of IFN-free treatment regimens [31], as limited retreatment options are available, and the presence of resistant viral strains may significantly affect their effectiveness [34]. For instance, retreatment with 24 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin led to 97% SVR12 in NS5A-xperienced genotype 1 patients and 91% in genotype 2, while among 13 patients with genotype 3 infection and Y93H NS5A-RAS, the SVR12 rate was reduced to 82% [35]. In this setting, EASL guidance currently suggests to defer HCV treatment for patients without indication for urgent retreatment [19]. Otherwise, retreatment strategies should be tailored on HCV resistance testing results, in the context of 24-week regimens plus [19, 34].

Relevant points

- When needed, retreatment may require 'unconventional' approaches with multiple DAAs along with genotype resistance testing.
- This possibility stresses the need to individualise DAA treatment not only before starting therapy, but also most importantly after failure.

Role of current and next generation DAA: divergence between guidelines

This discussion is based on the recommendations of the AASLD, EASL, CIHR, and AISF, which have been updated considering the newly approved combinations as first-line therapeutic options [8, 19, 36, 37].

Sofosbuvir/velpatasvir

The approved indications in Europe consider ribavirin as optional in combination with sofosbuvir and velpatasvir in the treatment of genotype 3 in subjects with cirrhosis, different from USA and Canada in which treatment for 12 weeks without ribavirin is recommended in all subjects with cirrhosis and reserving ribavirin only for those with heart failure. EASL, AASLD, and AISF recommendations consider the use of sofosbuvir and velpatasvir as optimal for all genotypes and all patients regardless of stage of disease and presence of hepatic decompensation. For sofosbuvir and velpatasvir, there is a recommendation for 12-week administration without ribavirin in all subjects with compensated liver disease and infection with a genotype that is different from 3, regardless of the stage of disease and previous exposure to IFN and ribavirin. For genotype 3, there is a discrepancy between the European and US recommendations with regard to subjects without cirrhosis and previously treated with IFN and ribavirin; all European recommendations require the use of ribavirin in combination with velpatasvir for 12 weeks. In subjects with cirrhosis, both recommendations suggest the use of ribavirin, although both suggest limiting the use of ribavirin in subjects with resistance mutations in the NS5A region as they affect resistance to velpatasvir.

Elbasvir/grazoprevir

In Europe, the combination is indicated for 12 weeks without ribavirin in genotype 1b. For genotype 1a, the FDA suggests a duration of 16-week treatment with ribavirin in patients with substitutions associated with resistance in the NS5a region, regardless of the level of viremia and stage of disease, while the Canadian regulatory authority suggests this schedule in patients who have failed a combination of IFN and ribavirin with non-negative HCV-RNA during treatment and the EMA in patients with viral load greater than 800,000 IU/mL and resistance mutations in the NS5A region. In the US and AISF recommendations, genotype 4 treatment is for 12–16 weeks with ribavirin in patients who showed any type of failure with a combination of IFN and ribavirin, while the Canadian regulations limit this schedule only to those who have not shown negativization of viremia during previous therapy with IFN and ribavirin; EMA indications reserve this schedule to all subjects with baseline viral load > 800,000 IU/mL regardless of response to previous IFN and ribavirin. In genotype 1a, US recommendations suggest ribavirin and a duration of 16 weeks of therapy in subjects with resistance mutations in the NS5A region prior to treatment, making pre-treatment evaluation

necessary. The European recommendations are based on the heterogeneity of healthcare systems, while taking into consideration the availability of resistance testing among different countries.

Relevant points

- Despite the absence of firm evidence, it is suggested to add ribavirin to sofosbuvir/velpatasvir in patients with genotype 3 infection who are unresponsive to treatment with peg-IFN and in those with decompensated cirrhosis.
- For individuals who are retreated with currently available regimens, tailoring retreatment based on NS5A and NS3 resistance profile is recommended. In addition, 24-week regimens and the association with ribavirin are generally indicated.
- With elbasvir/grazoprevir, the suggestion is to treat without ribavirin for 12 weeks in all patients with genotypes 1 and 4, with or without cirrhosis (Child–Pugh A), except in those with genotype 1a resistance mutation in the NS5A region at baseline and/or with HCV-RNA > 800,000 IU/mL and in those with genotype 4 HCV-RNA > 800,000 IU/mL.
- Treatment with elbasvir/grazoprevir can be considered for 8 weeks in naïve subjects with genotype 1b infection and fibrosis < 3.

Hepatocellular carcinoma and DAAs: a controversial story

The achievement of a SVR to interferon-based therapies has been shown to improve the course of hepatitis C in terms of reduced rates of liver-related complications and all-cause mortality. Hill and co-authors presented 5-year observational data of 34,563 patients with and without SVR who had been treated with antivirals. Elimination of HCV resulted in a decrease of 5-year-mortality by 62–84%; the risk for development of HCC was lowered by 68–79%; the risk for liver transplantation was lowered by 90% [38]. A post hoc analysis of the HALT-C trial confirmed two prior large retrospective follow-up studies from Italy and France in which the incidence of HCC among patients with SVR was significantly lower compared to those without SVR [39–41]. Morgan et al. [42] described a similar HCC risk reduction with SVR among patients with all stages of fibrosis (HR 0.24) with a separate analysis, although predominantly including studies from Asia where the risk of HCC is substantially higher.

Several meta-analyses [43–46] have suggested that IFN treatment may prevent HCC recurrence, with conflicting data on survival. Miao et al. [43] showed that IFN not only reduced late recurrent HCCs but also early ones, especially in patients with pure HCV infection. Cabibbo et al. [47] recently published a meta-analysis comparing IFN-based therapy with no treatment in patients with HCV-related early HCC who achieved complete response after surgical resection or ablation and that did not receive any adjuvant treatment. Pooled estimates of actuarial recurrence rates were 7.4% at 6 months and 47% at 2 years.

An increased risk of de novo HCC in patients has been reported in patients treated with DAAs. Kobayashi et al. [48] indicated that the risk of HCC after SVR is similar, independently of a DAA or IFN-based regimen.

Reig et al. [49] published the first report of HCC recurrence in patients who had achieved SVR following DAAs from four Spanish centers. Considering patients who started DAA treatment less than 4 months after HCC treatment, the HCC recurrence rate was 41.2%. After surgical resection or RFA, HCC recurrence at 1-year may be expected in about 20% of patients [50]. Conti et al. [51] evaluated the early occurrence of HCC in 285 cirrhotic patients without history of liver cancer and recurrence of HCC in 59 cirrhotic patients with a history of previously-treated HCC treated with DAAs who achieved SVR. HCC recurred in 29% of patients treated with either surgical resection, radiofrequency ablation, trans-arterial chemoembolization, or percutaneous ethanol injection. De novo HCC occurred in 3.2% of patients, similar to a historic population of untreated cirrhotic patients in which the cumulative occurrence rate of HCC was 3.2% at 1 year [50]. A French study on three distinct prospective multicenter cohorts including more than 6000 patients did not report an increased risk of HCC recurrence in DAA-treated patients vs. untreated patients [52]. In the ANRS CO22 HEPATHER cohort (267 patients previously treated for HCC of whom 189 received DAA and 78 did not) and in ANRS CO12 CirVir (79 cirrhotic patients who received curative treatment of HCC among whom 13 received DAA and 66 did not), the rates of HCC recurrence did not differ in DAA-treated and untreated patients.

Most recently, Reig and colleagues have reported on the recurrence rates of HCC associated in time with DAA therapy [53]. Among the 77 patients in the cohort, 31.2% had HCC recurrence. Considering those who started HCV treatment within 4 months after SVR, the rate of recurrence was 45%. Thus, it is possible that the timing of DAA therapy in patients undergoing first treatment for HCC may affect the recurrence rate, although more studies are needed in this regard.

Relevant points

- Sustained HCV clearance by either IFN-based or DAA regimens minimizes the rate of progression of HCC to cirrhosis and hence indirectly reduces the risk of HCC.

- The residual risk of HCC after SVR may be due also to age, severity of liver disease and comorbidities as the rates of HCC recurrence do not differ in DAA-treated and untreated patients.

HCV-related compensated cirrhosis

Treatment in patients with cirrhosis has been difficult due to low SVR rates and higher risks of serious adverse events compared to those without cirrhosis. DAA-based regimens are currently recommended by international guidelines as the standard of care for compensated cirrhotic patients because of their virological efficacy, ease of use, and tolerability [54].

Genotypes 1 and 4

Sofosbuvir/ledipasvir

In treatment-experienced patients with HCV-1 cirrhosis, the addition of ribavirin to sofosbuvir/ledipasvir allows for shortening treatment to 12 vs. 24 weeks of treatment without ribavirin, without compromising SVR [19, 54–60].

Paritaprevir/ritonavir, ombitasvir, and dasabuvir with/ without ribavirin

The US FDA has issued a warning that treatment with ritonavir-boosted paritaprevir, dasabuvir, and ombitasvir can cause serious liver injury in patients with more advanced liver disease [19, 54, 61–65]. Moreover, these combinations are no longer recommended by the AASLD or EASL [36, 66].

Sofosbuvir/daclatasvir

At present, 12 weeks of treatment without ribavirin are currently recommended for treatment-naïve patients with genotypes 1a, 1b, or 4 as well as in treatment-experienced (DAA-naive) genotype 1b patients; ribavirin addition or treatment prolongation to 24 weeks should be considered in genotype 1a and genotype 4 treatment-experienced patients [19, 67].

Elbasvir/grazoprevir

Treatment-naïve and treatment-experienced patients infected with subtype 1b as well as treatment-naive patients infected by genotype 4 should receive this combination for 12 weeks without ribavirin; treatment should be prolonged to 16 weeks with the addition of ribavirin in genotype 1a patients with higher viral load (≥ 800,000 IU/mL) or with baseline NS5A RASs conferring resistance to elbasvir, as well as in genotype 4 treatment-experienced patients with higher viral load (≥ 800,000 IU/mL) [14, 19, 54, 68–72]. C-SALVAGE examined the use of elbasvir/grazoprevir plus R ribavirin BV in patient with chronic HCV genotype 1 infection (cirrhotic and non-cirrhotic patients) after failure of peg-IFN and ribavirin [69]. The final results of that trial showed that SVR24 was achieved in 96.2% of patients; however, baseline resistance-associated variants reappeared at relapse in the three patients with virologic failure [68]. C-WORTHY also evaluated elbasvir/grazoprevir with or without ribavirin in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis, which reported SVR12 rates ranging from 90 to 100% [72]. Zeuzem et al. [14] studied elbasvir/grazoprevir in cirrhotic and non-cirrhotic treatment-naive patients with genotype 1, 4, or 6 infection, reporting SVR12 in 95% of cases with similar, high rates across genotypes, and virologic failure in only 4% of cases.

Sofosbuvir/velpatasvir

Sofosbuvir/velpatasvir for 12 weeks without ribavirin is currently recommended in treatment of HCV-1 and HCV-4 compensated cirrhotic patients. This recommendation is based on the results of the Phase III ASTRAL-1 trial where SVR12 was observed in 98% of patients, including 98% in those infected with genotype 1a and 99% in those infected with genotype 1b [19, 73].

Genotype 2 treatment options

Sofosbuvir/ribavirin

The combination of sofosbuvir plus ribavirin is no longer recommended in the most recent European guidelines. Nonetheless, in settings where another option is not available, this combination (or even the combination peg-IFN plus ribavirin) remains acceptable based on several studies [19, 54, 74–77].

Sofosbuvir/daclatasvir

Daclatasvir is active in vitro against HCV genotype 2. Although limited data are available with this genotype, and by analogy with the results obtained with sofosbuvir/velpatasvir, the combination of sofosbuvir/daclatasvir (12 weeks without ribavirin) appears as a reasonable option for patients with genotype 2 infection who are ribavirin-intolerant [19, 78]. Sofosbuvir and sofosbuvir/ledipasvir are no longer reimbursed by the Italian national healthcare system since May 2017.

Sofosbuvir/velpatasvir

The phase III ASTRAL programme evaluating the FDC of sofosbuvir and velpatasvir for 12 weeks (without ribavirin) reported an SVR12 rate of 100% [13, 19, 54, 73].

Genotype 3 treatment options

Sofosbuvir/peg-IFN/ribavirin

Although not clearly recommended by latest European guidelines, this combination remains a good therapeutic option in well compensated HCV-3 patients who are able to tolerate a short course of IFN-based therapy. This evidence was clearly pointed out by the BOSON study [79].

Sofosbuvir/daclatasvir

Following the latest European guidelines, both treatment-naïve and treatment-experienced patients infected with HCV genotype 3 with compensated cirrhosis should be treated with this combination for 24 weeks with daily weight-based ribavirin [19, 54, 80–82]. As already mentioned, at least in Italy, sofosbuvir and sofosbuvir/ledipasvir are no longer reimbursed by the national healthcare system since May 2017.

Sofosbuvir/velpatasvir

This combination is recommended by European guidelines with a treatment regimen of 12 weeks with ribavirin (mandatory in patients carrying the Y93H NS5A RAS at baseline) or 24 weeks without ribavirin (if a reliable test for RAS detection is not available at baseline) [13, 19, 54].

No reliable data are currently available on long-term follow-up of compensated cirrhotic patients achieving SVR by DAAs, as their introduction was too recent to infer such conclusions, while conflicting data are emerging on HCC de-novo onset and/or recurrence after viral eradication by DAAs-based therapy.

Relevant points

- While numerous new regimens lead to SVR rates never achieved in the past, the increasing recognition of difficult to cure subgroups indicates that there is still additional work to be done in cirrhotic treatment-experienced genotype 3 patients and in those who fail previous DAA-based regimens carrying RASs that confer resistance to multiple classes of DAAs.

- The continuous need of ribavirin in specific treatment regimens remains a critical issue that significantly limits their use in patients who are poorly tolerant or ribavirin intolerant.
- The next generation of DAAs promises to be pangenotypic, with a higher barrier of resistance and ribavarin-free, overcoming many of these limitations.

HCV infection in special populations

Patients with HCV-HIV co-infection

Treatment of HCV-HIV coinfections has been recently reviewed elsewhere, noting that drug interactions between DAA and medications given those with HIV infection can result in treatment failure and adverse events, and response to DAAs may be further impaired by viral interference [83]. In Europe, there are currently several IFN-free DAA regimens approved for patients with HCV and HIV co-infection. All these treatments have high rates of virologic response similar to those obtained in patients with HCV infection alone. In the era of highly effective antiretroviral therapies, HIV response does not seem to be affected by co-infection [84] and HCV virologic cure has been shown to reduce the risk of liver-related outcomes, including liver decompensation and mortality [85, 86].

The potential contribution of HCV to HIV disease pathogenesis still remains poorly understood. Relatively to immunity, patients with HCV co-infection have significantly lower CD4 counts and worse CD4 cell recovery after 6 months of antiretroviral therapy than HIV mono-infected patients [87], and a meta-analysis shows that co-infected patients have less immune reconstitution, as determined by CD4 cell count after 48 weeks of ART, than do patients with HIV infection alone [88]. Moreover, patients successfully treated with pegylated-IFN plus ribavirin with 24-month follow-up showed a significant annual increase in CD4+ T cells from baseline [89]. HCV is associated with increased apoptosis of T lymphocytes in HIV-infected patients and this could induce a negative impact on CD4+ cell homeostasis, and possibly explain the more pronounced decreases in CD4+ cell count and reduced CD4+ cell count recovery observed during antiretroviral therapy [90]. Despite sustained HIV suppression under antiretroviral therapy, HCV co-infection supports an expansion of the CD8+ cell compartment, which results in a poorer restoration of the CD4+/CD8+ ratio than in HIV mono-infected patients [91].

Increased immune activation has been proposed as one of the underlying mechanisms of poor clinical outcome in HIV/HCV co-infected patients. Co-infected patients display a high level of T cell activation and exhaustion in the peripheral blood that are correlated with the level

of HCV or HIV viremia [92]. Furthermore, activation of CD4+ T cells, macrophages, and dendritic cells enhances viral replication of HIV and HCV [93, 94], while higher HCV and HIV viral loads correlate with increased levels of systemic markers of immune activation, faster progression to AIDS, and cirrhosis [95]. There is general consensus, in successfully treated patients, that HIV replication at low copies (< 50 copies/mL) is correlated with the persistence of immune activation and disease progression [96]. Persistent levels of CD4+ and CD8+ T cell activation were demonstrated in patients with viremia < 50 copies/mL who had poor immunological reconstitution and in a group of 833 patients, on fully active antiretroviral therapy for more than 96 months, HIV residual viremia < 50 copies/mL was associated with HCV antibody positivity [97].

Furthermore, the extracellular HCV core induces secretion of pro-inflammatory cytokines, including TNF-α and IL-6 in antigen-presenting cells [98]. Thus, treatment of HCV infection could be followed by a reduction of inflammation that may be considered as an important strategy for reducing HIV viral replication and slowing disease progression. The combination IFN-α plus ribavirin has been associated with a significant reduction in markers of both T cell activation [99] and endothelial dysfunction [100] in HIV-HCV co-infected patients receiving antiretroviral therapy.

Lastly, it has been recently pointed out that men who have sex with men (MSM) initiating pre-exposure HIV prophylaxis are at risk of HCV infection, and indeed the prevalence of HCV among previously HIV-negative MSM is higher than expected [101]. This finding has obvious implications for HCV testing in MSM at high risk for HCV, especially before initiating any prophylaxis for HIV.

Patients with HCV-HBV co-infection

Another special population in chronic HCV infection is represented by those with chronic HBV. With regards to DAAS, there is some evidence to suggest that patients with chronic HCV and overt or occult HBV coinfection may reactivate HBV when HCV is suppressed or eradicated by DAAs [102]. HBV reactivation has been thought to occur earlier in HCV patients coinfected with overt and occult HBV who are treated with pan-oral DAAs vs. IFN-based treatments [103]. Accordingly, at least during therapy with pan-oral DAAs, clinicians should consider screening all patients for evidence of HBV infection. Anti-HBV therapy with nucleoside analogs should be considered if increases in HBV DNA are observed in patients with HBV/HCV co-infection [104].

Relevant points

- Curative HCV therapy in HIV co-infected patients is associated with better control of HIV replication at low copies and with better immune system recovery.
- Due to the known correlation between persistent inflammation and emergence of severe comorbidities in HIV/HCV co-infected subjects, the available data reinforce the importance of treatment for HCV in HIV co-infected patients, regardless of the degree of hepatic fibrosis.
- Elbasvir/grazoprevir can be considered in case of important drug to drug interactions and renal problems in co-infected patients.
- Patients with HBV-HCV coinfection should be closely monitored for changes in HBV DNA; therapy with nucleoside analogs should be considered when appropriate although clinical focus should be placed on the dominant viral disease (HCV vs. HBV).

HCV infection in people who inject drugs

In the developed world, a large percentage of HCV occurs in people who inject drugs (PWID); unfortunately, treatment uptake in this population remains low [105]. In Italy, 63.9% of PWID are HCV antibody positive, and 68.3% are HCV viremic [106]. In Italian jails, which have a very high number of PWID (32%), the prevalence of HCV antibodies ranges from 23 to 38% [107, 108]. Outcomes of HCV treatments in PWID either actively or with past history of drug injection, indicate SVR rates equal to other patients. The many problems in managing HCV treatment in these patients rarely lead to initiation of therapy [109], even with a short DAA regimens. Unfortunately, a high proportion of these subjects is unaware of being HCV-positive and, as occurs in HIV, present a four- to sixfold higher probability of transmitting the virus [110]. For these reasons, the WHO considers PWID as a target population for HCV eradication and relies on two basic elements: grant all HCV patients with access to care and eliminate virus transmission. In PWID, the elbasvir/grazoprevir combination has been assessed in the CO-EDGE CO-STAR trial, in which injecting drug use was reported by 25% of patients in the last 6 months, and by 21% of patients in the last month where an SVR12 was achieved in 95% of patients [111].

Relevant points

- All patients known as PWID, either actively or with past history of injecting should be evaluated for the presence of HCV.

- Screening programs in high risk groups for transmission, such as PWID, and extended access to therapy are of paramount importance.
- EBR/GZR demonstrated high efficacy in GT1 or 4-infected patients receiving OAT.

HCV+ patients with chronic kidney disease

In the HCV setting, patients with CKD remain a difficult-to-treat population even in the era of DAAs, which is related to the pharmacological properties of some classes of DAAs and the relative lack of data on safety and efficacy of DAAs in CKD, due to the strict inclusion/exclusion criteria on estimated glomerular filtration rate (eGFR) that have excluded these patients from Phase III RCTs [19]. Patients on hemodialysis and those with kidney transplantation (KT) show a high prevalence of HCV infection mainly as a consequence of increased risk of nosocomial transmission in dialysis facilities. Viral eradication reduces the risk of kidney failure and improves graft survival in KT patients [112–114]. In general, the available data from C-SURFER study imply that the grazoprevir/elbasvir combination has good efficacy in patients with HCV genotype 1 and CKD stage 4 or 5 including those on dialysis, with SVR12 approaching 100% [115].

DAA therapy of HCV patients with CKD

Sofosbuvir-free combination regimens based on protease inhibitors

Paritaprevir/ritonavir/ombitasvir + dasabuvir or elbasvir/grazoprevir are the only recommended regimens for patients with severe CKD (stage 4–5, eGFR < 30 mL/min/1.73 m^2) [19]. Whereas sofosbuvir together with its circulating metabolite GS-331007 is cleared by the kidney, it should be used with caution in subjects with severe renal impairment (CKD stage 4–5).

Due to the observed changes in pharmacological exposure, this regimen is not recommended in patients with Stage 4–5 CKD, while elbasvir/grazoprevir as well as the multi-DAA regimen of paritaprevir/ritonavir/ombitasvir plus dasabuvir has been shown to be safe and effective, achieving high rates of SVR [116, 117].

At the same time, it is important to underline that ribavirin is necessary in HCV-1a when treating with elbasvir/grazoprevir (in those with NS5A resistance-associated baseline polymorphisms at amino acid positions 28, 30, 31 or those with a baseline HCV-RNA value > 800,000 IU/mL) or paritaprevir/ritonavir/ombitasvir plus dasabuvir (in all cases). Since ribavirin is excreted renally and is associated with significant adverse effects, mainly anemia, in patients with CKD any regimen containing ribavirin should be viewed

as suboptimal. In addition, these regimens should not be prescribed to patients with decompensated cirrhosis due to increased serum concentrations of the protease inhibitor, which can lead to serious treatment-related adverse events and even death [19].

Owing to the lack of non sofosbuvir-based pangenotypic regimens, treatment of CKD stage 4–5 patients infected with HCV genotypes 2, 3, 5, and 6 remains an unmet clinical need, and second-generation PI-based regimens are expected to overcome the genotypic barrier of HCV therapy. Very limited data exist on sofosbuvir in CKD stage 4–5, as only relatively small cohort studies have been reported. The finding that sofosbuvir may impair kidney function has not been reported in Phase III studies and has not been highlighted in other small cohorts of patients with CKD or KT who received sofosbuvir-based regimens [118, 119]. Recently, the Phase 3 C-SURFER study has assessed the elbasvir/grazoprevir combination in 224 treatment-naive and treatment-experienced patients with HCV genotype 1 infection and stage 4–5 CKD; SVR12 was 99%, and the combination had a low rate of adverse events [116].

In the IFN era, treatment of HCV in KT recipients was severely restricted by an increased risk of infectious complications and graft rejection. A RCT in HCV-1 and 4 infected patients with long-term stable KT demonstrated the safety and efficacy (100% success rate) of a 12 week ribavirin-free regimen based on sofosbuvir/ledipasvir [120]. The favorable outcomes of IFN-free therapy for HCV in KT patients have been confirmed by a real-life study where the safety of treatment in terms of prevention of graft rejection was optimal in patients who started therapy at least 3 months after transplantation [121].

Relevant points

- Elbasvir/grazoprevir or Paritaprevir/ritonavir/ombitasvir + dasabuvir are the only recommended regimens for patients with Stage 4-5 CKD. However new KDIGO Guidelines recommend for HCV genotype 1 subtype A and subtype B the use of elbasvir/grazoprevir with a grade of recommendation 1A. (KDIGO 2017 clinical practice guideline on the prevention, diagnosis, evaluation and treatment of hepatitis C in CKD).
- In patients with CKD any regimen containing ribavirin should be viewed as suboptimal.
- IFN-free therapy for HCV in KT patients appear effective, but need further study.

HCV+ patients with inherited blood disorders

A significant number of subjects with inherited blood disorders (IBLD), including those with hemoglobinopathies

such as sickle cell disease and thalassemia or clotting factor deficiencies such as haemophilia and von Willebrand, have chronic HCV and many develop chronic liver disease. HCV infection is a main risk factor for development of liver damage, and increases steadily with longer duration of HCV infection.

Data for new regimens with DAAs in patients with IBLD are limited to a small number of studies. The first assessed the sofosbuvir/ledipasvir combination associated with ribavirin in 14 patients with HCV genotype 1 and inherited bleeding disorders (11 hemophilia, 2 von Willebrand disease, 1 factor XIII deficiency) [122]. All patients achieved a SVR after 12 weeks of follow-up. A cohort study [123] evaluated 12 weeks of sofosbuvir/ledipasvir in 43 Japanese hemophilia patients with genotype 1 or 4. 20 patients had HIV co-infection. SVR 12 was 90% in HIV-positive patients and 100% in HIV-negative patients. The rate of SVR in the patients with cirrhosis was significantly lower than that in non-cirrhosis patients ($p = 0.005$). Overall, 46% of patients had adverse events; most were mild to moderate, although 3 were serious including 1 death in the HIV-positive group.

Finally, a randomized, placebo-controlled, phase 3 trial assessed the safety and efficacy of elbasvir/grazoprevir administered for 12 weeks (159 adults with HCV infection and sickle cell anemia, thalassemia, or haemophilia A/B or von Willebrand disease) with inherited bleeding disorders and HCV infection [124]. Patients were randomized into a group that immediately received the drug or to a deferred-treatment group that received placebo followed by active treatment. In the former, 93.5% achieved SVR12 and no differences between pathologies were seen.

Relevant points

- Clinical data on new regimens with DAAs in patients with IBLD are limited, but appear to indicate that these new regimes are effective with an acceptable safety profile.
- Elbasvir/grazoprevir regimen has been studied also in patients with inherited bleeding disorders and HCV infection.

Extrahepatic manifestations of HCV: mixed cryoglobulinemia

Mixed cryoglobulinemia (MC) is the most frequent and largely investigated extrahepatic manifestation of HCV [125–127]; while it is clinically benign, it can be associated with severe symptoms and possibly evolve into lymphoma [128, 129]. In a cohort of 231 MC patients, 79 of 97 deaths were linked to vasculitis (46%, of which one-third due to renal involvement), cancer or hemopathy (23%), or liver disease (13%) [130].

In the "IFN era", antiviral treatment of MC followed the evolution of HCV treatment with small adjustments (i.e. in drug dose/duration, combination with non-antiviral therapies), essentially due to the possible side-effects of IFN and/or ribavirin therapy. Clinical remission correlated with virological response, although discordant data have been reported [131–134]. The rare persistence of MC after viral eradication obtained by different regimens may be due to several causes [135].

The introduction of first-generation DAAs in combination with peg-IFN and ribavirin was associated with increased SVR rates above historical levels, but with increased side-effects. Peg-IFN plus ribavirin plus boceprevir or telaprevir administered to 30 MC patients resulted in 67% of complete clinical and virological response, while 47% of patients had severe side effects [136]. Another study confirmed the good efficacy of this combination in 22 MC patients, and cryoglobulinemia resolution in 86% of cases, but a lower SVR rate in cryoglobulinemic patients than in patients without MC (23.8 vs 70%, $p = 0.01$) [137]. In a small case series of MC patients treated with peg-IFN plus ribavirin plus sofosbuvir or first generation DAAs, longer treatment for cirrhotic patients was suggested [138, 139].

The available data suggest that IFN-free regimens are safe, generally well-tolerated, and effective in MC patients [140–143]. In the IFN era, rituximab was administered mostly to patients who had failed or were not eligible for antiviral therapy, even if a rituximab plus antiviral combination was suggested for patients with severe manifestations (generally using rituximab before antiviral therapy) [132, 144–146]. With the introduction of DAAs, a role for rituximab remains to be established.

Antiviral therapy should be considered as the first-line approach in HCV-associated low grade lymphomas if there is no urgency of conventional treatment, irrespective of liver damage [147–150].

Relevant points

- First-generation DAAs in combination with peg-IFN and ribavirin have increased SVR rates over historical levels, while more data is needed on the safety profile in patients with MC.
- The available data suggest that IFN-free regimens are safe, generally well tolerated, and effective in MC patients.
- Antiviral therapy should be considered as the first-line approach in HCV-associated low-grade lymphomas if there is no urgency for conventional treatment, independently of liver damage.

Quality of life in HCV+ patients and role of cure

Chronic HCV infection is associated with a number of extrahepatic manifestations that may significantly affect the patient's health-related quality of life (HRQOL) [151]. Impairment in HRQOL in patients with chronic HCV infection is mainly driven by fatigue, insomnia, anxiety, and depression which are prevalent comorbid conditions, and may also affect adherence to antiviral treatment [152].

It is well known that in patients treated with peg-IFN and ribavirin show a decrease in both physical and mental component summary scores at the end of treatment (all $p < 0.05$), which reverts at the end of follow-up [153]. In general, by curing HCV, patient-reported outcomes (PROs) return to values similar to a healthy population. These findings are in line with the observation of patient-related assessments following treatment with sofosbuvir/ledipasvir with and without ribavirin [154]. Patients receiving this regimen showed significant improvement of PROs that coincide with early viral suppression after 2 weeks of treatment and maximized by the end of treatment. This finding provides support for the hypothesis that HCV itself is responsible for a significant component of HRQOL impairment; consequently, early viral suppression is followed by improvement in PROs.

The double-blind placebo-controlled study ASTRAL-1 is of particular importance in defining the role of viral suppression in improvement of PROs [155]. Patients receiving placebo did not experience any HRQOL improvement, and only those in the active regimen of sofosbuvir/velpatasvir had improvement in PROs. Multivariate analysis also indicated that HCV clearance was a strong predictor in improving PROsduring post-treatment follow-up. Also in ASTRAL, almost all patient-reported dimensions were significantly more affected in decompensated versus compensated and versus non-cirrhotic patients. The only three dimensions that were impaired to a similar degree in the three groups were mental health, mental component summary of SF-36, and social wellbeing of FACIT-F. This implies that the mental dimensions of HRQOL are not affected by physical conditions per se, but that they are under a direct influence of viral infection, which affects the mental well-being areas across the board regardless of the degree of severity of the concomitant liver disease.

Fatigue and other psychological comorbidities are relevant issue in chronic HCV patients. In 19% of HCV patients, clinically severe fatigue, both central and peripheral is observed, and anxiety, depression, and insomnia are reported in 23–26% of patients [156]. During treatment, ribavirin administration was associated with fatigue and psychiatric distress. However, 4 weeks after treatment, fatigue was reported to improve in all patients, and in ribavirin-free regimens peripheral fatigue showed a greater improvement.

Relevant points

- Ribavirin administration delays improvement in patient-reported outcomes potentially due to viral eradication, and is frequently followed by substantial improvement of all HRQOL domains.
- After achievement of SVR, significant improvement of patient-reported outcomes is observed regardless of the regimen employed.
- The breadth of improvement in patient-reported outcomes is higher in decompensated than in compensated cirrhosis, which supports the use of antiviral therapy at any stage of liver disease.

Conclusions

The availability of all new DAA regimens for treatment of HCV infection will dramatically change management approaches in routine practice. In general, the new DAAs are highly effective, well-tolerated and enable clinicians to an ever increasing number of patients. The newest DAA regimes, and especially elbasvir/grazoprevir and sofosbuvir/velpatasvir, are also changing routine management of chronic HCV infection in many patients with comorbidities, in addition to cirrhosis. In special populations, the new DAAs are also finding clinical utility, such as in those with HIV co-infection and in those who inject drugs, and are associated with high rates of sustained viral clearance. Patients with renal impairment are also another significant subpopulation of subject with chronic HCV infection. It is clear that HCV infection is associated with diminished quality of life considering a wide range of domains. As such, sustained viral clearance will improve patients' HRQOL, and as such achieving this should be a major clinical goal. Thus, antiviral therapy is warranted at any stage of liver disease or in the presence of other comorbidities to improve patients' overall well-being.

While international guidelines have been published to help clinicians in the management of patient with HCV infection, such recommendations may not be applicable to all healthcare settings for a variety of reasons. The present expert recommendations have aimed to bridge some of the remaining clinical gaps regarding the use of new DAAs, while keeping in mind the highly encouraging results that have been achieved to date with these regimens in patients with a range of comorbidities.

decision to submit the manuscript for publication. All views expressed are solely those of the authors.

Compliance with ethical standards

References

1. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. Lancet. 2015;385:1124–35. https://doi.org/10.1016/S0140-6736(14)62401-6.

2. WHO. http://www.who.int/medicines/areas/access/hepCtreat_key_facts/en/. Accesed 10 Sep 2017.

3. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol. 2007;13:2436–41.

4. Global Burden Of Hepatitis CWG. Global burden of disease (GBD) for hepatitis C. J Clin Pharmacol. 2004;44:20–9. https://doi.org/10.1177/0091270003258669.

5. Messina JP, Pigott DM, Golding N, Duda KA, Brownstein JS, Weiss DJ, et al. The global distribution of Crimean-Congo hemorrhagic fever. Trans R Soc Trop Med Hyg. 2015;109:503–13. https://doi.org/10.1093/trstmh/trv050.

6. Negro F, Forton D, Craxi A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology. 2015;149:1345–60. https://doi.org/10.1053/j.gastro.2015.08.035.

7. Vigano M, Colombo M. Extrahepatic Manifestations of Hepatitis C Virus. Gastroenterol Clin North Am. 2015;44:775–91. https://doi.org/10.1016/j.gtc.2015.07.006.

8. AISF. Documento di indirizzo dell'Associazione Italiana per lo Studio delFegato per l'uso razionale di antivirali diretti di seconda generazione nellecategorie di pazienti affetti da epatite C cronica ammessi alla rimborsabil-ità in Italia. Available at http://www.webaisf.org/media/38679/documento_hcv_17.05.2017.pdf. Accessed 30 Oct 2017.

9. European Association for Study of L. EASL recommendations on treatment of hepatitis C 2015. J Hepatol. 2015;63:199–236. https://doi.org/10.1016/j.jhep.2015.03.025.

10. Panel AIHG. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62:932–54. https://doi.org/10.1002/hep.27950.

11. Soriano V, Benitez-Gutierrez L, Arias A, Carrasco I, Barreiro P, Pena JM, et al. Evaluation of sofosbuvir, velpatasvir plus voxilaprevir as fixed-dose co-formulation for treating hepatitis C. Expert Opin Drug Metab Toxicol. 2017;13:1015–22. https://doi.org/10.1080/17425255.2017.1359254.

12. Gane E, Poordad F, Wang S, Asatryan A, Kwo PY, Lalezari J, et al. High efficacy of ABT-493 and ABT-530 treatment in patients with HCV genotype 1 or 3 infection and compensated cirrhosis. Gastroenterology. 2016;151:651–659e1. https://doi.org/10.1053/j.gastro.2016.07.020.

13. Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med. 2015;373:2608–17. https://doi.org/10.1056/NEJMoa1512612.

14. Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ben Ari Z, Zhao Y, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med. 2015;163:1–13. https://doi.org/10.7326/M15-0785.

15. Alric L, Bonnet D. Grazoprevir + elbasvir for the treatment of hepatitis C virus infection. Expert Opin Pharmacother. 2016;17:735–42. https://doi.org/10.1517/14656566.2016.1161028.

16. Zeuzem S, Feld JJ, Wang S, Bourlière M, Wedemeyer H, Gane EJ. ENDURANCE-1: efficacy and Safety of 8-versus 12-week treatment with ABT-493/ABT-530 in patients with chronic HCV genotype 1 infection. Hepatology. 2016;64:132A.

17. Asselah T, Hezode C, Zadeikis N, Elkhashab M, Colombo M. ENDURANCE-4: efficacy and safety of ABT-493/ABT-530 treatment in patients with chronic HCV genotype 4, 5, or 6 infection. Hepatology. 2016;64:63A.

18. Wyles DL, Poordad F, Wang S, Alric L, Felizarta F, Kwo PY. SURVEYOR-II, Part 3: efficacy and safety of ABT-493/ABT-530 in patients with hepatitis C virus genotype 3 infection with prior treatment experience and/or cirrhosis. Hepatology. 2016;64:62A.

19. European Association for the Study of the Liver. Electronic address eee. EASL recommendations on treatment of hepatitis C 2016. J Hepatol. 2017;66:153–94. https://doi.org/10.1016/j.jhep.2016.09.001.

20. Coburn CA, Meinke PT, Chang W, Fandozzi CM, Graham DJ, Hu B, et al. Discovery of MK-8742: an HCV NS5A inhibitor with broad genotype activity. ChemMedChem. 2013;8:1930–40. https://doi.org/10.1002/cmdc.201300343.

21. Harper S, McCauley JA, Rudd MT, Ferrara M, DiFilippo M, Crescenzi B, et al. Discovery of MK-5172, a macrocyclic hepatitis C virus NS3/4a protease inhibitor. ACS Med Chem Lett. 2012;3:332–6. https://doi.org/10.1021/ml300017p.

22. Summa V, Ludmerer SW, McCauley JA, Fandozzi C, Burlein C, Claudio G, et al. MK-5172, a selective inhibitor of hepatitis C virus NS3/4a protease with broad activity across genotypes and resistant variants. Antimicrob Agents Chemother. 2012;56:4161–7. https://doi.org/10.1128/AAC.00324-12.

23. Kirby BJ, Taylor J, Stamm LM. Evaluation of transporter and cytochrome P450-mediated drug-drug interactions with the pan genotypic HCV NS3/4A protease inhibitor voxilaprevir (GS-9857) or sofosbuvir/velpatasvir/voxilaprevir and phenotypic probe drugs. In: 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy. June 8–10, 2016, Washington, DC. (Abstract # O24 and O25). 2016.

24. Mogalian E. Drug-drug interaction studies between hepatitis C virus antivirals sofosbuvir and velpatasvir and HIV ntiretroviral therapies. Poster presented at: 66th annual meeting of the American association for the study of liver diseases. Boston, MA, 13–17 Nov 2015.

25. Epclusa. Summary of product characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004210/WC500211151.pdf. Accessed 30 Oct 2017.

26. Soriano V, Fernandez-Montero JV, de Mendoza C, Benitez-Gutierrez L, Pena JM, Arias A, et al. Treatment of hepatitis C with new fixed dose combinations. Expert Opin Pharmacother. 2017;18:1235–42. https://doi.org/10.1080/14656566.2017.1346609.

27. Wang T. Poster presented at: EASL 2015, April 22–26, Vienna, Austria.

28. Smolders EJ, de Kanter CT, van Hoek B, Arends JE, Drenth JP, Burger DM. Pharmacokinetics, efficacy, and safety of hepatitis C virus drugs in patients with liver and/or renal impairment. Drug Saf. 2016;39:589–611. https://doi.org/10.1007/s40264-016-0420-2.

29. Chen ZW, Li H, Ren H, Hu P. Global prevalence of pre-existing HCV variants resistant to direct-acting antiviral agents (DAAs): mining the GenBank HCV genome data. Sci Rep. 2016;6:20310. https://doi.org/10.1038/srep20310.

30. Zeuzem S, Mizokami M, Pianko S, Mangia A, Han KH, Martin R, et al. NS5A resistance-associated substitutions in patients with genotype 1 hepatitis C virus: prevalence and effect on treatment outcome. J Hepatol. 2017;66:910–8. https://doi.org/10.1016/j.jhep.2017.01.007.

31. Pawlotsky JM, Hepatitis C. Virus resistance to direct-acting antiviral drugs in interferon-free regimens. Gastroenterology. 2016;151:70–86. https://doi.org/10.1053/j.gastro.2016.04.003.

32. Sarrazin C, Dvory-Sobol H, Svarovskaia ES, Doehle BP, Pang PS, Chuang SM, et al. Prevalence of resistance-associated substitutions in HCV NS5A, NS5B, or NS3 and outcomes of treatment with ledipasvir and sofosbuvir. Gastroenterology. 2016;151:501–512 e1. https://doi.org/10.1053/j.gastro.2016.06.002.

33. Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med. 2015;373:2618–28. https://doi.org/10.1056/NEJMoa1512614.

34. Wyles DL, Luetkemeyer AF. Understanding hepatitis C virus drug resistance: clinical implications for current and future regimens. Top Antivir Med. 2017;25:103–9.

35. Gane E, Shiffman ML, Etzkorn K. Sofosbuvir/velpatasvir in combination with ribavirin for 24 weeks is effective retreatment for patients who failed prior NS5A containing DAA regimens: results of the GS-US-342-1553 study. J Hepatol. 2016;64:S147–8.

36. AASLD. Recommendations for testing, managing, and treating Hepatitis C. Available at: https://www.hcvguidelines.org. Accessed 30 Oct 2017.

37. Hull M, Shafran S, Wong A, Tseng A, Giguere P, Barrett L, et al. CIHR Canadian HIV trials network coinfection and concurrent diseases core research group: 2016 Updated Canadian HIV/hepatitis C adult guidelines for management and treatment. Can J Infect Dis Med Microbiol. 2016;2016:4385643. https://doi.org/10.1155/2016/4385643.

38. Hill AM, Saleem J, Heath KA, Simmons B. Effects of sustained virological response (SVR) on the risk of liver transplant, hepatocellular carcinoma, death and re-infection: meta-analysis of 129 studies in 23,309 patients with hepatitis C infection. J Hepatol. 2014;4:218A–9A.

39. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnu L, Mazzella G, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007;45:579–87. https://doi.org/10.1002/hep.21492.

40. Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol. 2010;52:652–7. https://doi.org/10.1016/j.jhep.2009.12.028.

41. Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010;52:833–44. https://doi.org/10.1002/hep.23744.

42. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013;158:329–37. https://doi.org/10.7326/0003-4819-158-5-201303050-00005.

43. Miao RY, Zhao HT, Yang HY, Mao YL, Lu X, Zhao Y, et al. Postoperative adjuvant antiviral therapy for hepatitis B/C virus-related hepatocellular carcinoma: a meta-analysis. World J Gastroenterol. 2010;16:2931–42.

44. Singal AK, Freeman DH Jr, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. Aliment Pharmacol Ther. 2010;32:851–8. https://doi.org/10.1111/j.1365-2036.2010.04414.x.

45. Zhang W, Song TQ, Zhang T, Wu Q, Kong DL, Li Q, et al. Adjuvant interferon for early or late recurrence of hepatocellular carcinoma and mortality from hepatocellular carcinoma following curative treatment: a meta-analysis with comparison of different types of hepatitis. Mol Clin Oncol. 2014;2:1125–34. https://doi.org/10.3892/mco.2014.386.

46. Zhuang L, Zeng X, Yang Z, Meng Z. Effect and safety of interferon for hepatocellular carcinoma: a systematic review and meta-analysis. PLoS One. 2013;8:e61361. https://doi.org/10.1371/journal.pone.0061361.

47. Cabibbo G, Petta S, Barbara M, Missale G, Virdone R, Caturelli E, et al. A meta-analysis of single HCV-untreated arm of studies evaluating outcomes after curative treatments of HCV-related hepatocellular carcinoma. Liver Int. 2017. https://doi.org/10.1111/liv.13357.

48. Kobayashi M, Suzuki F, Fujiyama S, Kawamura Y, Sezaki H, Hosaka T, et al. Sustained virologic response by direct antiviral agents reduces the incidence of hepatocellular carcinoma in patients with HCV infection. J Med Virol. 2017;89:476–83. https://doi.org/10.1002/jmv.24663.

49. Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016;65:719–26. https://doi.org/10.1016/j.jhep.2016.04.008.

50. Pompili M, Saviano A, de Matthaeis N, Cucchetti A, Ardito F, Federico B, et al. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma </=3 cm. Results of a multicenter Italian survey. J Hepatol. 2013;59:89–97. https://doi.org/10.1016/j.jhep.2013.03.009.

51. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016;65:727–33. https://doi.org/10.1016/j.jhep.2016.06.015.

52. stanislas.pol@aphp.fr AcsgohcEa. Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol. 2016;65:734–40. https://doi.org/10.1016/j.jhep.2016.05.045.

53. Reig M. Abstract #PS-031 Presented at: International Liver Congress; April 19–24, 2017; Amsterdam.

54. Majumdar A, Kitson MT, Roberts SK. Systematic review: current concepts and challenges for the direct-acting antiviral era in hepatitis C cirrhosis. Aliment Pharmacol Ther. 2016;43:1276–92. https://doi.org/10.1111/apt.13633.

55. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370:1483–93. https://doi.org/10.1056/NEJMoa1316366.

56. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370:1889–98. https://doi.org/10.1056/NEJMoa1402454.

57. Gane E, Stedman C, Hyland RH, Pang P, Ding X, Symonds W. All-oral sofosbuvir-based 12-week regimens for the treatment of chronic HCV infection: the ELECTRON study. J Hepatol. 2013;58:S6–7.

58. Bourliere MBJ, de Ledinghen V. Ledipasvir/sofosbuvir fixed dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy. Hepatology. 2014;60:1270A.

59. Bourliere M, Sulkowski M, Omata M. An integrated safety and efficacy analysis of > 500 patients with compensated cirrhosis treated with ledipasvir/sofosbuvir with or without ribavirin. Hepatology. 2014;60:239A.

60. Wyles D, Pockros P, Yang C. Retreatment of patients who failed prior sofosbuvir-based regimens with all oral fixed-dose combination ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Hepatology. 2014;60:317A.

61. Asselah T, Hezode C, Qaqish R. High SVR rates in patients with genotype 4 chronic hepatitis C infection and compensated cirrhosis with ombitasvir/paritaprevir/ritonavir co-administered with ribavirin (AGATE-I). J Hepatol. 2016;64:S827.

62. FDA. FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie, 2015. http://www.fda.gov/Drugs/DrugSafety/ucm468634. Accessed 30 Oct 2017.

63. Feld JJ, Moreno C, Trinh R, Tam E, Bourgeois S, Horsmans Y, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks. J Hepatol. 2016;64:301–7. https://doi.org/10.1016/j.jhep.2015.10.005.

64. Pol S, Reddy KR, Baykal T. Interferon-free regimens of ombitasvir and ABT-450/r with or without ribavirin in patients with HCV genotype 4 infection: PEARL-I study results. Hepatology. 2014;60:1129A.

65. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014;370:1973–82. https://doi.org/10.1056/NEJMoa1402869.

66. EASL. http://www.easl.eu/medias/cpg/HCV2016/Summary.pdf. Accessed 17 Jun 2017.

67. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology. 2016;63:1493–505. https://doi.org/10.1002/hep.28446.

68. Buti M, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H, et al. Grazoprevir, elbasvir, and ribavirin for chronic hepatitis C Virus genotype 1 infection after failure of pegylated interferon and ribavirin with an earlier-generation protease inhibitor: final 24-Week results from C-SALVAGE. Clin Infect Dis. 2016;62:32–6. https://doi.org/10.1093/cid/civ722.

69. Forns X, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H, et al. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. J Hepatol. 2015;63:564–72. https://doi.org/10.1016/j.jhep.2015.04.009.

70. Jacobson I, Lawitz E, Kwo P. An integrated analysis of 402 compensated cirrhotic patients with HCV genotype (GT) 1, 4 or 6 infection treated with grazoprevir/elbasvir. Hepatology. 2015;62:229A.

71. Kwo P, Gane E, Peng C-Y. Efficacy and safety of grazoprevir/elbasvir ± RBV for 12 weeks with HCV G1 or G4 infection who previously failed Peginterferon/RBV: C-EDGE treatment-experienced trial. J Hepatol. 2015;62:S674.

72. Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385:1075–86. https://doi.org/10.1016/S0140-6736(14)61795-5.

73. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and Velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med. 2015;373:2599–607. https://doi.org/10.1056/NEJMoa1512610.

74. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013;368:1867–77. https://doi.org/10.1056/NEJMoa1214854.

75. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368:1878–87. https://doi.org/10.1056/NEJMoa1214853.

76. Welzel TM, Nelson DR, Morelli G, Di Bisceglie A, Reddy RK, Kuo A, et al. Effectiveness and safety of sofosbuvir plus ribavirin for the treatment of HCV genotype 2 infection: results of the real-world, clinical practice HCV-TARGET study. Gut. 2016;. https://doi.org/10.1136/gutjnl-2016-311609.

77. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370:1993–2001. https://doi.org/10.1056/NEJMoa1316145.

78. Mangia A, Arleo A, Copetti M, Miscio M, Piazzolla V, Santoro R, et al. The combination of daclatasvir and sofosbuvir for curing genotype 2 patients who cannot tolerate ribavirin. Liver Int. 2016;36:971–6. https://doi.org/10.1111/liv.13069.

79. Foster GR, Pianko S, Brown A, Forton D, Nahass RG, George J, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. Gastroenterology. 2015;149:1462–70. https://doi.org/10.1053/j.gastro.2015.07.043.

80. Leroy V, Angus P, Bronowicki JP, Dore GJ, Hezode C, Pianko S, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: a randomized phase III study (ALLY-3+). Hepatology. 2016;63:1430–41. https://doi.org/10.1002/hep.28473.

81. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61:1127–35. https://doi.org/10.1002/hep.27726.

82. Welzel TM, Petersen J, Herzer K, Ferenci P, Gschwantler M, Wedemeyer H, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut. 2016;65:1861–70. https://doi.org/10.1136/gutjnl-2016-312444.

83. Soriano V, Labarga P, de Mendoza C, Fernandez-Montero JV, Esposito I, Benitez-Gutierrez L, et al. New hepatitis C therapies for special patient populations. Expert Opin Pharmacother. 2016;17:217–29. https://doi.org/10.1517/14656566.2016.1112790.

84. Law WP, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxrungtham K, Lange JM, et al. Impact of viral hepatitis co-infection on response to antiretroviral therapy and HIV disease progression in the HIV-NAT cohort. AIDS. 2004;18:1169–77.

85. Berenguer J, Alvarez-Pellicer J, Carrero A, Von Wichmann MA, Lopez-Aldeguer J, Mallolas J, et al. Clinical effects of viral relapse after interferon plus ribavirin in patients co-infected with human immunodeficiency virus and hepatitis C virus. J Hepatol. 2013;58:1104–12. https://doi.org/10.1016/j.jhep.2013.01.042.

86. Mira JA, Rivero-Juarez A, Lopez-Cortes LF, Giron-Gonzalez JA, Tellez F, de los Santos-Gil I, et al. Benefits from sustained virologic response to pegylated interferon plus ribavirin in HIV/hepatitis C virus-coinfected patients with compensated cirrhosis. Clin Infect Dis. 2013;56:1646–53. https://doi.org/10.1093/cid/cit103.

87. Chang S, Dolganiuc A, Szabo G. Toll-like receptors 1 and 6 are involved in TLR2-mediated macrophage activation by hepatitis C virus core and NS3 proteins. J Leukoc Biol. 2007;82:479–87. https://doi.org/10.1189/jlb.0207128.

88. Chen M, Wong WW, Law MG, Kiertiburanakul S, Yunihastuti E, Merati TP, et al. Hepatitis B and C Co-infection in HIV patients from the TREAT Asia HIV observational database: analysis of risk factors and survival. PLoS One. 2016;11:e0150512. https://doi.org/10.1371/journal.pone.0150512.

89. Miller MF, Haley C, Koziel MJ, Rowley CF. Impact of hepatitis C virus on immune restoration in HIV-infected patients who start highly active antiretroviral therapy: a meta-analysis. Clin Infect Dis. 2005;41:713–20. https://doi.org/10.1086/432618.

90. Dazley J, Sison R, Slim J. Long-term consequences of hepatitis c viral clearance on the CD4 (+) T cell lymphocyte course in HIV/HCV coinfected patients. AIDS Res Treat. 2015;2015:687629. https://doi.org/10.1155/2015/687629.

91. Nunez M, Soriano V, Lopez M, Ballesteros C, Cascajero A, Gonzalez-Lahoz J, et al. Coinfection with hepatitis C virus increases lymphocyte apoptosis in HIV-infected patients. Clin Infect Dis. 2006;43:1209–12. https://doi.org/10.1086/508355.

92. Feuth T, Arends JE, Fransen JH, Nanlohy NM, van Erpecum KJ, Siersema PD, et al. Complementary role of HCV and HIV in T-cell activation and exhaustion in HIV/HCV coinfection. PLoS One. 2013;8:e59302. https://doi.org/10.1371/journal.pone.0059302.

93. Lundquist CA, Tobiume M, Zhou J, Unutmaz D, Aiken C. Nef-mediated downregulation of CD4 enhances human immunodeficiency virus type 1 replication in primary T lymphocytes. J Virol. 2002;76:4625–33.

94. Tardif MR, Tremblay MJ. Tetraspanin CD81 provides a costimulatory signal resulting in increased human immunodeficiency virus type 1 gene expression in primary CD4+ T lymphocytes through NF-kappaB, NFAT, and AP-1 transduction pathways. J Virol. 2005;79:4316–28. https://doi.org/10.1128/JVI.79.7.4316-4328.2005.

95. Cooper CL, Klein MB. HIV/hepatitis C virus coinfection management: changing guidelines and changing paradigms. HIV Med. 2014;15:621–4. https://doi.org/10.1111/hiv.12161.

96. Sarmati L, D'Ettorre G, Parisi SG, Andreoni M. HIV replication at low copy number and its correlation with the HIV reservoir: a clinical perspective. Curr HIV Res. 2015;13:250–7.

97. Zheng L, Taiwo B, Gandhi RT, Hunt PW, Collier AC, Flexner C, et al. Factors associated with CD8+ T-cell activation in HIV-1-infected patients on long-term antiretroviral therapy. J Acquir Immune Defic Syndr. 2014;67:153–60. https://doi.org/10.1097/QAI.0000000000000286.

98. Sengupta S, Powell E, Kong L, Blackard JT. Effects of HCV on basal and tat-induced HIV LTR activation. PLoS One. 2013;8:e64956. https://doi.org/10.1371/journal.pone.0064956.

99. Chen TY, Ding EL, Seage Iii GR, Kim AY. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. Clin Infect Dis. 2009;49:1605–15. https://doi.org/10.1086/644771.

100. Gonzalez VD, Falconer K, Blom KG, Reichard O, Morn B, Laursen AL, et al. High levels of chronic immune activation in the T-cell compartments of patients coinfected with hepatitis C virus and human immunodeficiency virus type 1 and on highly active antiretroviral therapy are reverted by alpha interferon and ribavirin treatment. J Virol. 2009;83:11407–11. https://doi.org/10.1128/JVI.01211-09.

101. Hoornenborg E, Achterbergh RCA, van der Loeff MFS, Davidovich U, Hogewoning A, de Vries HJC, et al. MSM starting preexposure prophylaxis are at risk of hepatitis C virus infection. AIDS. 2017;31:1603–10. https://doi.org/10.1097/QAD.0000000000001522.

102. Calvaruso V, Ferraro D, Licata A, Bavetta MG, Petta S, Bronte F, et al. HBV reactivation in patients with HCV/HBV cirrhosis on treatment with direct-acting antivirals. J Viral Hepat. 2017;. https://doi.org/10.1111/jvh.12754.

103. Chen G, Wang C, Chen J, Ji D, Wang Y, Wu V, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: a systematic review and meta-analysis. Hepatology. 2017;66:13–26. https://doi.org/10.1002/hep.29109.

104. Takayama H, Sato T, Ikeda F, Fujiki S. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection. Hepatol Res. 2016;46:489–91. https://doi.org/10.1111/hepr.12578.

105. Soriano V, Gallego L. Viral hepatitis: treating hepatitis C in injection drug users. Nat Rev Gastroenterol Hepatol. 2013;10:568–9. https://doi.org/10.1038/nrgastro.2013.165.

106. Stroffolini T, D'Egidio PF, Aceti A, Filippini P, Puoti M, Leonardi C, et al. Hepatitis C virus infection among drug addicts in Italy. J Med Virol. 2012;84:1608–12. https://doi.org/10.1002/jmv.23370.

107. Babudieri S, Longo B, Sarmati L, Starnini G, Dori L, Suligoi B, et al. Correlates of HIV, HBV, and HCV infections in a prison inmate population: results from a multicentre study in Italy. J Med Virol. 2005;76:311–7. https://doi.org/10.1002/jmv.20375.

108. Sagnelli E, Starnini G, Sagnelli C, Monarca R, Zumbo G, Pontali E, et al. Blood born viral infections, sexually transmitted diseases and latent tuberculosis in italian prisons: a preliminary report of a large multicenter study. Eur Rev Med Pharmacol Sci. 2012;16:2142–6.

109. Almasio PL, Babudieri S, Barbarini G, Brunetto M, Conte D, Dentico P, et al. Recommendations for the prevention, diagnosis, and treatment of chronic hepatitis B and C in special population groups (migrants, intravenous drug users and prison inmates). Dig Liver Dis. 2011;43:589–95. https://doi.org/10.1016/j.dld.2010.12.004.

110. Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. J Acquir Immune Defic Syndr. 2005;39:446–53.

111. Dore GJ. C-EDGE CO-STAR: interim results from the 3-year follow-up trial on risk factors and rate of reinfection in patients on opiate agonist therapy previously treated with elbasvir/grazoprevir for 12 weeks. In: Presented at The Liver Meeting, November 11–15, 2016, Boston MA, USA. 2016.

112. Corouge M, Vallet-Pichard A, Pol S. HCV and the kidney. Liver Int. 2016;36:28–33. https://doi.org/10.1111/liv.13022.

113. Fabrizi F, Aghemo A, Messa P. Hepatitis C treatment in patients with kidney disease. Kidney Int. 2013;84:874–9. https://doi.org/10.1038/ki.2013.264.

114. Hsu YC, Ho HJ, Huang YT, Wang HH, Wu MS, Lin JT, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. Gut. 2015;64:495–503. https://doi.org/10.1136/gutjnl-2014-308163.

115. Fabrizi F, Messa P. Therapy of hepatitis C by direct-acting antivirals: the end of HCV in dialysis population? Expert Rev Clin Pharmacol. 2015;8:785–93. https://doi.org/10.1586/17512433.2015.1086266.

116. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour H Jr, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386:1537–45. https://doi.org/10.1016/S0140-6736(15)00349-9.

117. Pockros PJ, Reddy KR, Mantry PS, Cohen E, Bennett M, Sulkowski MS, et al. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. Gastroenterology. 2016;150:1590–8. https://doi.org/10.1053/j.gastro.2016.02.078.

118. Nazario HE, Ndungu M, Modi AA. Sofosbuvir and simeprevir in hepatitis C genotype 1-patients with end-stage renal disease on haemodialysis or GFR < 30 ml/min. Liver Int. 2016;36:798–801. https://doi.org/10.1111/liv.13025.

119. Singh T, Guirguis J, Anthony S, Rivas J, Hanouneh IA, Alkhouri N. Sofosbuvir-based treatment is safe and effective in patients with chronic hepatitis C infection and end stage renal disease: a case series. Liver Int. 2016;36:802–6. https://doi.org/10.1111/liv.13078.

120. Colombo M, Aghemo A, Liu H, Zhang J, Dvory-Sobol H, Hyland R, et al. Treatment with ledipasvir-sofosbuvir for 12 or 24 weeks in kidney transplant recipients with chronic hepatitis C virus genotype 1 or 4 infection: a randomized trial. Ann Intern Med. 2017;166:109–17. https://doi.org/10.7326/M16-1205.

121. Fernandez I, Munoz-Gomez R, Pascasio JM, Baliellas C, Polanco N, Esforzado N, et al. Efficacy and tolerability of interferon-free antiviral therapy in kidney transplant recipients with chronic hepatitis C. J Hepatol. 2017;66:718–23. https://doi.org/10.1016/j.jhep.2016.12.020.

122. Nagao A, Hanabusa H. Brief Report: the impact of ledipasvir/sofosbuvir on HIV-positive and HIV-negative Japanese hemophilia patients with 1, 4, and mixed-genotype HCV. J Acquir Immune Defic Syndr. 2017;74:418–22. https://doi.org/10.1097/QAI.0000000000001271.

123. Santagostino E, Pol S, Olveira A, Reesink HW, van Erpecum K, Bogomolov P, et al. Daclatasvir/peginterferon lambda-1a/ribavirin in patients with chronic HCV infection and haemophilia who are treatment naive or prior relapsers to peginterferon alfa-2a/ribavirin. Haemophilia. 2016;22:692–9. https://doi.org/10.1111/hae.12947.

124. Hezode C, Colombo M, Spengler U, Ben-Ari Z, Strasser S. C-EDGE IBLD: Efficacy and safety of elbasvir/grazoprevir in patients with chronic hepatitis C virus infection and inherited blood disorders. Poster presented at: The international liver congress; EASL-European association for the study of the liver. Barcelona, Spain, 13–17 Apr 2016

125. Cacoub P, Gragnani L, Comarmond C, Zignego AL. Extrahepatic manifestations of chronic hepatitis C virus infection. Dig Liver Dis. 2014;46:S165–73. https://doi.org/10.1016/j.dld.2014.10.005.

126. Zignego AL, Ferri C, Pileri SA, Caini P, Bianchi FB, Italian Association of the Study of Liver Commission on Extrahepatic Manifestations of HCVi. Extrahepatic manifestations of Hepatitis C Virus infection: a general overview and guidelines for a clinical approach. Dig Liver Dis. 2007;39:2–17. https://doi.org/10.1016/j.dld.2006.06.008.

127. Zignego AL, Ramos-Casals M, Ferri C, Saadoun D, Arcaini L, Roccatello D, et al. International therapeutic guidelines for patients with HCV-related extrahepatic disorders. A multidisciplinary expert statement. Autoimmun Rev. 2017;16:523–41. https://doi.org/10.1016/j.autrev.2017.03.004.

128. Peveling-Oberhag J, Arcaini L, Bankov K, Zeuzem S, Herrmann E. The anti-lymphoma activity of antiviral therapy in HCV-associated B-cell non-Hodgkin lymphomas: a meta-analysis. J Viral Hepat. 2016;23:536–44. https://doi.org/10.1111/jvh.12518.

129. Zignego AL, Gragnani L, Giannini C, Laffi G. The hepatitis C virus infection as a systemic disease. Intern Emerg Med. 2012;7:S201–8. https://doi.org/10.1007/s11739-012-0825-6.

130. Ferri C, Sebastiani M, Giuggioli D, Cazzato M, Longombardo G, Antonelli A, et al. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. Semin Arthritis Rheum. 2004;33:355–74.

131. Cacoub P, Lidove O, Maisonobe T, Duhaut P, Thibault V, Ghillani P, et al. Interferon-alpha and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. Arthritis Rheum. 2002;46:3317–26. https://doi.org/10.1002/art.10699.

132. Landau DA, Saadoun D, Halfon P, Martinot-Peignoux M, Marcellin P, Fois E, et al. Relapse of hepatitis C virus-associated mixed cryoglobulinemia vasculitis in patients with sustained viral response. Arthritis Rheum. 2008;58:604–11. https://doi.org/10.1002/art.23305.

133. Mazzaro C, Zorat F, Comar C, Nascimben F, Bianchini D, Baracetti S, et al. Interferon plus ribavirin in patients with hepatitis C virus positive mixed cryoglobulinemia resistant to interferon. J Rheumatol. 2003;30:1775–81.

134. Montalbano M, Pasulo L, Sonzogni A, Remuzzi G, Colledan M, Strazzabosco M. Treatment with pegylated interferon and ribavirin for hepatitis C virus-associated severe cryoglobulinemia in a liver/kidney transplant recipient. J Clin Gastroenterol. 2007;41:216–20. https://doi.org/10.1097/01.mcg.0000225569.04773.8b.

135. Zignego AL, Gragnani L, Visentini M, Casato M. The possible persistence of mixed cryoglobulinemia stigmata in spite of viral eradication: insufficient or too late antiviral treatment? Hepatology. 2016;. https://doi.org/10.1002/hep.28977.

136. Saadoun D, Resche Rigon M, Pol S, Thibault V, Blanc F, Pialoux G, et al. PegIFNalpha/ribavirin/protease inhibitor combination in severe hepatitis C virus-associated mixed cryoglobulinemia vasculitis. J Hepatol. 2015;62:24–30. https://doi.org/10.1016/j.jhep.2014.08.015.

137. Gragnani L, Fabbrizzi A, Triboli E, Urraro T, Boldrini B, Fognani E, et al. Triple antiviral therapy in hepatitis C virus infection with or without mixed cryoglobulinaemia: a prospective, controlled pilot study. Dig Liver Dis. 2014;46:833–7. https://doi.org/10.1016/j.dld.2014.05.017.

138. Cornella SL, Stine JG, Kelly V, Caldwell SH, Shah NL. Persistence of mixed cryoglobulinemia despite cure of hepatitis C with new oral antiviral therapy including direct-acting antiviral sofosbuvir: a case series. Postgrad Med. 2015;127:413–7. https://doi.org/10.1080/00325481.2015.1021660.

139. Stine JG, Cornella S, Shah NL. Treatment of chronic hepatitis C complicated by mixed cryoglobulinemia with new protease inhibitor, sofosbuvir. Ann Rheum Dis. 2014;73:e64. https://doi.org/10.1136/annrheumdis-2014-206180.

140. Saadoun D, Thibault V, Si Ahmed SN, Alric L, Mallet M, Guillaud C, et al. Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia vasculitis: VASCUVALDIC study. Ann Rheum Dis. 2016;75:1777–82. https://doi.org/10.1136/annrheumdis-2015-208339.

141. Sise ME, Bloom AK, Wisocky J, Lin MV, Gustafson JL, Lundquist AL, et al. Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents. Hepatology. 2016;63:408–17. https://doi.org/10.1002/hep.28297.

142. Gragnani L, Visentini M, Fognani E, Urraro T, De Santis A, Petraccia L, et al. Prospective study of guideline-tailored therapy with direct-acting antivirals for hepatitis C virus-associated mixed cryoglobulinemia. Hepatology. 2016;64:1473–82. https://doi.org/10.1002/hep.28753.

143. Bonacci M, Lens S, Londono MC, Marino Z, Cid MC, Ramos-Casals M, et al. Virologic, clinical, and immune response outcomes of patients with hepatitis C virus-associated cryoglobulinemia treated with direct-acting antivirals. Clin Gastroenterol Hepatol. 2017;15:575–583 e1. https://doi.org/10.1016/j.cgh.2016.09.158.

144. De Vita S, Quartuccio L, Fabris M. Hepatitis C virus infection, mixed cryoglobulinemia and BLyS upregulation: targeting the infectious trigger, the autoimmune response, or both? Autoimmun Rev. 2008;8:95–9. https://doi.org/10.1016/j.autrev.2008.05.005.

145. Petrarca A, Rigacci L, Caini P, Colagrande S, Romagnoli P, Vizzutti F, et al. Safety and efficacy of rituximab in patients with hepatitis C virus-related mixed cryoglobulinemia and severe

liver disease. Blood. 2010;116:335–42. https://doi.org/10.1182/blood-2009-11-253948.

146. Quartuccio L, Soardo G, Romano G, Zaja F, Scott CA, De Marchi G, et al. Rituximab treatment for glomerulonephritis in HCV-associated mixed cryoglobulinaemia: efficacy and safety in the absence of steroids. Rheumatology (Oxford). 2006;45:842–6. https://doi.org/10.1093/rheumatology/kel004.

147. Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, et al. ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. Ann Oncol. 2013;24:857–77. https://doi.org/10.1093/annonc/mds643.

148. European Association for Study of L. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2014;60:392–420. https://doi.org/10.1016/j.jhep.2013.11.003.

149. Torres HA, Mahale P. Most patients with HCV-associated lymphoma present with mild liver disease: a call to revise antiviral treatment prioritization. Liver Int. 2015;35:1661–4. https://doi.org/10.1111/liv.12825.

150. Zelenetz AD, Wierda WG, Abramson JS, Advani RH, Andreadis CB, Bartlett N, et al. Non-Hodgkin's lymphomas, version 1.2013. J Natl Compr Canc Netw. 2013;11:257–72 **quiz 73**.

151. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology. 2005;41(4):790–800.

152. Loria A, Doyle K, Weinstein AA, Winter P, Escheik C, Price J, et al. Multiple factors predict physical performance in people with chronic liver disease. Am J Phys Med Rehabil. 2014;93:470–6. https://doi.org/10.1097/PHM.0000000000000050.

153. Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, et al. Minimal impact of sofosbuvir and ribavirin on health related quality of life in chronic hepatitis C (CH-C). J Hepatol. 2014;60:741–7. https://doi.org/10.1016/j.jhep.2013.12.006.

154. Younossi ZM, Stepanova M, Marcellin P, Afdhal N, Kowdley KV, Zeuzem S, et al. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: results from the ION-1, -2, and -3 clinical trials. Hepatology. 2015;61:1798–808. https://doi.org/10.1002/hep.27724.

155. Younossi ZM, Stepanova M, Feld J, Zeuzem S, Jacobson I, Agarwal K, et al. Sofosbuvir/velpatasvir improves patient-reported outcomes in HCV patients: results from ASTRAL-1 placebo-controlled trial. J Hepatol. 2016;65:33–9. https://doi.org/10.1016/j.jhep.2016.02.042.

156. Gerber L, Estep M, Stepanova M, Escheik C, Weinstein A, Younossi ZM. Effects of Viral Eradication with ledipasvir and sofosbuvir, with or without ribavirin, on measures of fatigue in patients with chronic hepatitis C virus infection. Clin Gastroenterol Hepatol. 2016;14:156–164 e3. https://doi.org/10.1016/j.cgh.2015.07.035.