

# EASL Clinical Practice Guidelines: Management of hepatitis C virus infection

European Association for the Study of the Liver\*

## Introduction

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

These EASL Clinical Practice Guidelines (CPGs) are intended to assist physicians and other healthcare providers, as well as patients and other interested individuals, in the clinical decision-making process by describing the optimal management of patients with acute and chronic HCV infections. These guidelines apply to therapies that are approved at the time of their publication. Two protease inhibitors (PIs) have completed phase III development for patients infected with HCV genotype 1, and are currently registered for use in Europe and elsewhere. Therefore, these EASL CPGs on the management of HCV infection have been updated to include guidance on the use of these two drugs, and will be updated regularly based on approval of additional

new therapies and clinical experience with them. Also, substance users are increasingly considered as a treatable patient group at risk. The EASL CPGs have been updated in this respect. The preceding HCV CPGs were published as recently as 2011 [1]. These updated CPGs have built upon the earlier published work, so much remains unchanged. In particular, dual therapy remains the standard of care for patients with genotype non-1, and for some patients with genotype 1 infection. The authors of the current CPGs acknowledge the work undertaken by Professor Craxi and the authors of the 2011 CPGs which forms the basis of the current revision.

## Context

### Epidemiology

It is estimated that approximately 160 million individuals, i.e. 2.35% of the world population, are chronically infected with HCV [2]. Current estimates are that between 7.3 and 8.8 million persons are infected with HCV in the European Union, i.e. twice as many as an estimate made in 1997 [3]. Overall, HCV prevalence across Europe ranges between 0.4% and 3.5%, with wide geographical variation and higher rates in the south and the east [4–6].

HCV is a positive strand RNA virus, characterized by high sequence heterogeneity. Seven HCV genotypes, numbered 1 to 7, and a large number of subtypes have been described [6]. Genotypes and subtypes (which are identified by lowercase letters), differ among themselves by about 30% and 20% of their sequences, respectively. Genotype 1 is the most prevalent genotype worldwide, with a higher proportion of subtype 1b in Europe and 1a in the USA. Genotype 3a is highly prevalent in the European population of people who inject drugs (PWID). This group is currently experiencing an increasing incidence and prevalence of infections with HCV genotype 4. Genotype 2 is found in clusters in the Mediterranean region, while 5 and 6 are rare in Europe [7]. The novel genotype 7 was identified in patients from Canada and Belgium, possibly infected in Central Africa [8]. The identification of HCV genotypes and subtypes is not only of epidemiological interest, but it determines the type and duration of antiviral therapy, including the risk of selecting resistance-associated variants during therapy.

Up to the 1990's, the principal routes of HCV infection were blood transfusion, unsafe injection procedures, and intravenous drug use (IDU). Taken together, these routes are estimated to be responsible for approximately 70% of chronic cases in developed countries. Currently, however, screening of blood products

Received 5 November 2013; accepted 5 November 2013

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Abbreviations: AE, adverse event; ALT, alanine aminotransferase; BMI, body mass index; BOC, boceprevir; BT, viral breakthrough; CPGs, Clinical Practice Guidelines; CYP3A4, cytochrome p450 3A4; DAA, direct-acting antiviral; DVR, delayed virological response; EIA, enzyme immunoassays; EPO, erythropoietin; eRVR, extended rapid virological response; EVR, early virological response; G-CSF, granulocyte colony stimulating factor; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IDU, intravenous/injecting drug use; IFN, interferon; IU, international units; LSM, liver stiffness measurement; LT, liver transplant; OST, opiate/opioid substitution treatment/therapy; PegIFN/RBV, pegylated interferon- $\alpha$  and ribavirin; PI, protease inhibitor; PWID, people who inject drugs; RVR, rapid virological response; SCAR, severe cutaneous adverse reaction; SVR, sustained virological response; TSH, thyroid stimulating hormone; TVR, telaprevir.



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for HCV by means of enzyme immunoassays (EIA) and nucleic acid testing has virtually eradicated transfusion-associated hepatitis C. Similarly, in the developed world, new HCV infections are infrequently related to unsafe medical or surgical procedures. Spread among the PWID community – facilitated by sharing paraphernalia, unstable housing, frequent cocaine use, and history of imprisonment – now accounts for the vast majority of incident cases in developed countries. High coverage of combined harm reduction programs (e.g. opiate substitution treatment and needle exchange programs) may reduce HCV incidence in the PWID community, and some modelling studies suggest that implementation of HCV treatment may even reduce transmission within this population [9]. Other invasive behaviours, such as tattooing or acupuncture with unsafe materials, are also implicated in occasional HCV transmissions. The risk of perinatal and of heterosexual transmission of HCV is low, while male homosexual activity has become an important transmission route in Western countries [10]. On the other hand, the situation is quite different in resource-poor countries, where lack of public awareness and continuous use of unsafe medical tools still account for a considerable proportion of new HCV infections.

#### *Natural history and public health burden*

Acute hepatitis C is rarely severe, and symptoms occur in 10 to 50% of cases. In Europe, HCV infection is responsible for about 10% of cases of acute hepatitis [11]. The incidence of acute HCV infection has decreased and is now about 1/100,000 per year, but this figure is probably an underestimate because it mainly refers to symptomatic patients. Progression to persistent or chronic infection occurs in about three quarters of cases, is influenced by the *IL28B* genotype, and is associated with chronic hepatitis of a variable degree and with variable rates of fibrosis progression. Only exceptionally does infection clear spontaneously in the chronic stage. Chronic hepatitis C proceeds towards cirrhosis over several decades. On average, 10 to 20% of patients develop cirrhosis over 20–30 years of infection [12]. In a meta-analysis of cross-sectional studies of HCV-infected PWID, the 20-year cirrhosis prevalence was 15% [13]. Once at the cirrhotic stage, the risk of developing HCC is approximately 1 to 5% per year. Patients diagnosed with HCC have a 33% probability of death during the first year after diagnosis [14].

In Europe, and dependent on the relative proportion of patients with hepatitis B virus (HBV) infection in the same geographical area, the prevalence of anti-HCV antibodies among patients with cirrhosis ranges from 11 to 61% [15]. Similarly, the prevalence of anti-HCV antibodies in patients with HCC ranges from 18 to 64% [15]. Overall, the standardized mortality rate in anti-HCV-positive persons ranges from 1.6 to 4.5, and was as high as 25 in a recent study from Scotland [16]. It has been estimated that, in countries where injecting drug use (IDU) is the major risk factor for HCV infection, 20 to 25% of deaths among HCV-infected individuals are from liver disease and 15 to 30% are from drug-related causes, although the attributable risk of death varies and is age-related [17].

In addition to the healthcare burden associated with HCV mono-infection, Europe has a significant population that is HCV/HIV co-infected. Though they represent a small proportion of all HCV-positives, they tend to have more advanced liver injury and (to date) have exhibited disappointing response rates to antiviral therapy.

Hepatitis C progression to cirrhosis is highly variable, depending on the presence of cofactors capable of accelerating the fibrotic process. Proven cofactors for fibrosis progression include older age at infection, male gender, chronic alcohol consumption, obesity, insulin resistance and type 2 diabetes, and immunosuppression (such as that occurring after solid organ transplantation and in untreated HIV infection). Importantly, despite slow HCV disease progression over the initial 20 years of infection, advancing age may accelerate fibrosis progression [18]. Tobacco smoking may increase inflammation and accelerate fibrosis [19]. Similarly, daily cannabis use has been associated with more advanced liver fibrosis, though recently published data have questioned this association [20]. Coffee consumption is associated with lower inflammatory activity, less advanced fibrosis and reduced risk of developing HCC [21–23]. For all of the above reasons, a mainstay of HCV management is the modification of cofactors. An additional consideration is the fact that many of these cofactors also reduce the rate of response to interferon (IFN)-based therapy.

#### *The current standard of care and developing therapies*

The primary goal of HCV therapy is to cure the infection, which is generally associated with resolution of liver disease in patients without cirrhosis. Patients with cirrhosis remain at risk of life-threatening complications, albeit at a lower rate, even after viral infection has been eradicated. The infection is cured in more than 99% of patients who achieve a sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after treatment completion. Until 2011, the combination of pegylated interferon- $\alpha$  (pegylated IFN- $\alpha$ ) and ribavirin (subsequently referred to as PegIFN/RBV) was the approved treatment for chronic hepatitis C [24]. With this regimen, patients infected with HCV genotype 1 had SVR rates of approximately 40% in North America and 50% in Western Europe. Higher SVR rates were achieved in patients infected with HCV genotypes 2, 3, 5, and 6 (up to about 80%, and better for genotype 2 than for genotypes 3, 5, and 6) and intermediate SVR rates were achieved in those with HCV genotype 4 [7]. In 2011, telaprevir (TVR) and boceprevir (BOC) were licensed for use in HCV genotype 1 infection. These two drugs are first-generation direct-acting antivirals (DAAs), both targeting the HCV NS3/4A serine protease and thus referred to as protease inhibitors (PIs), i.e. both TVR and BOC must be administered in combination with PegIFN/RBV. These triple therapy regimens have proven effective for treatment-naïve and for treatment-experienced patients, including previous null responders to dual PegIFN/RBV therapy. Indications for therapy, dosages, schedules, side effects, and precautions are detailed in the sections below.

There are other DAAs at different stages of clinical development, some of them targeting HCV genotype 1 as well as other genotypes. Investigational drugs include second generation NS3/4A serine protease inhibitors, nucleoside/nucleotide and non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase, and NS5A inhibitors. Additionally, host-targeting antiviral drugs (HTAs), such as cyclophilin inhibitors, target host cell functions which are involved in the HCV life cycle. New therapeutic strategies aim towards higher efficacy, pan-genotypic activity, shortened treatment duration, easier administration and improved tolerability and patient adherence [25]. It is highly likely that IFN-sparing and IFN-free regimens with or without

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ribavirin, which are being evaluated in clinical trials, will enter clinical practice in the next few years. Decisions about the need for and timing of antiviral treatment will need to take into account this rapid rate of change.

### Methodology

These EASL CPGs have been developed by a panel of experts chosen by the EASL Governing Board. The recommendations were peer-reviewed by external expert reviewers and approved by the EASL Governing Board. The CPGs were established using data collected from PubMed and Cochrane database searches. The CPGs have been based as far as possible on evidence from existing publications, and, if evidence was unavailable, the experts' personal experiences and opinion. Where possible, the level of evidence and recommendation are cited. The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated [26]. The quality of the evidence in the CPG has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2) (Table 1). The CPGs thus consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted.

The HCV CPG Panel has considered the following questions:

- How should acute and chronic hepatitis C be diagnosed?
- What are the goals and endpoints of treatment?
- What are the results of current therapies and the predictors of response?
- How should patients be assessed before therapy?
- What are the contra-indications to therapy?
- Who should be treated with current licensed drugs?
- For whom can treatment be deferred?
- What first-line treatment should be prescribed?
- How should treatment be managed?
- How should treatment be tailored to the virological response?
- How can SVR rates of antiviral treatment be improved?
- How should patients with SVR be followed?
- What should be offered to those who fail to achieve SVR?
- How should patients with severe liver disease be treated?
- How should special groups of patients be treated?
- How should patients, infected after substance use, be treated?
- How should we treat patients with acute hepatitis C?
- How should untreated patients and non-sustained responders be followed?
- What are the perspectives of new treatments?

### Guidelines

#### Diagnosis of acute and chronic hepatitis C

The diagnosis of acute and chronic HCV infection is based on the detection of HCV RNA by a sensitive molecular method (lower limit of detection <15 international units [IU]/ml). Anti-HCV

antibodies are detectable by enzyme immunoassay (EIA) in the vast majority of patients with HCV infection but EIA results may be negative in early acute hepatitis C and in profoundly immunosuppressed patients. Following spontaneous or treatment-induced viral clearance anti-HCV antibodies persist in the absence of HCV RNA but may decline and finally disappear in some individuals [27,28].

The diagnosis of **acute hepatitis C** can be confidently made only if seroconversion to anti-HCV antibodies can be documented, since there is no serological marker, which proves that HCV infection is in the acute phase. About 50% of patients with acute hepatitis C will be anti-HCV positive at diagnosis. In these cases, acute hepatitis C can be suspected if the clinical signs and symptoms are compatible with acute hepatitis C (alanine aminotransferase [ALT] >10× the upper limit of normal, 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 can be detected during the acute phase although brief periods of undetectable HCV RNA may occur.

The diagnosis of **chronic hepatitis C** is based on the detection of both HCV antibodies and HCV RNA in the presence of signs of chronic hepatitis, either by elevated aminotransferases or by histology. Since, in the case of a newly acquired HCV infection, spontaneous viral clearance is very rare beyond four to six months of infection, the diagnosis of chronic hepatitis C can be made after that time period.

### Recommendations

- Anti-HCV antibodies are the first line diagnostic test for HCV infection (**recommendation A1**)
- In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation (**recommendation A1**)
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method (**recommendation A1**)
- Anti-HCV positive, HCV RNA negative individuals should be retested for HCV RNA 3 months later to confirm a recovered infection (**recommendation A1**)

### Goals and endpoints of HCV therapy

The **goal of therapy** is to eradicate HCV infection in order to prevent the complications of HCV-related liver and extrahepatic diseases, including liver necroinflammation, fibrosis, cirrhosis, HCC, and death.

The **endpoint of therapy** is the SVR, defined by undetectable HCV RNA 24 weeks after the end of therapy, as assessed by a sensitive molecular method with a lower limit of detection <15 IU/ml (SVR24). Long-term follow-up studies have shown that an SVR corresponds to a definitive cure of HCV infection in more than 99% of cases [29]. The validity of using undetectable HCV

Table 1. Evidence grading used in the EASL HCV Clinical Practice Guidelines (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

RNA at 12 weeks after the end of therapy (SVR12) has been accepted by regulators in the US and Europe, given that the concordance with SVR24 is 99% [30]. This concordance needs to be further validated in ongoing clinical trials.

Recommendations

- The goal of therapy is to eradicate HCV infection to prevent liver cirrhosis, HCC, and death. The endpoint of therapy is undetectable HCV RNA in a sensitive assay (<15 IU/ml) 12 and 24 weeks after the end of treatment (i.e. an SVR) **(recommendation A1)**
- In patients with cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, albeit not abolish, the risk of HCC. In these patients screening for HCC should be continued **(recommendation A1)**

Pretherapeutic assessment

The causal relationship between HCV infection and liver disease must be established, liver disease severity must be assessed, and baseline virological parameters that will be useful to tailor therapy should be determined.

Search for other causes of liver disease

Other causes of chronic liver disease, or factors which are likely to affect the natural history or progression of liver disease, should be systematically investigated and all patients should be tested for other hepatotropic viruses, particularly HBV. Alcohol consumption should be assessed and quantified, and specific counselling to stop any use of alcohol should be given. Possible co-morbidities, including alcoholism, co-infection with HIV, autoimmunity, genetic or metabolic liver diseases (for instance genetic hemochromatosis, diabetes or obesity) and the possibility of drug-induced hepatotoxicity should be assessed.

Assessment of liver disease severity

Assessment of liver disease severity is recommended prior to therapy. Identifying patients with cirrhosis is of particular importance, as the likelihood of response to therapy and post-treatment prognosis are proportional to the stage of fibrosis. The absence of significant fibrosis may also have important implica-

tions for the choice or timing of therapy. Assessment of the stage of fibrosis by biopsy is not required in patients with clinical evidence of cirrhosis. Patients with likely cirrhosis need screening for HCC. Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT patterns.

Liver biopsy remains the reference method. The risk of severe complications is very low (1/4,000 to 1/10,000). Based on the abundant literature, in chronic hepatitis C alternative, non-invasive methods can now be used instead of liver biopsy to assess liver disease severity prior to therapy at a safe level of predictability. Liver stiffness measurement (LSM) can be used to assess liver fibrosis in patients with chronic hepatitis C, provided that consideration is given to factors that may adversely affect its performance such as obesity. Well established panels of biomarkers of fibrosis can also be applied. Both LSM and biomarkers perform well in the identification of cirrhosis or no fibrosis but they perform less well in resolving intermediate degrees of fibrosis.

The combination of blood biomarkers or the combination of LSM and a blood test improve accuracy and reduce the need for liver biopsy to resolve uncertainty [31,32]. These tests are of particular interest in patients with clotting disorders, though transjugular liver biopsy may also be used safely in this situation with the bonus that portal pressure can also be assessed. In case of contradictory results with non-invasive markers, liver biopsy may be indicated. Also, histology may be required in cases of known or suspected mixed etiologies (e.g. HCV infection with HBV infection, metabolic syndrome, alcoholism or autoimmunity).

HCV titre and genotype determination

HCV quantification is indicated for the patient who may undergo antiviral treatment. HCV quantification should be made by a reliable sensitive assay, and levels should be expressed in IU/ml. The HCV genotype should also be assessed prior to treatment initiation. As the current therapy for genotype 1-infected patients includes first-generation PIs, subtyping is also relevant. Genotype 1a/b subtyping provides relevant information with respect to different response rates and genetic barriers to resistance to PIs when used as components of triple therapy for genotype 1 infection [33]. For instance, emerging trial data show that subtype 1a may be less susceptible than subtype 1b to treatment with some DAA drug combinations.

Determination of host genetics

IL28B genotyping may provide useful information for making clinical decisions in selected patients with genotypes 1 or 4. The negative predictive value of an unfavourable IL28B genotype

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is not sufficient to be considered a futility rule. A favourable *IL28B* genotype (*IL28B* CC) identifies patients who are more likely to achieve a rapid virological response (RVR) and who have a significant chance of cure with dual therapy [34,35]. In selected cases with genotype 1, it may assist the physician and patient in management decisions.

### Recommendations

- The causal relationship between HCV infection and liver disease should be established (**recommendation A1**)
- The contribution of co-morbid conditions to the progression of liver disease must be evaluated and appropriate corrective measures implemented (**recommendation A1**)
- Liver disease severity should be assessed prior to therapy. Identifying patients with cirrhosis is of particular importance, as their prognosis, their likelihood of response and the duration of therapy are altered (**recommendation A1**)
- Fibrosis stage can be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional etiologies (**recommendation B1**)
- HCV RNA detection and quantification should be made by a sensitive assay (lower limit of detection of <15 IU/ml) (**recommendation A1**)
- The HCV genotype must be assessed prior to treatment initiation and will determine the choice of therapy, the dose of ribavirin and treatment duration (**recommendation A1**)
- Subtyping of genotype 1a/1b may be relevant to PI-based triple therapy (**recommendation B2**)
- *IL28B* genotyping is not a prerequisite for treating hepatitis C (**recommendation B2**)

### Contra-indications to therapy

#### *IFN- $\alpha$* and ribavirin

Treatment of chronic hepatitis C with PegIFN/RBV-containing regimens is absolutely contra-indicated in the following patient groups: uncontrolled depression, psychosis or epilepsy; pregnant women or couples unwilling to comply with adequate contraception; severe concurrent medical diseases; decompensated liver disease (though treatment of patients with advanced liver disease whose parameters exceed label recommendations may be feasible in experienced centres under careful monitoring).

#### *Telaprevir or boceprevir based triple therapy*

Generally, the same contra-indications apply to TVR- or BOC-based triple therapy as to dual therapy with PegIFN/RBV ('IFN- $\alpha$  and ribavirin', above). In patients with compensated cirrhosis, treatment should be performed with special care as the incidence of side effects (especially hematological disorders and severe infections) is significantly increased in triple vs. dual PegIFN/RBV therapy, especially when serum albumin is <3.5 g/dl or platelets <100,000 before starting treatment [36].

### Indications for treatment: Who should be treated?

All treatment-naïve patients with compensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, should be considered for therapy. Treatment should be scheduled, rather than deferred, in patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extrahepatic manifestations (symptomatic cryoglobulinemia or HCV immune complexes nephropathy). For patients with minimal or no fibrosis, the timing of therapy is debatable, and treatment may be deferred pending the development and availability of new therapies. The decision to defer treatment for a specific patient should also consider the patient's preference and priorities, the natural history and risk of progression, the presence of co-morbidities and the patient's age. Patients who have treatment deferred should be assessed on a regular basis for evidence of progression, to reconsider the indication for treatment, and to discuss new therapies as they emerge.

Patients infected with HCV genotype 1 who failed to eradicate HCV on prior therapy with PegIFN/RBV or with combination non-pegylated IFN- $\alpha$  and ribavirin should be considered for treatment with PI-based triple therapy. In this setting, triple therapy yields SVR rates of 29 to 88%, depending on the type of previous non-response and on the stage of liver disease. Re-treatment with PegIFN/RBV, without the addition of a PI, is associated with low SVR rates.

Patients with HCV genotypes other than 1 who have failed previous IFN- $\alpha$ -based treatment can be considered for treatment with PegIFN/RBV depending on careful assessment of factors such as adequacy of prior treatment and stage of liver disease. The decision to treat or to wait should also consider the likely availability of new antiviral drugs.

### Recommendations

- All treatment-naïve patients with compensated disease due to HCV should be considered for therapy (**recommendation A1**)
- Treatment should be scheduled, not deferred, for patients with significant fibrosis (METAVIR score F3 to F4) (**recommendation A1**)
- In patients with less severe disease, the indication for and timing of therapy can be individualized (**recommendation B1**)

Table 2. Sustained virological response rates in phase III trials of boceprevir and telaprevir in HCV genotype 1 treatment-naïve patients.

Study	Sustained virological response (%)
<b>SPRINT-2</b>	
PegIFN/RBV 48 wk	38
PegIFN/RBV 4 wk then PegIFN/RBV + BOC response guided duration	63
PegIFN/RBV 4 wk then PegIFN/RBV + BOC 44 wk	66
<b>ADVANCE</b>	
PegIFN/RBV 48 wk	44
PegIFN/RBV + TVR 8 wk then PegIFN/RBV response guided duration	69
PegIFN/RBV + TVR 12 wk then PegIFN/RBV response guided duration	75
<b>ILLUMINATE</b> (patients with an eRVR only)	
PegIFN/RBV + TVR 12 wk then PegIFN/RBV 12 wk	92
PegIFN/RBV + TVR 12 wk then PegIFN/RBV 36 wk	88

First-line treatment of chronic hepatitis C: Results of current therapies and predictors of response

Phase III data on telaprevir and boceprevir in treatment-naïve genotype 1 infection

In the phase III trials of BOC and TVR in HCV-1 treatment-naïve patients, triple therapy regimens achieved higher SVR rates than PegIFN/RBV dual therapy.

In the SPRINT-2 study of BOC, patients were randomized to three treatment arms [37]. All patients received 4 weeks of lead-in treatment with PegIFN/RBV. Subsequent treatment was determined by the outcome of randomization to one of three treatment arms. Group 1 (control arm) received an additional 44 weeks of PegIFN/RBV plus placebo. Group 2 (BOC response-guided arm) received PegIFN/RBV plus BOC 800 mg three times daily. Treatment duration was guided by on-treatment virological response, so that patients who were HCV RNA undetectable at week 8 and 24 stopped all drugs at week 28, while patients who were HCV RNA detectable at any time point between week 8 and 24 stopped BOC at week 28, but then continued PegIFN/RBV for a total treatment duration of 48 weeks. Group 3 (fixed duration BOC arm) received 44 weeks of PegIFN/RBV plus BOC. The SVR rates were 38%, 63%, and 66% in groups 1, 2, and 3 respectively (Table 2). Similar SVR rates were achieved by the proportions of groups 2 and 3 patients who were HCV RNA undetected from week 8 through 24, whether they stopped all drugs at week 28 after 24 weeks triple therapy (part of Group 2) or continued treatment until week 48 with 44 weeks triple therapy (Group 3) (SVR rates 96% in both groups). However, in patients where HCV RNA was still detected at week 8, SVR rates were lower when BOC was stopped at week 28 (with continuation of dual therapy) than when it was continued as triple therapy until week 48 (SVR rates 66% vs. 75%). Based on these findings, and on a *post hoc* analysis of individual patient data undertaken by the European Medicines Agency (EMA), the recommended response-guided therapy for HCV-1 naïve patients receiving BOC as part of triple therapy is as follows:

- (1) Patients who are HCV RNA undetectable at week 8 and remain undetectable at week 24 can stop all drugs at week 28.
- (2) Patients with detectable HCV RNA at any time point between week 8 and 24, should continue triple therapy

until week 36, then BOC should be stopped and PegIFN/RBV continued until week 48.

- (3) Response-guided therapy should be avoided in the presence of cirrhosis, where the recommended treatment schedule is a 4 week lead-in phase of PegIFN/RBV followed by 44 weeks of PegIFN/RBV plus BOC. This recommendation stems from caution rather than from detailed data in this category of patients.

The 4 week PegIFN/RBV lead-in phase permits an assessment of patient adherence and tolerance of treatment, and also an assessment of the so-called 'IFN- $\alpha$  sensitivity' of the patient, thus providing some estimate of the chances of an SVR in treatment-naïve patients receiving BOC. In the SPRINT-2 study, patients with less than a 1 log<sub>10</sub> IU/ml decline in HCV RNA at week 4 had SVR rates of 4%, 28%, and 38% in groups 1, 2, and 3 respectively. In contrast, SVR rates were high in patients with a more than 1 log<sub>10</sub> IU/ml decline: 51%, 81%, and 79% in groups 1, 2, and 3, respectively. Indeed, SVR rates in patients reaching HCV RNA undetectability during the lead-in phase were not increased by the addition of BOC: 97%, 90%, and 90% in groups 1, 2, and 3, respectively.

TVR for treatment-naïve patients was investigated in two phase III trials, ADVANCE and ILLUMINATE. In ADVANCE [38], treatment-naïve patients were enrolled and randomized into three treatment groups: Group 1 (control, PR) received PegIFN/RBV plus placebo for 48 weeks. Group 2 (T8PR) received 8 weeks of triple therapy with TVR 750 mg/Q8h plus PegIFN/RBV followed by a response-guided tail of PegIFN/RBV. Group 3 (T12PR) received 12 weeks of triple therapy with TVR 750 mg/Q8h plus PegIFN/RBV followed by a response guided tail of PegIFN/RBV. In both the T8PR and the T12PR arms, treatment duration was based on HCV RNA values at week 4 and 12. Patients in whom HCV RNA was undetectable at week 4 to 12, the so-called extended rapid virological response (eRVR; Table 3), stopped treatment at week 24, while those in whom HCV RNA was detectable at either of these time points continued PegIFN/RBV up to week 48. The SVR rates were 44%, 69%, and 75% in the PR, T8PR, and T12PR groups, respectively (Table 2). Patients with an eRVR achieved extremely high SVR rates with the 24 week treatment arm both in the T8PR arm (83%) and in the T12PR arm (89%). In the few patients in the PR arm who achieved eRVR (only 8%), the SVR rate was also extremely high (97%). In patients

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**Table 3. Monitoring of on-therapy response during dual or triple therapy: definitions of virological response levels.**

Drug combination/response level	Abbreviation	Definition
<b>PegIFN/RBV</b>		
Rapid virological response	RVR	Undetectable HCV RNA in a sensitive assay at week 4 of therapy
Early virological response	EVR	HCV RNA detectable at week 4 but undetectable at week 12, maintained up to end of treatment
Delayed virological response	DVR	More than 2 log <sub>10</sub> IU/ml decrease from baseline but detectable HCV RNA at week 12, then undetectable at 24 wk and maintained up to end of treatment
Null response	NR	Less than 2 log <sub>10</sub> IU/ml decrease in HCV RNA level from baseline at 12 wk of therapy
Partial response	PR	More than 2 log <sub>10</sub> IU/ml decrease in HCV RNA level from baseline at 12 wk of therapy but HCV RNA detectable at 24 wk
Breakthrough*	BT	Reappearance of HCV RNA at any time during treatment after a negative result or increase of 1 log <sub>10</sub> IU/ml from nadir
<b>PegIFN/RBV + TVR</b>		
Extended rapid virological response	eRVR	Undetectable HCV RNA in a sensitive assay at week 4 and 12 of therapy
<b>PegIFN/RBV + BOC</b>		
Early response	ER	Undetectable HCV RNA in a sensitive assay at week 8 of therapy (after 4 wk of BOC)
Late response	LR	Detectable HCV RNA in a sensitive assay at week 8 of therapy, but negative at week 12 (after 8 wk of BOC)

\*Definition applies also to TVR and BOC regimens.

without an eRVR, the SVR rates were 39%, 50%, and 54% in the PR, T8PR, and T12PR arms respectively.

These data were the foundation for the phase III optimization study ILLUMINATE [39], which used a randomized study design to assess the relative benefit to patients achieving an eRVR of following 12 weeks of TVR plus PegIFN/RBV triple therapy with either 12 or 36 weeks of PegIFN/RBV dual therapy. All patients received 12 weeks of TVR 750 mg/Q8h plus PegIFN/RBV. Patients with an eRVR were randomized to receive either a further 12 week tail of PegIFN/RBV (T12PR24) or a 36 week tail of PegIFN/RBV (T12PR48). In the 60% of patients with an eRVR, the SVR rates were 92% in the T12PR24 cohort and 87.5% in the T12PR48 cohort (Table 2). Based on the results of these 2 studies, overall treatment duration with triple therapy containing TVR can be shortened to 24 weeks in naïve patients with an eRVR, while treatment needs to be continued until week 48 in those without an eRVR. In patients with cirrhosis, treatment with PegIFN/RBV is to be continued until week 48 regardless of HCV RNA kinetics since, in the ILLUMINATE trial, SVR rate in cirrhotics with an eRVR was higher when therapy was continued until week 48 (92% vs. 67%). Thus, based on these three phase III studies, which evaluated BOC or TVR in genotype 1 treatment-naïve patients, it can be concluded that triple therapy comprising PegIFN/RBV with either of the PIs is the treatment of choice.

### *A potential role for dual therapy in genotype 1 infection*

Dual therapy may be appropriate for selected treatment-naïve patients with baseline features predicting a high likelihood of RVR and SVR to PegIFN/RBV. Cost savings and better tolerability of dual therapy must be taken into account. Moreover, occasional patients may have co-morbid conditions which require medication known or predicted to have adverse drug-drug interaction with the first-generation PIs. In the pivotal clinical trials for registration of PegIFN/RBV therapy, SVR was achieved in 46% and 42% of patients infected with HCV genotype 1 when treated with pegylated IFN- $\alpha$ 2a or pegylated IFN- $\alpha$ 2b and ribavirin, respec-

tively [40–42]. SVR rates in these patients were slightly higher in Europe than in the US. These results were confirmed in the IDEAL trial that compared two approved treatment regimens in the United States: 41% of patients achieved SVR when treated with pegylated IFN- $\alpha$ 2a (180  $\mu$ g/week) plus weight-based ribavirin (1.0 to 1.2 g/day) for 48 weeks, vs. 40% of patients treated with pegylated IFN- $\alpha$ 2b (1.5  $\mu$ g/kg/week) plus weight-based ribavirin (0.8 to 1.4 g/day) for the same period (SVR rates not significantly different) [43].

In addition to those patients who may have a contraindication to PI treatment, dual treatment with PegIFN/RBV can achieve very high SVR rates in selected patients with highly IFN- $\alpha$ -sensitive infection, an approach which can avoid the cost and additional side-effects associated with PI treatment [44]. For instance, *post hoc* subgroup analysis showed that, in HCV genotype 1 patients with the favourable *IL28B* genotype, dual therapy obtained similar SVR rates to triple therapy including BOC. This was also true for patients achieving an RVR during the PegIFN/RBV week 4 lead-in phase. TVR can also be used with a 4 week lead-in period of dual therapy, possibly for those with a favourable *IL28B* genotype. Under that situation, achievement of RVR could justify the continuation of dual PegIFN/RBV treatment without the addition of TVR. In this highly IFN- $\alpha$ -responsive category of patients, the main advantage of triple therapy is the possibility of shortening overall treatment duration to 24 weeks with the TVR-containing regimen and to 28 weeks with BOC-containing regimen. With dual therapy, treatment should only be abbreviated if the baseline HCV RNA level is less than 400,000 IU/ml, an RVR is achieved and no further negative predictor of treatment outcome is present.

### *Drug dosing in HCV genotype 1 therapy*

Pegylated IFN- $\alpha$ 2a should be used at the dose of 180  $\mu$ g/week, whereas pegylated IFN- $\alpha$ 2b should be used at the weight-based dose of 1.5  $\mu$ g/kg/week. In triple therapy, ribavirin dose should be 1000–1200 mg/day based on body weight for pegylated

IFN- $\alpha$ 2a, and 800–1400 mg/day based on body weight for pegylated IFN- $\alpha$ 2b. TVR is dosed 750 mg/every 8 h, though recently presented clinical trial data showed that 12-hourly dosing (1125 mg 12 hourly) does not have inferior efficacy in comparison with the licensed schedule (750 mg 8 hourly) [45]. BOC is dosed 800 mg/every 7–9 h. Both PIs need to be taken with food. Each TVR dose needs to be taken with a 20 g fat content snack. In phase III studies, TVR was associated with peg IFN- $\alpha$ 2a, while BOC was studied with both pegylated IFNs. In a randomised study, TVR therapy achieved equivalent SVR rates used with either of these pegylated IFNs [46].

Recommendations

- The combination of PegIFN/RBV and TVR or BOC is the approved standard of care for chronic hepatitis C genotype 1 (**recommendation A1**). There is no head-to-head comparison to allow recommendation of TVR or BOC as preferred therapy
- Patients with cirrhosis should never receive abbreviated treatment in BOC or TVR treatment regimens (**recommendation B1**)
- Selected patients with high likelihood of SVR to PegIFN/RBV or with contraindications to BOC or TVR can be treated with dual therapy
- When lead-in is used to identify patients with IFN- $\alpha$ -sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment (**recommendation B2**)
- Both pegylated IFN- $\alpha$  molecules, pegylated IFN- $\alpha$ 2a (180  $\mu$ g/wk) and pegylated IFN- $\alpha$ 2b (1.5  $\mu$ g/kg/wk), can be used in dual or triple therapy (**recommendation B1**)
- Ribavirin should be dosed following the pegylated IFN- $\alpha$  label for triple therapy (**recommendation B2**)
- Ribavirin should be given at a weight-based dose of 15 mg/kg in dual therapy (**recommendation B2**)

*Treatment-naïve patients with genotypes 2, 3, 4, 5, or 6*  
 In patients infected with HCV genotypes 2 and 3, SVR was achieved in the pivotal trials in 76% and 82% of cases with pegylated IFN- $\alpha$ 2a plus ribavirin and pegylated IFN- $\alpha$ 2b plus ribavirin, respectively. Some real-life studies have recently reported lower SVR rates for genotype 3 infection [47,48].

Patients with HCV genotype 4 were under-represented in the pivotal trials of PegIFN/RBV. Therefore most data on SVR rates derive from subsequent studies. Reported SVR rates range between 43% and 70% with the 48 week schedule of pegylated IFN- $\alpha$  plus weight-based ribavirin. Some studies have shown lower SVR rates in HCV genotype 4 patients of European descent compared with patients from other geographical areas [49].

In patients infected by HCV genotype 2, 3, 4, 5, or 6, the standard of care regimen consists of the combination of either of the

two pegylated IFN- $\alpha$ 's with ribavirin. Pegylated IFN- $\alpha$ 2a should be used at the dose of 180  $\mu$ g/week, whereas pegylated IFN- $\alpha$ 2b should be used at the weight-based dose of 1.5  $\mu$ g/kg/week. The ribavirin dose depends on the HCV genotype. Patients infected with HCV genotypes 4, 5, and 6 should receive a weight-based dose of ribavirin, i.e. 15 mg/kg body weight. Patients infected with genotypes 2 and 3 can be treated with a flat dose of 800 mg of ribavirin daily, but those with a body mass index (BMI) beyond 25 or who have baseline factors suggesting low responsiveness (insulin resistance, metabolic syndrome, severe fibrosis or cirrhosis, older age) should receive a weight-based dose of ribavirin.

There is no indication to the use of first-generation PIs in patients with non-1 genotype HCV infection.

Recommendations

- The combination of pegylated IFN- $\alpha$  and ribavirin is the approved standard of care for chronic hepatitis C genotype 2, 3, 4, 5, and 6 (**recommendation A1**)
- Ribavirin should be given at a weight-based dose of 15 mg/kg for genotypes 4, 5, and 6 and at a flat dose of 800 mg/day for genotypes 2 and 3 (**recommendation A2**)
- Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at the dose of 15 mg/kg (**recommendation C2**)

Treatment monitoring

Treatment monitoring includes monitoring of treatment efficacy and of safety and side effects.

Monitoring of treatment efficacy

Monitoring of treatment efficacy is based on repeated measurements of HCV RNA levels. A sensitive, accurate assay with a broad dynamic range of quantification should be used. The same assay, ideally from the same laboratory, should be used in each patient to measure HCV RNA at different time points, in order to assure consistency of results [50–52]. In order to monitor treatment efficacy and guide decisions on treatment duration, HCV RNA level measurements should be performed at specific time points. Measurements should only be made if and when the result of the measurement will have some influence on the scheduled treatment, i.e. if the result will determine that treatment should be abandoned (futility rules), that treatment can be abbreviated (response-guided therapy), or that treatment has been successful (end of treatment and post-treatment SVR assessment).

In dual therapy, HCV RNA levels should be assessed at baseline, week 4, week 12, week 24, end of treatment, and 12 or 24 weeks after the end of therapy in order to assess the SVR. In triple therapy with BOC, HCV RNA should be measured at weeks 4, 8, 12, 24, end of treatment, and 12 or 24 weeks after the end of therapy. For BOC therapy, here and elsewhere in the Guidelines, the timing of RNA quantitation refers to weeks after commencement of the dual therapy lead-in. In triple therapy

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with TVR (here assuming no dual therapy lead-in), HCV RNA should be assessed at weeks 4, 12, 24, end of treatment, and 12 or 24 weeks after the end of therapy.

For patients receiving dual therapy, a low vs. high baseline HCV RNA level may be used to guide treatment decisions based on the on-treatment virological response. There is no current agreement on the best discriminating HCV RNA level, which ranges between 400,000 and 800,000 IU/ml (5.6–5.9 log<sub>10</sub> IU/ml) [40,53–59].

### Stopping (futility) rules

With dual therapy, treatment should be stopped at week 12 if the HCV RNA decrease is less than 2 log<sub>10</sub> IU/ml. The SVR rate achieved by treatment continuation in these patients is less than 2%. In patients with detectable HCV RNA at week 24, there is a very small chance of SVR (1–3%) and treatment should be stopped [40,53,58,60]. This stopping rule was defined by analysis of data at a time when detection assays were less sensitive than the currently available assays. Logically, treatment should be

continued for those patients with undetectable RNA using current assays.

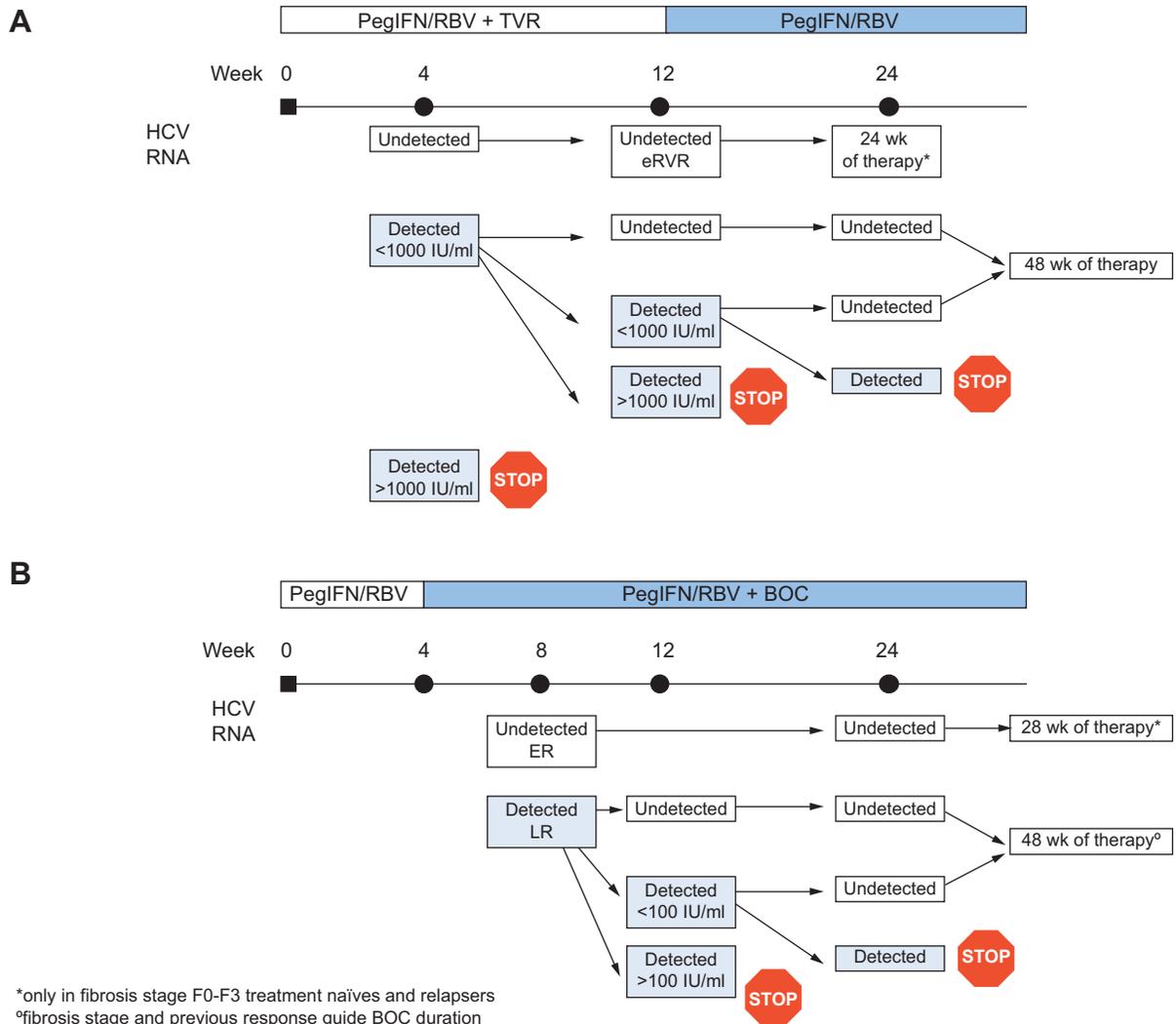
In triple therapy with BOC, stopping rules have been retrospectively derived from analysis of the SPRINT-2 study. All drugs should be stopped if HCV RNA is >100 IU/ml at treatment week 12, if HCV RNA is detectable at treatment week 24, and in case of viral breakthrough (BT) later on.

In TVR-based regimens the stopping rules were retrospectively modelled from the ADVANCE database. All drugs should be stopped if HCV RNA is >1000 IU/ml at week 4 or 12 of therapy, and in case of BT later on.

### Virological response-guided triple therapy

The evidence and principles for response-guided therapy of treatment-naïve patients were discussed in section 'Phase III data on telaprevir and boceprevir in treatment-naïve genotype 1 infection'.

The treatment algorithms for BOC and TVR, including guidance for response-guided therapy and stopping rules, are presented in Fig. 1A and B.



**Fig. 1. Management algorithms.** For the use of triple therapy comprising PegIFN/RBV and either (A) TVR or (B) BOC. **STOP**, stop treatment; eRVR, extended rapid virological response; ER, early response; LR, late response.

*Virological response-guided dual therapy*

PegIFN/RBV treatment duration can be tailored to the on-treatment virological response. Upon treatment, HCV RNA levels should be assessed at three time points, regardless of the HCV genotype: baseline and weeks 4 and 12. The likelihood of SVR is directly proportional to the speed of HCV RNA disappearance (Fig. 2).

Treatment should be stopped at week 12 if the HCV RNA decrease is less than 2 log<sub>10</sub> IU/ml. Patients with a more than 2 log<sub>10</sub> drop or an undetectable HCV RNA at week 12 can be classified into three groups according to their virological response (Table 3).

- (1) The **rapid virological response** (RVR) is defined as an undetectable HCV RNA at week 4 of therapy.
- (2) The **early virological response** (EVR) is defined as an HCV RNA, which is undetectable at week 12. In some literature, this is referred to as complete EVR (cEVR).
- (3) The **delayed virological response** (DVR) is defined as a more than 2 log<sub>10</sub> drop with detectable HCV RNA at week 12, and undetectable HCV RNA at week 24. In some literature, this is referred to as partial EVR (pEVR).

Reappearance of HCV RNA at any time during treatment after virological response is classified as breakthrough (BT).

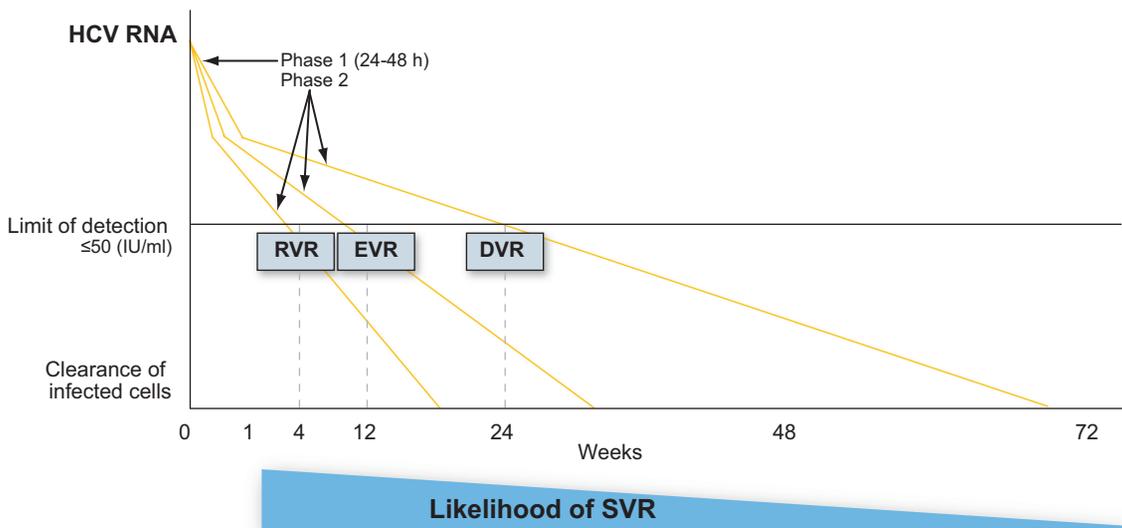
The following treatment durations should be applied according to the virological response:

- (1) Patients infected with HCV genotype 1, with an RVR can be treated for 24 weeks. A recent meta-analysis suggested that this applies only to those with a low baseline HCV RNA level. As uncertainties remain as to which threshold should be used to distinguish low and high baseline HCV RNA levels, patients infected with HCV genotype 1 (and possibly also those infected with genotype 4) with a

baseline viral level <400,000 IU/ml should be treated for 24 weeks, whereas it is reasonable to prolong therapy for a total of 48 weeks in patients with a higher baseline HCV RNA level [41,56,57,59,61,62]. Some suggest a higher threshold.

- (2) Patients infected with HCV genotype 1 (and possibly also those infected with genotype 4) and who achieve an EVR without an RVR should be treated for 48 weeks [61,63–68].
- (3) Patients with HCV genotype 1 and a delayed virological response (DVR) can be treated for 72 weeks, provided that their HCV RNA is undetectable at week 24. Insufficient data exist for other genotypes [61,63–68]. (Recommendations (2) and (3) clearly refer to patients with genotype 1 infection who are being treated in a setting where PIs are unavailable or contraindicated.)
- (4) In patients infected with HCV genotypes 2 and 3 with an RVR and low baseline viral load (<400,000 IU/ml), shortening of treatment duration to 16 weeks can be considered at the expense of a slightly higher chance of post-treatment relapse [54,69–72].
- (5) In patients with HCV genotypes 2 and 3 who have advanced fibrosis, cirrhosis or cofactors affecting response (insulin resistance, metabolic syndrome, non-viral steatosis) shortening of treatment duration to 16 weeks should not be considered, even if they have low baseline HCV RNA and RVR. There is insufficient evidence of an equal efficacy [55,73–75].
- (6) Patients with genotypes 2 and 3 without RVR and with negative cofactors affecting response could be treated for 48 weeks, provided that their HCV RNA is undetectable at week 24 [41,76].

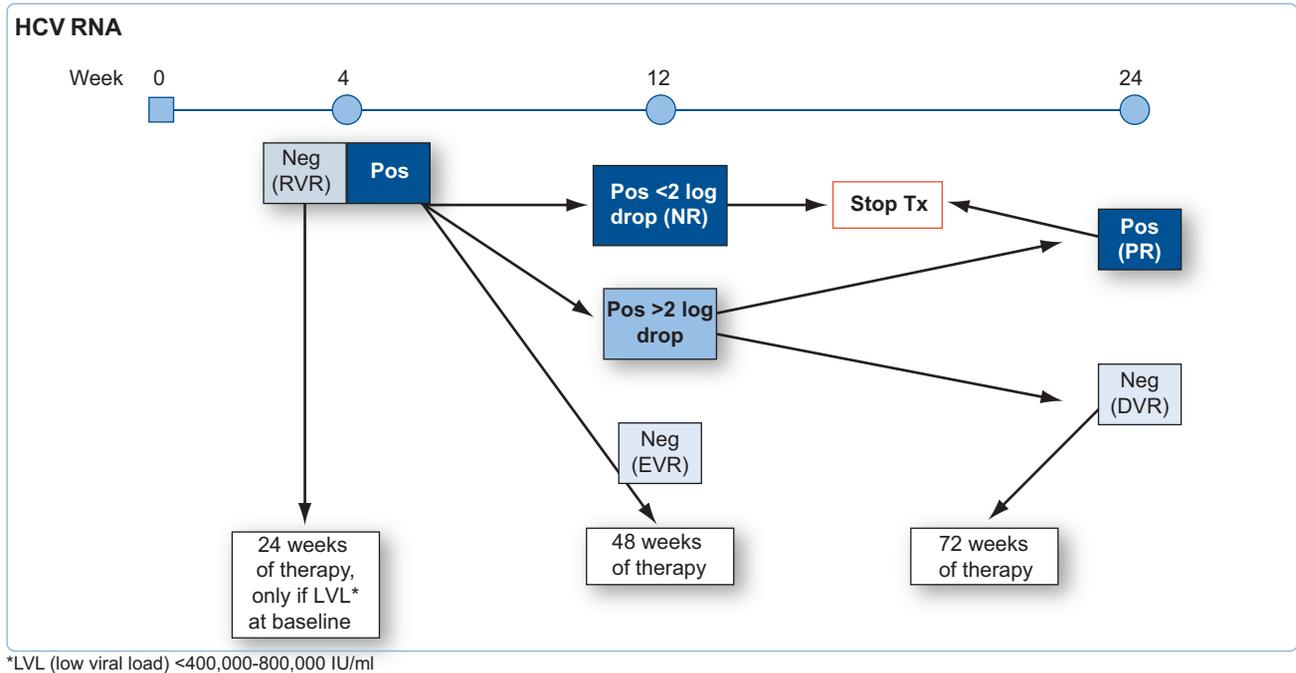
For patients receiving dual PegIFN/RBV therapy, response-guided treatment profiles are outlined in Fig. 3 for HCV genotype 1 and Fig. 4 for HCV genotypes 2 and 3.



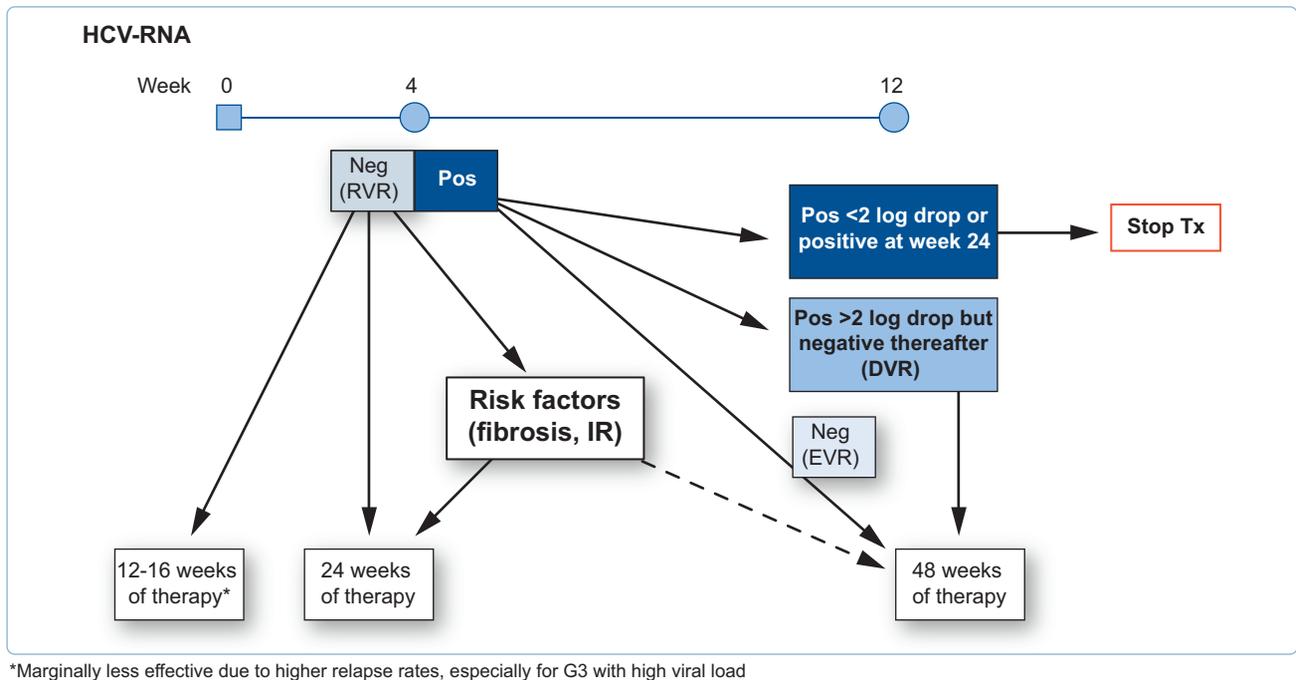
DVR, delayed virological response; EVR, early virological response; RVR, rapid virological response.

Fig. 2. Likelihood of SVR according to viral response in the first weeks of dual therapy with PegIFN/RBV.

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**Fig. 3. Response-guided therapy in patients with genotype 1 receiving dual therapy with PegIFN/RBV (applies also to genotype 4 at a B2 grade of evidence).** DVR, delayed virological response; EVR, early virological response; Neg, HCV RNA not detected; NR, null response; Pos, HCV RNA detected; PR, partial response; RVR, rapid virological response; Tx, therapy.



**Fig. 4. Response-guided therapy in patients with genotypes 2 and 3 receiving dual therapy with PegIFN/RBV (applies also to genotypes 5 and 6, excluding 12-16 weeks, at a C2 grade of evidence).** DVR, delayed virological response; EVR, early virological response; IR, insulin resistance; Neg, HCV RNA not detected; Pos, HCV RNA detected; RVR, rapid virological response; Tx, therapy.

Recommendations

- A real-time PCR-based assay with a lower limit of detection of <15 IU/ml should be used to monitor triple therapy (**recommendation B1**)
- During triple therapy in HCV genotype 1 patients, HCV RNA measurements should be performed at weeks 4, 8, 12, 24, and end of treatment when giving BOC, and at weeks 4, 12, 24, and end of treatment when giving TVR (**recommendation A2**)
- During dual therapy in any HCV genotype, HCV RNA levels should be assessed at baseline, weeks 4, 12, 24 and end of treatment (**recommendation A2**)
- The end-of-treatment virological response and the SVR at 12 or 24 weeks after the end of treatment must be assessed (**recommendation A1**)
- Whether the baseline HCV RNA level is low or high may be a useful criterion to guide treatment decisions during dual therapy (**recommendation B2**). The safest threshold level for discriminating low and high baseline HCV RNA is 400,000 IU/ml (**recommendation C2**)
- Dual therapy for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is less than  $2 \log_{10}$  IU/ml and at week 24 if HCV RNA is still detectable (**recommendation B1**)
- Triple therapy with BOC should be stopped if HCV RNA is >100 IU/ml at treatment week 12 or if HCV RNA is detectable at treatment week 24 (**recommendation B1**)
- Triple therapy with TVR should be stopped if HCV RNA is >1000 IU/ml at weeks 4 or 12 of therapy (**recommendation B1**)
- Dual therapy duration should be tailored to the on-treatment virological response at weeks 4 and 12. The likelihood of SVR is directly proportional to the rapidity of HCV RNA disappearance (**recommendation B1**)
- For patients receiving dual therapy who achieve an RVR and who have low baseline viral titre (<400,000 IU/ml), treatment for 24 weeks (genotype 1) or 16 weeks (genotype 2/3) can be considered. If negative predictors of response (i.e. advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) are present, published evidence for equal efficacy of shortened treatment is lacking (**recommendation B2**)
- Patients receiving dual therapy with genotypes 2 or 3, and with any adverse predictor of SVR, and who achieve an EVR or a DVR without an RVR, can be treated for 48 weeks (**recommendation B2**)
- Genotype 1 patients receiving dual therapy who demonstrate a DVR can be treated for 72 weeks, provided that their HCV RNA is undetectable at week 24 (**recommendation B2**)

Monitoring treatment safety

Flu-like symptoms are often present after pegylated IFN- $\alpha$  injections. They are easily controlled by paracetamol and tend to attenuate after 4–6 weeks of therapy. At each visit, the patients should be assessed for clinical side effects, such as severe fatigue, depression, irritability, sleeping disorders, skin reactions, and dyspnoea. Thyroid stimulating hormone (TSH) levels should be measured every 12 weeks while on therapy [77].

Hematological side effects of pegylated IFN- $\alpha$  and ribavirin include neutropenia, anemia, thrombocytopenia and lymphopenia. These parameters should be assessed at weeks 1, 2, and 4 of therapy and at 4 to 8 week intervals thereafter. Both BOC and TVR increase the risk of anemia, especially in patients with liver cirrhosis.

Dermatological adverse events (AEs) are frequent during HCV therapy, in both dual and PI-containing regimens. TVR can cause skin rashes, which may be severe and may demand early termination of the TVR component of therapy. In TVR trials, dermatological AEs with TVR-based triple therapy were generally similar to those observed with PegIFN/RBV but approximately half of TVR-treated patients reported a rash [38]. More than 90% of these were grade 1 or 2 (mild/moderate), and in the majority of cases, progression to a more severe grade did not occur. In a small number of cases (6%), rash led to TVR discontinuation, whereupon symptoms commonly resolved. A few cases were classified as severe cutaneous adverse reactions (SCAR), a group of rare conditions that are potentially life-threatening. The TVR prescribing information does not suggest TVR discontinuation for grade 1 or 2 rash, which can be treated using emollients/moisturizers and topical corticosteroids. For grade 3 rash, the prescribing information mandates immediate TVR discontinuation, with ribavirin interruption (with or without pegylated IFN- $\alpha$ ) within 7 days of stopping TVR if there is no improvement (or sooner if it worsens). In case of suspicion or confirmed diagnosis of SCAR, all medication must be discontinued.

Recommendations

Treatment dose reductions

The pegylated IFN- $\alpha$  dose should be reduced in case of severe side effects, such as clinical symptoms of severe depression, and if the absolute neutrophil count falls below  $750/\text{mm}^3$ , or the platelet count falls below  $50,000/\text{mm}^3$ . When using pegylated IFN- $\alpha$ 2a, the dose can be reduced from 180  $\mu\text{g}/\text{week}$  to 135  $\mu\text{g}/\text{week}$ , and then to 90  $\mu\text{g}/\text{week}$ . When using pegylated IFN- $\alpha$ 2b, the dose can be reduced from 1.5  $\mu\text{g}/\text{kg}/\text{week}$  to 1.0  $\mu\text{g}/\text{kg}/\text{week}$  and then to 0.5  $\mu\text{g}/\text{kg}/\text{week}$ . Pegylated IFN- $\alpha$  should be stopped in case of marked depression, if the neutrophil count falls below  $500/\text{mm}^3$  or the platelet count falls below  $25,000/\text{mm}^3$ . If and when neutrophil or platelet counts rise from those nadir values, treatment can be restarted, but at a reduced dose. Interferon treatment interruptions should be as brief as possible. Prolonged interruption of IFN administration will reduce treatment efficacy and may contribute to emergence of PI resistance during triple therapy. Thus, in cases where neutrophil and platelet counts determine that there is significant delay in IFN resumption, treatment should be abandoned. There is no role for prolonged IFN-free dual therapy with ribavirin and first generation PIs for genotype 1 infection. If significant anemia occurs (hemoglobin <10 g/dl), the dose of ribavirin should be adjusted downward

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by 200 mg at a time. Hemoglobin decline is accelerated by the addition of first generation PIs to PegIFN/RBV. A more rapid reduction of dose may be required for patients with rapidly declining hemoglobin, particularly if the baseline hemoglobin was low, and particularly during triple therapy. Ribavirin administration should be stopped if the hemoglobin level falls below 8.5 g/dl. Alternatively, growth factors can be used to enable high doses of pegylated IFN- $\alpha$  and/or ribavirin to be maintained (see below) [40,41,53,77–82].

Treatment should be promptly stopped in case of a hepatitis flare (ALT levels above 10 times normal, if not already present at the time of starting treatment) or if a severe bacterial infection occurs at any site, regardless of neutrophil count.

BOC or TVR doses should not be reduced during therapy, as this will favour the development of antiviral drug resistance. For both PIs, treatment should either be stopped completely, because of side effects, or be continued at the same dose provided that adjuvant therapy is prescribed. The decision should take into consideration the type of side effects and the likelihood of achieving SVR with on-going therapy. Once BOC or TVR have been stopped, they should never be reintroduced in the same course of treatment.

### Measures to improve treatment success rates

Simple measures to enhance adherence to treatment should be implemented since this has been shown to be associated with significantly higher SVR rates.

### Treatment adherence

Full adherence to both pegylated IFN- $\alpha$  and ribavirin is associated with improved SVR rates. It is recommended that dose reductions are reviewed and that the optimum dose is restored as soon as possible in order to attain and sustain maximum exposure to each drug. Adherence to HCV therapy has been defined as receipt of  $\geq 80\%$  of scheduled pegylated IFN- $\alpha$  and ribavirin doses for  $\geq 80\%$  of the treatment period, but this definition does not distinguish between missed doses and treatment discontinuations [83]. Suboptimal IFN exposure is mainly due to early treatment discontinuation rather than to occasional missed doses [84]. It is of note that both physicians [85] and individuals [86] overestimate adherence to HCV therapy. Suboptimal exposure to IFN may also permit the emergence of resistance-associated variants in regimens containing a DAA, especially during the early phase of treatment.

Before starting antiviral therapy, patients must be instructed about the schedule and the side effects to be expected during treatment. Patients should also be instructed about the preventive and therapeutic measures to ameliorate these side effects, for example by using antipyretics, analgesics, or antidepressants (see below). Regular follow-up visits must be scheduled so that treatment progress and management of side effects can be discussed. Easy access to physicians or to specialized nursing staff in case of side effects should be facilitated in order to reduce discontinuation rates to a minimum. Patient recall procedures in cases of missed appointments should be instituted.

Examples of strategies that have been successful for enhancing clinical assessment, management adherence and achievement of SVR include hospital-based [87] and primary care-based integrated care [88], community-based tele-health

[89], nurse-led education [90], psychoeducation [91], directly observed therapy [92–95], peer support groups [88,96] and peer support workers [97]. The key element of effective HCV clinical management within all these settings is access to a multidisciplinary team, generally including clinician and nursing clinical assessment and monitoring, drug and alcohol services, psychiatric services, and social work and other social support services (including peer support, if available). Measures to increase adherence are interdisciplinary HCV education and monitoring services and, particularly, the help of a dedicated nurse [98,99]. For foreign patients, the language and comprehension difficulties should be addressed before starting treatment.

To maximize the likelihood of benefit for patients who begin new HCV treatment regimens, resources should be devoted to patient pre-treatment assessment and preparation, as well as to on-treatment adherence monitoring and support [100,218].

### Recommendations

- HCV treatment should be delivered within a multidisciplinary team setting (**recommendation A1**)
- HCV infected patients should be counselled on the importance of adherence for attaining an SVR (**recommendation A1**)
- In patients with socioeconomic difficulties and in migrants, social support services should be a component of HCV clinical management (**recommendation B2**)
- In persons who actively inject drugs, access to harm reduction programs is mandatory (**recommendation A1**)
- Peer-based support should be evaluated as a means to improve HCV clinical management (**recommendation B2**)
- HCV treatment can be considered also for patients actively using drugs, provided they wish to receive treatment and are able and willing to maintain regular appointments. Also, the potential for drug-drug interactions involving prescribed and non-prescribed drugs needs to be considered (**recommendation A1**)

### Correction of cofactors

**Body weight.** High body weight (BMI) adversely influences the response to PegIFN/RBV, even after dose adjustments [101]. Body weight reduction prior to therapy is recommended but the data suggesting that this may be associated with better SVR rates is scanty.

**Lipids.** The HCV life cycle is tightly linked to lipid metabolism. Thus, some cholesterol lowering drugs have been shown to inhibit HCV replication and may improve response rate to treatment, but the data are limited.

**Alcohol.** Alcohol consumption has an impact on treatment adherence [102]. Patients should therefore be advised to stop or to reduce alcohol consumption before start of treatment. HCV patients who consume alcohol but are able to adhere to a full course of HCV treatment have similar SVR rates to non-drinkers [103,104]. Treatment for patients not able to abstain from alcohol should be fitted to the individual, focussing on their ability to adhere to medication and appointments. Hepatitis C patients with on-going alcohol consumption during treatment profit from additional support during antiviral therapy [102–105].

**Metabolic syndrome.** Insulin resistance and type 2 diabetes, independently of their pathogenesis, accelerate liver disease progression and increase the risk for the development of HCC. They also reduce response to the standard combination of PegIFN/RBV. However, it seems unlikely that they may also decrease response to PI-containing regimens [106]. HCV infection *per se* does not carry an increased risk of metabolic syndrome, but is able to perturb glucose homeostasis through several direct and indirect mechanisms, leading to both hepatic and extrahepatic insulin resistance. This translates into an increased risk for development of type 2 diabetes in susceptible persons. HCV may also cause hepatic steatosis, especially in patients infected with genotype 3, although the clinical impact of 'viral' steatosis is debated. Possibly as a result of HCV-induced insulin resistance, and despite a paradoxically favourable lipid profile, the cardiovascular risk is moderately increased in chronic hepatitis C. Thus, targeted lifestyle and pharmacological measures are warranted in chronic hepatitis C with metabolic alterations. However, results of attempts to increase the SVR rate to PegIFN/RBV by the use of insulin sensitizers are not conclusive and do not justify the use of this class of drugs for this purpose [107].

#### Supportive therapy

**Growth factors.** It has been suggested that the use of hematologic growth factors is helpful in limiting the need for treatment dose reductions. Recombinant erythropoietin (EPO) can be used to maintain or to improve hemoglobin levels in order to avoid ribavirin dose reductions or interruptions. Although no prospective trials have been designed to date to definitely demonstrate that the use of EPO has a positive impact on SVR, it is widely used to enable high doses of ribavirin to be maintained and to improve the quality of life during therapy [108]. EPO can be administered when the hemoglobin level falls below 10 g/dl, and titrated thereafter to maintain hemoglobin levels between 10 and 12 g/dl. However, no general consensus exists regarding the use of EPO, particular concerning optimal dosing, treatment benefits, potential risks and cost-effectiveness, and the cost of EPO is not reimbursed in many European countries [109,110]. Anemia is more profound during PI-base triple therapy than during PegIFN/RBV treatment. In a prospective study, which compared EPO administration vs. ribavirin dose reduction in response to anemia during BOC-based triple therapy, SVR rate was unaffected by ribavirin dose reduction. The results imply that ribavirin dose reduction should be the initial response to anemia in this setting, and

that anemia-driven dose reduction does not compromise the likelihood of SVR [111].

At the moment, there is no clear evidence to indicate that neutropenia during PegIFN/RBV therapy has adverse effects. While administration of granulocyte colony stimulating factor (G-CSF) may enable patients to remain on or resume optimal HCV therapy, in a systematic review there was weak evidence that this improves the likelihood of SVR compared with IFN dose reduction. Adverse effects of G-CSF are mild. An economic evaluation was inconclusive [112].

Treatment discontinuation rates due to thrombocytopenia are rare and patients with low platelet counts can generally be initiated on PegIFN/RBV therapy without an increase in major bleeding episodes. Thrombopoietin receptor agonists can raise blood platelet counts. Two are currently available i.e. romiplostim and eltrombopag. The latter has been shown to increase platelet counts in thrombocytopenic patients with HCV-related cirrhosis [113]. Both agents have been granted marketing authorization for use in patients with primary immune thrombocytopenia unresponsive to conventional treatments. Clinical trials with these agonists are ongoing in HCV-related thrombocytopenia [114]. There is FDA approval for eltrombopag to be used to initiate and maintain IFN- $\alpha$ -based antiviral treatment of HCV in patients with thrombocytopenia. Approval was based solely on data derived from studies of dual PegIFN/RBV therapy. Portal vein thrombosis is a potential and feared complication of raised platelet counts in this setting, particularly in patients with advanced cirrhosis. Thus, the aim of supportive therapy should be to raise platelet counts to a safe level but not into the normal range.

**Antidepressants.** Depression has a severe adverse impact on health-related quality of life during PegIFN/RBV therapy and was the most frequent reason for treatment discontinuation in the pivotal trials. Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy initiation in order to assess the risk. They should be under psychiatry follow-up thereafter if needed. Antidepressant therapy should be initiated during therapy if felt appropriate, and appropriate follow-up is required to decide whether IFN treatment interruption is needed.

Poorer social functioning is associated with new-onset depression during IFN treatment. Psychiatric co-morbidity is not associated with lower adherence, reduced treatment completion, or reduced SVR during IFN treatment [218]. Relative psychiatric contraindications to HCV therapy include acute major and uncontrolled psychiatric disorders. Although data are conflicting, studies show that prophylactic antidepressants can reduce IFN-induced depression, particularly in those with previous or ongoing depression. Depression-specific symptoms are highly responsive to serotonergic antidepressants. IFN-associated psychiatric AEs can be managed without dose adjustments or discontinuation of IFN [218]. Irritability and anxiety resulting from IFN-induced sleep deprivation should not be confused with depression and should be adequately treated with anxiolytics rather than with hypnotics or antidepressants [115].

## Clinical Practice Guidelines

### Recommendations

- Full adherence to all antiviral drugs should be the objective in order to optimize SVR rates and to reduce the risk of emergence of specific drug resistance (**recommendation A1**)
- Body weight adversely influences the response to pegylated IFN- $\alpha$  and ribavirin (**recommendation A2**). Body weight reduction in overweight patients prior to therapy may increase likelihood of SVR (**recommendation C2**)
- Insulin resistance is associated with treatment failure for dual therapy (**recommendation B2**). Insulin sensitizers have no proven efficacy in improving SVR rates in insulin-resistant patients (**recommendation C2**)
- Patients should be counselled to abstain from alcohol during antiviral therapy (**recommendation C2**)
- In dual therapy, the use of EPO when the hemoglobin level falls below 10 g/dl may reduce the need to reduce ribavirin dose (which may, in turn, have reduced the chance of achieving SVR) (**recommendation C2**)
- In patients receiving BOC/TVR-based triple therapy, ribavirin dose reduction should be the initial response to significant anemia (**recommendation B1**)
- There is no evidence that neutropenia during PegIFN/RBV therapy is associated with more frequent infection episodes (**recommendation C2**), or that the use of G-CSF reduces the rate of infections and/or improves SVR rates (**recommendation B2**)
- Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy (**recommendation C2**). Patients who develop depression during therapy should be treated with antidepressants. Preventive antidepressant therapy in selected subjects may reduce the incidence of depression during treatment, without any impact on the SVR (**recommendation C2**)

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

Non-cirrhotic patients who achieve an SVR should be retested for HCV RNA at 48 weeks post-treatment. If HCV RNA is still not detected, the infection can be considered as definitely eradicated and HCV RNA need not be retested. As hypothyroidism may occur after stopping therapy, TSH levels should also be assessed 1 and 2 years after treatment. Patients with pre-existing cofactors of liver disease (notably, history of alcohol drinking and/or type 2 diabetes) should be carefully and periodically subjected to a thorough clinical assessment, as needed.

Cirrhotic patients who achieve an SVR should remain under surveillance for HCC every 6 months by ultrasound, and for oesophageal varices by endoscopy if varices were present at pre-treatment endoscopy (though first variceal bleed is seldom observed after SVR). The presence of cofactors of liver disease, such as history of alcohol drinking and/or type 2 diabetes may determine that additional assessments are necessary.

### Re-infection following successful HCV treatment

There remains some concern that re-infection due to recurrent or persistent risk behaviour may negate the potential benefit of treatment. Reported rates of re-infection following successful HCV treatment among patients at high risk, such as PWID, are low, with estimates of 1–5% risk per year [116–120,218].

### Recommendations

- Non-cirrhotic patients with SVR should be retested for ALT and HCV RNA at 48 weeks post-treatment, then discharged if ALT is normal and HCV RNA is negative (**recommendation C2**)
- Cirrhotic patients with SVR should undergo surveillance for HCC every 6 months by means of ultrasound (**recommendation B1**)
- Guidelines for management of portal hypertension and varices should be implemented, though index variceal bleed is seldom seen in low-risk patients after the achievement of SVR (unless additional causes for ongoing liver damage are present and persist) (**recommendation A2**)
- Patients with ongoing drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection (**recommendation B1**)
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on PWID with ongoing risk behaviour (**recommendation B2**)

### Retreatment of non-sustained virological responders to pegylated IFN- and ribavirin

There are a substantial number of patients with genotype 1 hepatitis C who have had previous therapy with pegylated or standard IFN- $\alpha$  and ribavirin who have not achieved an SVR with that therapy. These patients can broadly be divided into three groups according to the pattern of response and virological failure during dual therapy. This terminology is now routinely applied in patient selection criteria for clinical trials, and in description of outcomes of clinical trials.

- (1) **Virological relapse:** Patients who have undetectable HCV RNA at the end of treatment, but do not achieve an SVR.
- (2) **Virological partial response:** Patients who have a  $>2 \log_{10}$  IU/ml drop in HCV RNA by 12 weeks of treatment, but never achieve undetectable HCV RNA.

- (3) **Virological null response:** Patients who have a  $<2 \log_{10}$  - IU/ml drop in HCV RNA by 12 weeks of treatment.

It should be acknowledged that a sizable proportion of patients with a history of PegIFN/RBV treatment failure do not have a precise record of their modality of non-response.

HCV genotype 1 patients who fail to achieve SVR with PegIFN/RBV have a small likelihood of achieving an SVR when re-treated with the same drugs at the same doses. The likelihood does not exceed 10–15% for prior null responders and 30–40% for response/relapsers. BOC and TVR are not licensed for genotypes other than 1. Non-genotype 1 patients can thus be retreated with PegIFN/RBV if they have an urgent indication for therapy and/or if there is evidence of under-exposure to either pegylated IFN- $\alpha$  or ribavirin during the first course of therapy (due to dose adjustments or poor adherence). Longer retreatment durations (48 weeks for genotypes 2 and 3, 72 weeks for genotype 4 patients) can be considered, especially for patients with DVR in the first cycle of treatment.

Maintenance therapy with a low dose of pegylated IFN- $\alpha$  is not recommended as it has shown no general efficacy in preventing chronic hepatitis C complications in the long-term. With the current clinical development of a number of new drugs for the treatment of chronic HCV infection, it is recommended that patients who failed to respond to a first course of PegIFN/RBV should be included in clinical trials with these new drugs if possible.

*Triple therapy for genotype 1 patients who experienced virological failure during previous dual PegIFN/RBV therapy – results of phase III studies with BOC and TVR*

Phase II and III studies have now been conducted using BOC and TVR in patients who have not achieved an SVR despite prior treatment with dual antiviral therapy. The RESPOND-2 study, using BOC, enrolled a total of 403 patients with previous relapse or partial response [121]. Patients with previous null response were not included in this study. All patients were treated with lead-in treatment for 4 weeks with PegIFN/RBV. Patients were then randomized to three groups. Group 1 received PegIFN/RBV for 44 additional weeks (total 48 weeks). Group 2 received response-guided therapy, with all patients receiving PegIFN/RBV and BOC for 32 additional weeks (up to week 36). Those patients in group 2 with undetectable HCV RNA at week 8 and 12 completed therapy at week 36, whereas those patients who had detectable HCV RNA at week 8 but were negative at week 12 continued PegIFN/RBV alone from week 36 until week 48. Group 3 received PegIFN/RBV and BOC for an additional 44 weeks. SVR rates were 21%, 59%, and 66% in groups 1, 2, and 3 respectively. Subgroup analyses showed SVR rates in patients with previous relapse of 29%, 69%, and 75%, and in patients with previous partial response of 7%, 40%, and 52% in groups 1, 2, and 3 respectively.

In the REALIZE study, using TVR, 663 patients with previous relapse, partial response or null response were randomized into three groups [122]. The PR48 group (control) received PegIFN/RBV for 48 weeks, the T12PR48 group received PegIFN/RBV for 48 weeks with TVR (i.e. triple therapy) for the first 12 weeks, and the lead-in T12PR48 group received the same as T12PR48 but preceded by 4 weeks lead-in with PegIFN/RBV. Overall SVR rates were 17%, 64%, and 66% for the 3 groups respectively. Subgroup analysis indicated SVR rates of 24%, 83%, and 88% for prior relapsers, 15%, 59%, and 54% for prior partial responders, and 5%, 29%, and 33% for prior null responders.

In summary, there is a significant benefit in retreatment by PI-containing triple therapy of patients who have previously had virological failure with PegIFN/RBV therapy. The benefits of triple therapy over dual therapy are observed for patients with prior relapse, partial response and null response patterns of failure. The regimens used for BOC and TVR in the two studies are quite different, but achieved similar SVR rates. BOC has not been used extensively in patients with a prior null response. The PROVIDE study of patients who were in the control arms of phase II or III studies and who were classified there as null responders, and were then re-treated with BOC triple therapy, showed an SVR rate of 38%, with better results in those having a  $>1 \log$  drop in HCV RNA during the 4 week lead-in [123].

Cirrhotic patients had inferior outcomes in all treatment groups and response-guided therapy is not licensed for cirrhotic patients, irrespective of the prior treatment response to dual therapy. For non-cirrhotic relapsers, response-guided therapy can be used with either drug. Prior partial or null responders require a full duration of therapy with either drug and response-guided therapy should not be used.

The stopping rules for futility are identical to those applied in treatment-naïve patients for both BOC and TVR. Treatment failure is strongly associated with the emergence of viral resistance. The long term significance of viral resistance is unknown but, in patients with a low chance of response to PI-based triple therapy (cirrhotic prior null responders), the balance of potential for cure should be set against the on-going and rapid development of new oral antivirals and the possibility that failed PI treatment may have an impact on the effectiveness of future agents (by selection of PI-resistant species).

Patients failing to respond to BOC should not be retreated with TVR or *vice versa*.

*Recommendations*

- Patients infected with HCV genotype 1 who failed to eradicate HCV on prior therapy with PegIFN/RBV should be considered for re-treatment with the triple combination of PegIFN/RBV and a PI (**recommendation A1**)
- The previous response to IFN-based therapy is an important predictor of success of triple therapy, with relapsers having higher cure rates than partial responders, who in turn have higher cure rates than null responders. If the pattern of prior response to dual therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy (**recommendation A2**)
- Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with either PI (**recommendation B2**)
- Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated IFN- $\alpha$ , with or without ribavirin, can be re-treated with pegylated IFN- $\alpha$  and ribavirin (**recommendation B2**)

## Clinical Practice Guidelines

### Treatment of patients with severe liver disease

#### Compensated cirrhosis

Treatment is strongly recommended for patients with compensated cirrhosis, in order to prevent the complications of chronic HCV infection that occur exclusively in this group in the short to mid-term. Indeed, large cohort studies and meta-analyses have shown that an SVR in patients with advanced fibrosis is associated with a significant decrease of the incidence of clinical decompensation and HCC [124,125]. However, the SVR rates with PegIFN/RBV are lower in patients with advanced fibrosis or cirrhosis than in patients with mild to moderate fibrosis. Though superior to dual therapy, SVR rates in response to PI-inclusive triple therapy of genotype 1 patients are also negatively affected by fibrosis stage.

Particular care should be taken in monitoring and management of the side-effects of dual and triple therapy in this group of patients, who are generally older and have a worse tolerance than patients with less advanced liver disease. Emerging data emphasise a significant rate of side-effects and AEs during treatment of cirrhotic patients with PI-containing regimens, especially those with a platelet count  $<100,000/\text{mm}^3$  and serum albumin levels  $<35 \text{ g/dl}$  at baseline [36]. For this reason PI-based triple therapy in patients with compensated advanced liver disease should be managed in reference centres. There is no role for current triple therapy in patients with decompensated liver disease. Due to portal hypertension and hypersplenism, leukocyte and platelet counts at baseline may be low in cirrhotic patients. Hematological side effects are more frequent in cirrhotic than in non-cirrhotic patients [126], and may contraindicate therapy. Growth factors might be particularly useful in this group. For instance, the thrombopoietin agonist eltrombopag has been used to raise the platelet count in patients with HCV cirrhosis, and higher platelet counts may enable administration of IFN- $\alpha$  [113]. There may be a risk of portal vein thrombosis, particularly if high platelet counts are achieved for patients with advanced cirrhosis. Therefore, eltrombopag should be used cautiously and simply to raise platelets to a low but safer level.

Irrespective of the achievement of an SVR, patients with cirrhosis should undergo regular surveillance for the occurrence of HCC and for portal hypertension, as the risk of complications is decreased but not abolished when HCV infection has been eradicated.

#### Recommendations

- Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications (**recommendation B2**)
- Monitoring and management of side-effects, especially in patients with portal hypertension, low platelet count and low serum albumin, should be done particularly carefully. Growth factors may be useful in this group (**recommendation C2**)
- Patients with cirrhosis should undergo regular surveillance for HCC, irrespective of SVR (**recommendation A1**)

#### Patients with an indication for liver transplantation

Liver transplantation (LT) is the treatment of choice for patients with end-stage liver disease. However, hepatitis C recurrence due to graft reinfection is universal after transplantation [127].

Antiviral therapy in patients awaiting transplantation prevents graft reinfection if SVR is achieved [128–130]. More than half of patients have contraindications to the use of PegIFN/RBV, and the results of therapy are generally poor in this group of individuals with liver disease in a very advanced phase. Antiviral therapy is indicated in patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC. In patients with Child-Pugh B cirrhosis, antiviral therapy may be offered on an individual basis in experienced centres, preferentially in patients with predictors of good response, such as patients infected with HCV genotypes 2 or 3, or patients with a low baseline HCV RNA level. Patients with Child-Pugh C cirrhosis should not be treated with IFN- $\alpha$ -based regimens, due to a high risk of life-threatening complications [128–130].

In those individuals with severe liver disease who can be treated before transplantation, antiviral therapy should be started as soon as possible, with the goal of achieving an SVR [130], or at least to achieve serum HCV RNA negativity at the time of transplantation [128,129]. Treatment can be started at low doses of pegylated IFN- $\alpha$  and ribavirin, following a low accelerated dose regimen, or at full doses. In the latter case, dose reductions and treatment interruptions are required in more than 50% of cases. Hematological AEs (anemia, neutropenia, and thrombocytopenia) are particularly frequent in patients with end-stage liver disease because of portal hypertension. Treatment therefore requires close monitoring and dose modifications. The use of growth factors (EPO and filgrastim) might be helpful to control hematological side effects. There are no published data to describe the use of PI-based regimens in the treatment of waiting list patients with very advanced liver disease. Both TVR and BOC exhibit hematologic toxicity and an increased risk of severe infections, so the side-effect profile in this patient group may be particularly challenging.

#### Recommendations

- In patients awaiting transplantation, antiviral therapy, when feasible, prevents graft re-infection if an SVR is achieved (**recommendation B2**)
- Antiviral therapy can be started while awaiting LT, with the goal of achieving an SVR or at least serum HCV RNA negativity before LT (**recommendation C2**)
- In patients with Child-Pugh B cirrhosis, antiviral therapy is offered on an individual basis in experienced centres, preferentially in patients with predictors of good response (**recommendation C2**)
- Patients with Child-Pugh C cirrhosis should not be treated with the current IFN- $\alpha$ -based antiviral regimens, due to a high risk of life-threatening complications (**recommendation A1**)
- Treatment can be started at low doses of pegylated IFN- $\alpha$  and ribavirin, following a low accelerated dose regimen, or at full doses. In the latter case, dose reductions and treatment interruptions are required in more than 50% of cases (**recommendation C2**)

*Post-liver transplantation recurrence*

HCV infection recurrence is universal in patients with detectable HCV RNA at the time of liver transplantation [127]. The course of HCV-related liver disease is accelerated in LT recipients and approximately one third of them develop cirrhosis within 5 years following transplantation [131,132]. Successful therapy has been shown to have a positive impact on both graft and patient survival [133].

Patients with post-transplant recurrence of HCV infection should be considered for therapy once chronic hepatitis is established and histologically proven. These patients generally have a better background for therapy than at the acute stage of re-infection and related hepatitis, i.e. less immunosuppression, an improved clinical status that ensures better tolerability, and a lower risk of triggering graft rejection upon IFN- $\alpha$ -based therapy. The presence of significant fibrosis or portal hypertension one year after transplantation is predictive of rapid disease progression and graft loss, and urgently indicates antiviral treatment [134,135]. In patients with less advanced disease, such as those with fibrosis restricted to the portal tract and no portal hypertension, the indication of therapy must be weighted to the likelihood of a sustained viral eradication and to the risk of antiviral treatment-associated complications. Nevertheless, patients with less severe graft fibrosis have a better chance of an SVR than those with more advanced disease.

Published efficacy data are limited to the experience with Peg-IFN/RBV dual therapy, though preliminary reports of PI-based triple therapy for post-transplant patients are emerging. With dual therapy, the likelihood of an SVR in the post-transplant setting is in the order of 30% overall, with better response rates in patients infected with HCV genotype 2 or 3 than genotype 1 [136–138]. As renal dysfunction is common in LT recipients, ribavirin doses need to be adjusted accordingly. The relatively low efficacy of PegIFN/RBV therapy in HCV-infected transplant recipients is at least partly due to the high incidence of side effects that demand frequent dose adjustments and treatment interruptions. Anemia is the most common cause of treatment interruption in this setting (10–40% of the patients) [136,137]. Therefore, the use of EPO has been recommended, but without supporting evidence to show that SVR rates are enhanced. Liver dysfunction may be observed during IFN- $\alpha$  therapy, and graft rejection is an important cause of this [139]. Whenever liver tests deteriorate significantly during the course of antiviral therapy, a liver biopsy should be performed to diagnose the cause and to guide treatment decisions. There is no evidence for a benefit of low-dose pegylated IFN- $\alpha$  maintenance therapy in patients who do not achieve an SVR with dual therapy.

Drug-drug interactions are particularly important in the post-transplant setting. IFN- $\alpha$  and ribavirin are relatively free of significant interactions. The PIs, TVR and BOC, are potent inhibitors of hepatic cytochrome P450 3A4 (CYP3A4), the main enzyme responsible for tacrolimus and cyclosporin metabolism. Co-administration of these drugs with a PI causes a dramatic increase in exposure to the tacrolimus or cyclosporin [140,141]. Thus, commencement of a PI-containing regimen requires an immediate and profound reduction of cyclosporin or tacrolimus dose. In addition, cessation of the PI requires an immediate restoration of pre-treatment immunosuppressive dose. Emerging, but as yet unpublished experience confirms that PI-based treatment

can be delivered with caution in the post-transplant setting [142].

*Recommendations*

- Patients with post-transplant recurrence of HCV infection should be considered for therapy once chronic hepatitis is established and histologically proven (**recommendation B2**). Significant fibrosis or portal hypertension one year after transplantation predict rapid disease progression and graft loss, and indicate more urgent antiviral treatment (**recommendation B2**)
- For patients with HCV genotype 1 infection, PI-based triple therapy can be used, but frequent monitoring and dose adjustment of tacrolimus and cyclosporin are required (**recommendation B1**)
- Graft rejection is rare but may occur during IFN- $\alpha$  treatment (**recommendation C2**). A liver biopsy should be performed whenever liver tests worsen on antiviral therapy (**recommendation C2**)

*Treatment of special groups*

*HIV co-infection*

Progression of liver disease is accelerated in patients with HIV-HCV co-infection, in particular for those with a low CD4-positive cell count and impaired immune function. For this reason, early antiretroviral therapy should be considered in patients with HIV-HCV co-infection [143]. If the patient has severe immunodeficiency, with a CD4-positive cell count <200 cells/ $\mu$ l, the CD4 count should be improved using highly active antiretroviral therapy prior to commencing anti-HCV treatment. During PegIFN/RBV treatment, didanosine, stavudine, and zidovudine should be avoided. The role of abacavir is debated and recently published data do not contraindicate its use with ribavirin [144]. Liver disease severity should be assessed prior to therapy by means of a liver biopsy or by non-invasive assessment (serological tests or LSM).

Indications for HCV treatment are identical to those in patients with HCV mono-infection [145]. The same pegylated IFN- $\alpha$  regimen should be used in HIV-co-infected patients as in patients without HIV infection. For patients receiving dual therapy with PegIFN/RBV, published data do not clearly define the preferred dose of ribavirin and the optimal duration of treatment. For genotypes 2 and 3, fixed dose 800 mg/day of ribavirin can be recommended. For HCV genotype 1 patients, the total treatment exposure to ribavirin is associated with the likelihood of achieving SVR [146]. However, the efficacy of weight-based (1 to 1.2 g/day) ribavirin is not clearly superior to fixed dose (800 mg/day) treatment [147]. The higher dose is associated with greater hemoglobin reduction. For easy-to-treat HCV genotypes, a randomized comparison of 48 vs. 24 weeks of treatment has not

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been made. Monitoring of viral kinetics on treatment should be performed and the patients should be treated according to their virological responses at weeks 4 and 12. For patients with favourable genotypes who achieve serum HCV RNA negativity at 4 weeks (RVR), a 24 week duration of therapy may be sufficient. For those who achieve an EVR, but not an RVR, 48 weeks duration is recommended regardless of HCV genotype. For a given genotype treated with PegIFN/RBV dual therapy, rates of SVR are generally lower for co-infected than for HCV mono-infected patients.

HIV-positive patients who are infected with HCV genotype 1, whether HCV treatment-naïve or treatment-experienced, should be considered for HCV antiviral triple therapy with pegylated IFN- $\alpha$ , ribavirin, and TVR or BOC. Recently presented data show that these combinations can be used safely with selected concomitantly-given HIV antiviral regimens, and that SVR rates are enhanced by the inclusion of the HCV PI [148,149]. In those studies, permitted HIV antivirals included nucleoside analogues, efavirenz, raltegravir and selected ritonavir-boosted HIV protease inhibitors. Emerging data will clarify the clinically relevant drug-drug interactions between TVR, BOC and the established HIV antivirals. Collaborative management including the hepatologist, the HIV physician, and the pharmacist, and awareness of known and potential drug-drug interactions, will be the key to safe and successful use of these and future HCV DAAs in HIV-positive patients [150].

Consensus guidelines for the management of acute HCV in HIV-infected individuals were published in 2011 [151]. Regardless of infecting genotype, the guideline recommended the combination of pegylated IFN- $\alpha$  and weight-based ribavirin for treatment. Duration of treatment can be determined by kinetics of response, with 24 weeks of treatment given to those with serum RNA negativity at 4 weeks (RVR), and 48 weeks for those with first serum RNA negativity delayed beyond 4 weeks.

### Recommendations

- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection **(recommendation B2)**
- The same pegylated IFN- $\alpha$  regimen can be used in HIV-co-infected patients as in patients without HIV infection, though prolongation of treatment can be considered for patients with genotypes 2 and 3 who exhibit slow early viral kinetics **(recommendation B2)**
- HIV patients who are co-infected with HCV genotype 1 should be considered for TVR-containing or BOC-containing triple therapy, but special care should be taken to minimise or avoid potential drug-drug interactions **(recommendation B1)**
- HIV patients with a diagnosis of acute HCV infection should be treated with PegIFN/RBV, with duration dependent on viral kinetics independent of HCV genotype **(recommendation B2)**

### HBV co-infection

In patients with HCV-HBV co-infection, the HBV DNA level is often low or undetectable, although it may fluctuate widely, and HCV is usually the main driver of chronic hepatitis activity. Patients should be carefully characterized for the replicative status of both HBV and HCV, and hepatitis delta virus infection should be sought. When HCV is replicating and causes liver disease, it should be treated with PegIFN/RBV following the same rules as applied to mono-infected patients. The SVR rates in this group are broadly comparable to those in HCV mono-infected patients, or even higher [152]. There is a potential risk of HBV reactivation during or after HCV clearance [153]. In that case, or if HBV replication is detectable at a significant level, concurrent HBV nucleoside/nucleotide analogue therapy may be indicated, though there may be drug interactions with PIs. There is no information on the use of PI-based triple therapy in this population of patients, though HCV PIs should be used for treatment of patients who are co-infected by HBV and HCV genotype 1.

### Recommendations

- Patients should be treated with pegylated IFN- $\alpha$ , ribavirin, and PIs following the same rules as mono-infected patients **(recommendation B2)**
- If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy may be indicated **(recommendation C2)**

### Treatment of patients with co-morbidities

**Hemodialysis patients.** HCV infection is prevalent in the hemodialysis population and is associated with an increased risk for all-cause and liver-related mortality. Cardiovascular disease remains, however, the main cause of death in dialysis patients irrespective of HCV status. As in all settings, the candidacy of a dialysis patient for antiviral therapy requires special consideration of co-morbid conditions, since the liver disease may have little impact on predicted morbidity and mortality of that patient. HCV-associated liver damage may be accelerated by immunosuppression, and IFN- $\alpha$  may precipitate renal graft rejection. For these reasons, antiviral therapy should be considered for all hemodialysis patients who will be candidates for renal transplantation. Reflecting concerns about the use of ribavirin in this setting, most published data describe the use of IFN- $\alpha$  monotherapy, mostly in small studies using conventional IFN- $\alpha$  [154]. Pegylated IFN- $\alpha$  can be used and may be associated with improved SVR rates [155,156]. Pegylated IFN- $\alpha$  accumulates in patients with advanced renal dysfunction, so dose reduction is required. The recommended dose of PEG IFN- $\alpha$  2a in this setting is 135  $\mu$ g/week. Combination treatment with PegIFN/RBV can be considered by experienced physicians, and may enhance SVR rates [157]. Individualized ribavirin dosing of 200 mg/day or 200 mg/every other day or 200 mg thrice weekly after hemodialysis, and substantial hematopoietic support is essential. Pharmacokinetic studies in patients with end-stage renal disease reveal no significant impact of renal dysfunction on drug expo-

sure, suggesting that both TVR and BOC might be used to treat HCV infection in this setting [158,159]. There are no published data to describe the safety and efficacy of PI-inclusive antiviral treatment of renal failure patients with HCV, so clinical studies in this population are essential. A recently presented study that included 36 treatment-naïve genotype 1 hemodialysis patients showed that TVR-containing triple therapy had superior efficacy than PegIFN/RBV dual therapy, but triple therapy was associated with more anemia [160].

*Recommendations*

- Hemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy **(recommendation A2)**
- Antiviral treatment should comprise pegylated IFN- $\alpha$  at an appropriately reduced dose **(recommendation A1)**
- Ribavirin can be used at very low doses, but with caution **(recommendation B2)**
- BOC and TVR can be used with caution in patients with impaired creatinine clearance, and dose adjustment is probably unnecessary **(recommendation C1)**

*Non-hepatic solid organ transplant recipients.* HCV infection in kidney transplant recipients may be associated with an increased rate of liver fibrosis progression. Most studies of kidney transplant cohorts show that HCV positivity is associated with impaired renal graft and patient survival. 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 [161]. As cirrhosis is an important predictor of poor post-transplant survival after kidney transplantation, it is advisable to make an assessment of liver fibrosis stage in all HCV-positive kidney transplant candidates [162]. For patients with established cirrhosis who fail (or are unsuitable for) HCV antiviral treatment, isolated renal transplantation may be contraindicated and consideration should be given to combined liver and kidney transplantation [163].

Treatment of chronic HCV infection with PegIFN/RBV in kidney transplant recipients is associated with a risk of acute or chronic cellular rejection of 30% or more, resulting in graft loss and reduced patient survival. Therefore, PegIFN/RBV therapy has additional risks in these patients, and the decision to give antiviral therapy must consider these risks. Where possible, patients with an indication for kidney transplantation should be treated for hepatitis C prior to transplantation [164].

Data on HCV infection after heart transplantation are scarce and controversial, with studies showing unaltered or decreased survival rates in patients infected with HCV. No studies on the risks and benefits of antiviral therapy are available in these patients and the risk of graft rejection on IFN- $\alpha$  treatment remains unclear. In this context, treatment of chronic HCV infection in heart transplant recipients cannot be recommended and the indication should be assessed on a case-by-case basis, if HCV infection is life-threatening.

International guidelines list chronic HCV infection as a contraindication to lung transplantation [165]. Treatment of lung transplant candidates before transplantation has been recommended by some authors, but there is limited experience with this approach. No data are available on the impact of HCV infection and its treatment after pancreas or small bowel transplantation.

*Recommendations*

- HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. Where possible, antiviral therapy should be given to potential transplant recipients before listing for renal transplantation **(recommendation B1)**
- IFN- $\alpha$ -based antiviral treatment is associated with a significant risk of renal graft rejection, and it should be avoided unless there is a powerful indication for antiviral treatment, e.g. aggressive cholestatic hepatitis **(recommendation A1)**

*Active drug addicts and patients on stable maintenance substitution.* Ageing cohorts of PWID with chronic HCV and low treatment uptake are making a significant contribution to the population with advanced liver disease and to liver-related mortality [166,167]. In several countries where PWID are the major population affected by HCV, 20–25% of deaths among HCV-infected individuals are from liver disease and 15–30% are from drug-related causes [17]. The prevalence of HCV among PWID is ~65% [168–170] and >80% among long-term PWID [169]. HCV genotypes 1a, 1b, and 3a are common among PWID [171], while 4d is common among PWID in Europe [172,173], and 6 is common in Southeast Asia [7]. The incidence of HCV in PWID is 5–45% *per annum* [174,175]. Factors associated with HCV among PWID include female gender [176], ethnicity [177], unstable housing [178], frequent injecting cocaine use [176,179], imprisonment [180], injecting networks [181] and borrowing injecting equipment [179]. High coverage of combined harm-reduction programs (e.g. opiate substitution treatment [OST] and needle exchange programs) can reduce HCV incidence [182,218].

Despite misconceptions among affected populations and health care workers, no liver toxicity is reported for heroin [183] or methadone [184]. Buprenorphine occasionally increases transaminases [185]. Methylenedioxymetamphetamine (MDMA)

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rarely causes acute liver failure due to direct liver toxicity [186] and little is known about methamphetamine-related liver toxicity [187]. Daily cannabis use may be associated with more advanced liver fibrosis, after adjustment for alcohol and age [188], and with liver steatosis [189]. Heavy alcohol consumption is associated with a higher risk of cirrhosis [190]. Tobacco smoking may increase inflammation and fibrosis progression [19], but further studies are needed [218].

HCV treatment can be considered for PWID, provided they wish to receive treatment and are able and willing to maintain regular appointments. Guidelines for pre-therapeutic assessment for HCV-infected individuals are available [17,24]. Modelling studies suggest that implementation of HCV treatment for PWID could reduce transmission [9,191]. A history of IDU and recent drug use at treatment initiation are not associated with reduced SVR and decisions to treat must be made on a case-by-case basis. PWID with ongoing social issues and/or with a history of psychiatric disease or with more frequent drug-use during therapy are at risk of lower adherence and reduced likelihood of achieving SVR and need to be monitored closely during therapy, and also need more supporting measures. Factors independently associated with impaired adherence and failure of treatment completion among drug users include lower levels of education and unstable housing [84]. Factors independently associated with lower SVR among drug users include poor social functioning [192], a history of untreated depression [193] and ongoing frequent drug use during treatment [193,218].

HCV-infected PWID often have complex social, medical and psychiatric comorbidities, complicating decisions around care [194]. Poor knowledge and inaccurate perceptions about HCV are barriers for accessing HCV care [195,196]. Factors associated with not receiving HCV treatment include older age [197], minority ethnicity [197], ongoing or former drug use [194,198–200], ongoing alcohol use [197,198], advanced liver disease [199], co-morbid medical disease [197,200], psychiatric disease [197,199] and opioid substitution therapy (OST) [194,198]. A number of these factors are relevant to PWID [218].

HCV treatment has been delivered successfully to drug users through various clinical models, including within general hospital liver disease and viral hepatitis clinics, drug detoxification clinics, OST clinics, prisons, and community-based clinics. Strategies to enhance treatment adherence were discussed in section 'Treatment adherence' [218].

In general, studies find that a history of IDU does not compromise adherence [84,85], treatment completion [84,201] or SVR. Indeed, recent drug use at treatment initiation has limited impact on adherence [84,85], treatment completion [202–204], or SVR [192,203–206]. However, one study has reported lower treatment completion in those with recent drug use at treatment initiation [202]. Occasional drug use during treatment does not seem to impact adherence [84], treatment completion [84,204], or SVR [204,206]. However, lower adherence [84,85] and SVR [94,207] has been observed

in persons with frequent drug use (daily/every other day) during treatment. When discontinuation occurs, it often occurs early during therapy [208]. In adherent patients, alcohol use has no negative impact on SVR [102]. HCV treatment does not have an impact on drug dependency treatment or increase drug use [206,218].

DAA clinical development programs have excluded individuals with active drug use, but many trials have included those on OST. DAA-based safety and treatment outcome data has not been presented on clinical trial sub-populations of individuals on OST. Drug-drug interaction studies have been undertaken with TVR and methadone [209] and buprenorphine [210], with no clinically important interactions observed. Interaction studies have also been undertaken for BOC with methadone and buprenorphine, and clinically significant changes in exposure to the methadone and buprenorphine were not observed [211,212,218].

In addition to OST, antidepressants, antipsychotics and sedatives are frequently used in patients or used by patients with addiction problems. Escitalopram and most probably citalopram can be used with both HCV PIs. Zolpidem can be considered safe. Because of CYP3A4 inhibition by the PIs, midazolam and alprazolam should not be coadministered with BOC and TVR. Pimozid should not be coadministered with BOC and TVR. CYP3A4 is also involved in the metabolism of sertraline and mirtazepine. In contrast, olanzapine can be considered without significant interaction. Fluoxetine and paroxetine appear safe with BOC and TVR [213–216,218].

Of course, pharmacokinetic studies on recreational and illicit drug use have not been performed. However the practical importance in patients with a background of drug use is evident. Heroin, as a 3,6-diacetyl derivative of morphine, is finally metabolized mainly by CYP3A4. Because of this, an increase of heroin levels is possible when BOC or TVR is used. Unfortunately no pharmacokinetic data are available. For tetrahydrocannabinol (THC) a profound interaction is not likely. The concomitant use of amphetamine (MDMA) and ecstasy (PMA, PMMA) should be avoided. The consequences of overdosing can be fatal due to hyperthermia, cardiac arrhythmia or liver failure. Because of the complexity of the metabolism of cocaine the effect of a concomitant use with BOC or TVR is difficult to predict and should be avoided. The same applies to crack cocaine use. Interactions of barbiturates and benzodiazepines with TVR and BOC may increase the levels of barbiturates and benzodiazepines (resulting in potentially life-threatening midazolam overdose), and also reduce the levels of TVR and BOC, thus affecting antiviral efficacy. In summary, illicit drug use should be avoided during antiviral treatment with TVR and BOC [217–219].

The proportion of patients with a history of IDU undergoing liver transplantation for HCV-related cirrhosis or HCC is 5–10% [220,221]. Relapse to drug use following transplantation is rare [220,221]. Selection criteria for liver transplantation include: 6–24 months of drug abstinence, controlled psychiatric disease and the presence of stable social support networks [221,222]. OST is not a contraindication [218,220,222–228].

## Recommendations

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

*Hemoglobinopathies.* The most frequent hemoglobinopathy 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. In the few published clinical trials, these patients had a higher incidence of anemia during PegIFN/RBV therapy. Therefore, they can be treated with standard combination therapy, but these complications should be carefully managed with growth factors and blood transfusions when needed [229].

Chronic HCV infection is also frequent in individuals with sickle cell anemia. No trials with antiviral therapy have been published in this population. Individual cases have been successfully treated with PegIFN/RBV. In the absence of published studies to examine the safety of BOC and TVR in the treatment of patients with hemoglobinopathies, there is no reason to consider that these drugs are specifically contraindicated. Both are associated with anemia when used with PegIFN/RBV, so blood transfusion may be needed.

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

Untreated patients with chronic hepatitis C and those who failed to respond to previous treatment should be regularly followed. The reason(s) for non-treatment and treatment failure should be clearly documented. For patients who have failed prior treatment with PegIFN/RBV or PI-based triple therapy, the pattern of virological response and failure should be carefully documented. Review should include an assessment of patient suitability for clinical trials of investigational DAAs, and suitability for retreatment with newly licensed drugs, when available. Previous guidelines recommended performing a liver biopsy every 3 to 5 years. With non-invasive methods, more frequent screening can be performed. Thus, untreated patients should be assessed every 1 to 2 years with a non-invasive method. Patients with cirrhosis should undergo specific screening for HCC every 6 months.

#### Recommendations

- Untreated patients with chronic hepatitis C and those who failed prior treatment should be regularly followed (**recommendation C2**)
- Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals (**recommendation C2**)
- HCC screening must be continued indefinitely in patients with cirrhosis (**recommendation A2**)

### Treatment of acute hepatitis C

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

Patients with acute hepatitis C should be considered for antiviral therapy in order to prevent progression to chronic hepatitis C. High SVR rates (>90%) have been reported with pegylated IFN- $\alpha$  monotherapy, essentially in series of symptomatic patients, regardless of the HCV genotype. Combination therapy with ribavirin does not increase the SVR rate in this setting, but may be considered during treatment in patients with slow response and other negative predictors of treatment response [230–236]. No data are available on the use of triple therapy in this group.

The ideal time point for starting therapy has not been firmly established. Some investigators estimate that the onset of ALT elevation, with or without clinical symptoms, may be the ideal time point for treatment [237–240]. It has also been suggested that patients should be followed with 4-weekly HCV RNA quantification and that only those who remain HCV positive at 12 weeks from onset should be treated [241]. The treatment of

acute hepatitis C should be based on pegylated IFN- $\alpha$  monotherapy, i.e. pegylated IFN- $\alpha$ 2a, 180  $\mu$ g/week, or pegylated IFN- $\alpha$ 2b, 1.5  $\mu$ g/kg/week, for 24 weeks. Patients who fail to achieve an SVR with this regimen may be retreated for 48 weeks, with or without ribavirin at the usual doses. For those with genotype 1 infection who fail to respond to IFN- $\alpha$  monotherapy, PI-based triple therapy including TVR or BOC could also be considered.

There is currently no indication for administering IFN- $\alpha$  as post-exposure prophylaxis in the absence of documented HCV transmission.

#### Recommendations

- Pegylated IFN- $\alpha$  monotherapy (pegylated IFN- $\alpha$ 2a, 180  $\mu$ g/week or pegylated IFN- $\alpha$ 2b, 1.5  $\mu$ g/kg/week, for 24 weeks) is recommended in patients with acute hepatitis C, and achieves SVR in as many as 90% of treated patients (**recommendation B2**)
- Patients failing to respond to monotherapy should be re-treated with PegIFN/RBV or PI-based triple therapy (**recommendation C2**)

### Perspective of new and emerging treatments

The protease inhibitors, TVR and BOC, have changed but not transformed the management of chronic HCV infection. They are licensed only for genotype 1 infection, and the outcome of triple therapy remains dependent on the use of IFN and on the sensitivity of the patient and the virus to treatment with IFN and ribavirin. Thus, the largest impact has been on treatment of previously untreated HCV genotype 1 patients and on treatment of those HCV genotype 1 patients who relapsed after prior treatment with PegIFN/RBV. Side-effects of triple therapy are significant, particularly in patients with cirrhosis. Response rates to triple therapy for patients with prior partial and null response to PegIFN/RBV remain disappointing, particularly for those with cirrhosis, and despite longer duration of therapy.

Meanwhile, we are feasting on the results of trials of DAA drugs and combinations, including IFN-free regimens [25]. SVR rates in excess of 90% for treatment duration of 12 weeks have been reported. Most studies continue to focus on genotype 1 infection, and most exclude cirrhosis. Nevertheless, doctors and patients share optimism that emerging antivirals will treat all genotypes, with cure for the majority and with few side-effects in short duration therapy. Reflecting that optimism, many doctors and patients with all HCV genotypes are choosing to defer, rather than to proceed with dual or triple therapy. An assessment of liver disease stage is probably the main factor that influences that choice. However, the threshold for deferral vs. immediate treatment varies between experts, and is probably shifting in response to the most recent trial results. As a consequence of the shortcomings of dual and triple therapy, and reflecting our optimism about drugs in development, our clinics are swelling with patients who have high but realistic expectations that they will be cured by a painless antiviral regimen, and in the not-too-distant future. Where possible, patients should be

encouraged to participate in clinical trials, which are essential for the timely development and licensing of new antiviral drugs and regimens.

It seems likely that there will be a steady flow of drugs to the market. However, many of these drugs will have had little exposure to the difficult-to-treat groups with cirrhosis, liver failure, renal failure, or HIV co-infection and other forms of immunosuppression. Nor are they likely to have been much exposed to patients with other co-morbidities that demand treatment with a range of drugs that will interact in a variety of ways with the emerging antivirals. We need to be cautious in raising the expectations of these difficult-to-treat patients. We also need to focus on the likely future problems of service provision, an issue not addressed to a significant extent by these guidelines. The accumulation of difficult patients, combined with the “warehousing” of the relatively easy-to-treat patients, followed by the marketing and availability of a range of DAA regimens, will create an enormous practical and logistic challenge. Physicians need to acquire the appropriate expertise, develop an appropriate service for delivery and guarantee adequate and proportionate funding to manage the cohort. Failure to deliver on any of these aspects will limit the enormous capacity that recent and on-going developments in drug development have the potential to deliver.

**Conflict of interest**

Alessio Aghemo: Grant and research support: Roche, Gilead Sciences. Advisory Board: Roche. Speaking and teaching: Roche, Janssen, Merck.

Helmut Diepolder: no relevant disclosures.

David Mutimer: Advisor to Roche, MSD, Janssen, Gilead, Boehringer-Ingelheim, BMS, AbbVie.

Francesco Negro: Advisor for Roche, MSD, Janssen, Gilead. Unrestricted research funding from Roche, Novartis.

Geert Robaey: Advisory Board: Merck, Gilead, Janssen. Speaking and Teaching: Janssen, Merck. Grant and research support: Merck.

Stephen Ryder has attended Advisory Boards and/or acted as Consultant for Janssen, MSD, Roche, Boehringer.

Fabien Zoulim: Advisor to Janssen, BMS and Gilead.

**Acknowledgements**

The contributors thank Andrew Ferguson and Lampyrismedia (<http://lampyrismedia.com/>) for editorial assistance.

**References**

[1] EASL Clinical Practice Guidelines. Management of hepatitis C virus infection. *J Hepatol* 2011;55:245–264.  
 [2] Lavanchy D. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect* 2011;17:107–115.  
 [3] Hepatitis C. *Wkly Epidemiol Rec* 1997;72:65–69.  
 [4] Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. *Liver Int* 2011;31:30–60.  
 [5] Blachier M, Leleu H, Peck-Radosavljevic M, Valla D-C, Roudot-Thoraval F. The burden of liver disease in Europe, a review of available epidemiological data. Geneva: European Association for the Study of the Liver; 2013. [www.easl.eu](http://www.easl.eu).  
 [6] Rantala M, van de Laar M. Surveillance and epidemiology of hepatitis B and C in Europe – a review. *Eur Surveill* 2008;13(21): <<http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18880>>.

[7] Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, et al. Expanded classification of hepatitis C Virus into 7 genotypes and 67 Subtypes: updated criteria and assignment web resource. *Hepatology* 2013. <http://dx.doi.org/10.1002/hep.26744> [Epub ahead of print, PubMed PMID: 24115039].  
 [8] Antaki N, Craxi A, Kamal S, Mouchari R, Van der Merwe S, Haffar S, et al. The neglected hepatitis C virus genotypes 4, 5, and 6: an international consensus report. *Liver Int* 2010;30:342–355.  
 [9] Murphy D, Chamberland J, Dandavino R, Sablon E. A new genotype of hepatitis C virus originating from central Africa. *Hepatology* 2007;46:623A.  
 [10] Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *J Hepatol* 2011;54:1137–1144.  
 [11] van de Laar TJ, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. *AIDS* 2010;24:1799–1812.  
 [12] Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. *J Hepatol* 2008;48:148–162.  
 [13] Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008;48:418–431.  
 [14] John-Baptiste A, Krahn M, Heathcote J, Laporte A, Tomlinson G. The natural history of hepatitis C infection acquired through injection drug use: meta-analysis and meta-regression. *J Hepatol* 2010;53:245–251.  
 [15] Yang JD, Roberts LR. Hepatocellular carcinoma: a global view. *Nat Rev Gastroenterol Hepatol* 2010;7:448–458.  
 [16] Hepatitis B and C in the EU neighbourhood: prevalence, burden of disease and screening policies. Stockholm: European Centre for Disease Prevention and Control; 2010.  
 [17] McDonald SA, Hutchinson SJ, Bird SM, Mills PR, Dillon J, Bloor M, et al. A population-based record linkage study of mortality in hepatitis C-diagnosed persons with or without HIV coinfection in Scotland. *Stat Methods Med Res* 2009;18:271–283.  
 [18] Grebely J, Dore GJ. What is killing people with hepatitis C virus infection? *Semin Liver Dis* 2011;31:331–339.  
 [19] Seeff LB. The history of the “natural history” of hepatitis C (1968–2009). *Liver Int* 2009;29:89–99.  
 [20] Mallat A, Hezode C, Lotersztajn S. Environmental factors as disease accelerators during chronic hepatitis C. *J Hepatol* 2008;48:657–665.  
 [21] Brunet L, Moodie EE, Rollet K, Cooper C, Walmsley S, Potter M, et al. Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: a longitudinal cohort analysis. *Clin Infect Dis* 2013;57:663–670.  
 [22] Costentin CE, Roudot-Thoraval F, Zafrani ES, Medkour F, Pawlowsky JM, Mallat A, et al. Association of caffeine intake and histological features of chronic hepatitis C. *J Hepatol* 2011;54:1123–1129.  
 [23] Modi AA, Feld JJ, Park Y, Kleiner DE, Everhart JE, Liang TJ, et al. Increased caffeine consumption is associated with reduced hepatic fibrosis. *Hepatology* 2010;51:201–209.  
 [24] Ohfuji S, Fukushima W, Tanaka T, Habu D, Tamori A, Sakaguchi H, et al. Coffee consumption and reduced risk of hepatocellular carcinoma among patients with chronic type C liver disease: a case-control study. *Hepatol Res* 2006;36:201–208.  
 [25] Manns MP, von Hahn T. Novel therapies for hepatitis C – one pill fits all? *Nat Rev Drug Discov* 2013;12:595–610.  
 [26] Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013;66:719–725.  
 [27] Chevaliez S, Pawlowsky JM. Diagnosis and management of chronic viral hepatitis: antigens, antibodies and viral genomes. *Best Pract Res Clin Gastroenterol* 2008;22:1031–1048.  
 [28] Kamili S, Drobeniuc J, Araujo AC, Hayden TM. Laboratory diagnostics for hepatitis C virus infection. *Clin Infect Dis* 2012;55:S43–S48.  
 [29] Swain MG, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, Dieterich DT, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology* 2010;139:1593–1601.  
 [30] Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, Leclere L, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. *Hepatology* 2010;51:1122–1126.

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- [31] Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005;128:343–350.
- [32] Castera L, Sebastiani G, Le Bail B, de Ledinghen V, Couzigou P, Alberti A. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. *J Hepatol* 2010;52:191–198.
- [33] Chevaliez S, Bouvier-Alias M, Brillet R, Pawlotsky JM. Hepatitis C virus (HCV) genotype 1 subtype identification in new HCV drug development and future clinical practice. *PLoS One* 2009;4:e8209.
- [34] Thompson AJ, Muir AJ, Sulkowski MS, Ge D, Fellay J, Shianna KV, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology* 2010;139:e118.
- [35] Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009;461:399–401.
- [36] Hezode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPLIC) – NCT01514890. *J Hepatol* 2013;59:434–441.
- [37] Poordad F, McCone Jr J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1195–1206.
- [38] Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405–2416.
- [39] Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011;365:1014–1024.
- [40] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncalves Jr FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975–982.
- [41] Hadziyannis SJ, Sette Jr H, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346–355.
- [42] Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. *Gut* 2006;55:1350–1359.
- [43] McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580–593.
- [44] Poordad F, Bronowicki JP, Gordon SC, Zeuzem S, Jacobson IM, Sulkowski MS, et al. Factors that predict response of patients with hepatitis C virus infection to boceprevir. *Gastroenterology* 2012;143:e601–e605.
- [45] Buti M, Agarwal K, Horsmans YJ, Sievert W, Janczewska E, Zeuzem S, et al. OPTIMIZE trial: non-inferiority of twice-daily telaprevir vs. administration every 8 h in treatment-naive, genotype 1 HCV infected patients. In: 63rd annual meeting of the American Association for the Study of Liver Diseases, Boston, MA, November 9–13; 2012 [abstract LB8].
- [46] Marcellin P, Forns X, Goester T, Ferenci P, Nevens F, Carosi G, et al. Telaprevir is effective given every 8 or 12 h with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. *Gastroenterology* 2011;140:459–468, [quiz e414].
- [47] Manns M, Zeuzem S, Sood A, Lurie Y, Cornberg M, Klinker H, et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. *J Hepatol* 2011;55:554–563.
- [48] Marcellin P, Cheinquer H, Curescu M, Dusheiko GM, Ferenci P, Horban A, et al. High sustained virologic response rates in rapid virologic response patients in the large real-world PROPHECY cohort confirm results from randomized clinical trials. *Hepatology* 2012;56:2039–2050.
- [49] De Nicola S, Aghemo A, Rumi MG, Galmozzi E, Valenti L, Soffredini R, et al. Interleukin 28B polymorphism predicts pegylated interferon plus ribavirin treatment outcome in chronic hepatitis C genotype 4. *Hepatology* 2012;55:336–342.
- [50] Vermehren J, Kau A, Gartner BC, Gobel R, Zeuzem S, Sarrazin C. Differences between two real-time PCR-based hepatitis C virus (HCV) assays (RealTime HCV and Cobas AmpliPrep/Cobas TaqMan) and one signal amplification assay (Versant HCV RNA 3.0) for RNA detection and quantification. *J Clin Microbiol* 2008;46:3880–3891.
- [51] Chevaliez S, Bouvier-Alias M, Brillet R, Pawlotsky JM. Overestimation and underestimation of hepatitis C virus RNA levels in a widely used real-time polymerase chain reaction-based method. *Hepatology* 2007;46:22–31.
- [52] Sarrazin C, Shiffman ML, Hadziyannis SJ, Lin A, Colucci G, Ishida H, et al. Definition of rapid virologic response with a highly sensitive real-time PCR-based HCV RNA assay in peginterferon alfa-2a plus ribavirin response-guided therapy. *J Hepatol* 2010;52:832–838.
- [53] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958–965.
- [54] Diago M, Shiffman ML, Bronowicki JP, Zeuzem S, Rodriguez-Torres M, Pappas SC, et al. Identifying hepatitis C virus genotype 2/3 patients who can receive a 16-week abbreviated course of peginterferon alfa-2a (40KD) plus ribavirin. *Hepatology* 2010;51:1897–1903.
- [55] Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007;357:124–134.
- [56] Jensen DM, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ, et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alfa-2a (40 kd)/ribavirin therapy. *Hepatology* 2006;43:954–960.
- [57] Ferenci P, Laferl H, Scherzer TM, Gschwantler M, Maieron A, Brunner H, et al. Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. *Gastroenterology* 2008;135:451–458.
- [58] Berg T, Sarrazin C, Herrmann E, Hinrichsen H, Gerlach T, Zachoval R, et al. Prediction of treatment outcome in patients with chronic hepatitis C: significance of baseline parameters and viral dynamics during therapy. *Hepatology* 2003;37:600–609.
- [59] Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianciara J, et al. Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. *J Hepatol* 2006;44:97–103.
- [60] Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2003;38:645–652.
- [61] Mangia A, Minerva N, Bacca D, Cozzolongo R, Ricci GL, Carretta V, et al. Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial. *Hepatology* 2008;47:43–50.
- [62] Moreno C, Deltenre P, Pawlotsky JM, Henrion J, Adler M, Mathurin P. Shortened treatment duration in treatment-naive genotype 1 HCV patients with rapid virological response: a meta-analysis. *J Hepatol* 2010;52:25–31.
- [63] Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 vs. 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006;130:1086–1097.
- [64] Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis C genotype 1-infected slow responders. *Hepatology* 2007;46:1688–1694.
- [65] Sanchez-Tapias JM, Diago M, Escartin P, Enriquez J, Romero-Gomez M, Barcena R, et al. Peginterferon-alfa2a plus ribavirin for 48 vs. 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006;131:451–460.
- [66] Ferenci P, Laferl H, Scherzer TM, Maieron A, Hofer H, Stauber R, et al. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. *Gastroenterology* 2010;138:503–512, [512 e501].
- [67] Buti M, Lurie Y, Zakharova NG, Blokhina NP, Horban A, Teuber G, et al. Randomized trial of peginterferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response. *Hepatology* 2010;52:1201–1207.
- [68] Farnik H, Lange CM, Sarrazin C, Kronenberger B, Zeuzem S, Herrmann E. Meta-analysis shows extended therapy improves response of patients with chronic hepatitis C virus genotype 1 infection. *Clin Gastroenterol Hepatol* 2010;8:884–890.
- [69] Dalgard O, Bjoro K, Ring-Larsen H, Bjornsson E, Holberg-Petersen M, Skovlund E, et al. Pegylated interferon alfa and ribavirin for 14 vs. 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology* 2008;47:35–42.
- [70] Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005;352:2609–2617.
- [71] von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, et al. Peginterferon-alfa-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology* 2005;129:522–527.

- [72] Yu ML, Dai CY, Huang JF, Hou NJ, Lee LP, Hsieh MY, et al. A randomised study of peginterferon and ribavirin for 16 vs. 24 weeks in patients with genotype 2 chronic hepatitis C. *Gut* 2007;56:553–559.
- [73] Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. *J Hepatol* 2008;49:634–651.
- [74] Romero-Gomez M, Fernandez-Rodriguez CM, Andrade RJ, Diago M, Alonso S, Planas R, et al. Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. *J Hepatol* 2008;48:721–727.
- [75] Zeuzem S, Hultcrantz R, Bourliere M, Goeser T, Marcellin P, Sanchez-Tapias J, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol* 2004;40:993–999.
- [76] Berg T, Shiffman ML, Zeuzem S, Berg CP, de Figueiredo-Mendes C, Dore GJ, et al. 48 Weeks of peginterferon alfa-2a/ribavirin improves SVR24 and decreases relapse across HCV genotype 2/3 patient subgroups not achieving a rapid virological response: N-CORE study. *J Hepatol* 2013;58:S323.
- [77] Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology* 2002;36:S237–S244.
- [78] Soza A, Everhart JE, Ghany MG, Doo E, Heller T, Promrat K, et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. *Hepatology* 2002;36:1273–1279.
- [79] Shiffman ML, Salvatore J, Hubbard S, Price A, Sterling RK, Stravitz RT, et al. Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alfa. *Hepatology* 2007;46:371–379.
- [80] Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004;126:1302–1311.
- [81] Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, et al. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *Hepatology* 2004;40:1450–1458.
- [82] Sulkowski MS, Poordad F, Manns MP, Bronowicki JP, Rajender Reddy K, Harrison SA, et al. Anemia during treatment with peginterferon Alfa-2b/ribavirin and boceprevir: analysis from the serine protease inhibitor therapy 2 (SPRINT-2) trial. *Hepatology* 2013;57:974–984.
- [83] Weiss JJ, Brau N, Stivala A, Swan T, Fishbein D. Review article: adherence to medication for chronic hepatitis C – building on the model of human immunodeficiency virus antiretroviral adherence research. *Aliment Pharmacol Ther* 2009;30:14–27.
- [84] Grebely J, Matthews GV, Hellard M, Shaw D, van Beek I, Petoumenos K, et al. Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users. *J Hepatol* 2011;55:76–85.
- [85] Marcellin P, Chousterman M, Fontanges T, Ouzan D, Rotily M, Varastet M, et al. Adherence to treatment and quality of life during hepatitis C therapy: a prospective, real-life, observational study. *Liver Int* 2011;31:516–524.
- [86] Smith SR, Wahed AS, Kelley SS, Conjeevaram HS, Robuck PR, Fried MW. Assessing the validity of self-reported medication adherence in hepatitis C treatment. *Ann Pharmacother* 2007;41:1116–1123.
- [87] Evon DM, Simpson K, Kixmiller S, Galanko J, Dougherty K, Golin C, et al. A randomized controlled trial of an integrated care intervention to increase eligibility for chronic hepatitis C treatment. *Am J Gastroenterol* 2011;106:1777–1786.
- [88] Grebely J, Knight E, Genoway KA, Viljoen M, Khara M, Elliott D, et al. Optimizing assessment and treatment for hepatitis C virus infection in illicit drug users: a novel model incorporating multidisciplinary care and peer support. *Eur J Gastroenterol Hepatol* 2010;22:270–277.
- [89] Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med* 2011;364:2199–2207.
- [90] Larrey D, Salse A, Ribard D, Boutet O, Hyrilles-Blanc V, Niang B, et al. Education by a nurse increases response of patients with chronic hepatitis C to therapy with peginterferon-alpha2a and ribavirin. *Clin Gastroenterol Hepatol* 2011;9:781–785.
- [91] Schmidt C, Schulte B, Gansefort D, Goelz J, Gerken G, Scherbaum N, et al. Optimizing HCV therapy: the impact of psychoeducation on retention and SVR in opiate substituted patients. *Hepatology* 2011;54:821A–822A.
- [92] Lindenburg CE, Lambers FA, Urbanus AT, Schinkel J, Jansen PL, Krol A, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: results from the DUTCH-C project. *Eur J Gastroenterol Hepatol* 2011;23:23–31.
- [93] Waizmann M, Ackermann G. High rates of sustained virological response in hepatitis C virus-infected injection drug users receiving directly observed therapy with peginterferon alpha-2a (40KD) (PEGASYS) and once-daily ribavirin. *J Subst Abuse Treat* 2010;38:338–345.
- [94] Grebely J, Raffa JD, Meagher C, Duncan F, Genoway KA, Khara M, et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. *J Gastroenterol Hepatol* 2007;22:1519–1525.
- [95] Bonkovsky HL, Tice AD, Yapp RG, Bodenheimer Jr HC, Monto A, Rossi SJ, et al. Efficacy and safety of peginterferon alfa-2a/ribavirin in methadone maintenance patients: randomized comparison of direct observed therapy and self-administration. *Am J Gastroenterol* 2008;103:2757–2765.
- [96] Sylvestre DL, Zweben JE. Integrating HCV services for drug users: a model to improve engagement and outcomes. *Int J Drug Policy* 2007;18:406–410.
- [97] Norman J, Walsh NM, Mugavin J, Stooze MA, Kelsall J, Austin K, et al. The acceptability and feasibility of peer worker support role in community based HCV treatment for injecting drug users. *Harm Reduct J* 2008;5:8.
- [98] Rodis JL, Kibbe P. Evaluation of medication adherence and quality of life in patients with hepatitis C virus receiving combination therapy. *Gastroenterol Nurs* 2010;33:368–373.
- [99] Alavian SM, Aalaei-Andabili SH. Education by a nurse increases the adherence to therapy in chronic hepatitis C patients. *Clin Gastroenterol Hepatol* 2012;10:203. [author reply 203].
- [100] Weiss JJ, Alcorn MC, Rabkin JG, Dieterich DT. The critical role of medication adherence in the success of boceprevir and telaprevir in clinical practice. *J Hepatol* 2012;56:503–504.
- [101] Bressler BL, Guindi M, Tomlinson G, Heathcote J. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. *Hepatology* 2003;38:639–644.
- [102] Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, et al. Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. *Gastroenterology* 2006;130:1607–1616.
- [103] Le Lan C, Guillygomarc'h A, Danielou H, Le Dreau G, Laine F, Vedeilhie C, et al. A multi-disciplinary approach to treating hepatitis C with interferon and ribavirin in alcohol-dependent patients with ongoing abuse. *J Hepatol* 2012;56:334–340.
- [104] Bruggmann P, Dampz M, Gerlach T, Kravec L, Falcato L. Treatment outcome in relation to alcohol consumption during hepatitis C therapy: an analysis of the Swiss Hepatitis C Cohort Study. *Drug Alcohol Depend* 2010;110:167–171.
- [105] Siu L, Foont J, Wands JR. Hepatitis C virus and alcohol. *Semin Liver Dis* 2009;29:188–199.
- [106] Serfaty L, Fornis X, Goeser T, Ferenci P, Nevens F, Carosi G, et al. Insulin resistance and response to telaprevir plus peginterferon alpha and ribavirin in treatment-naive patients infected with HCV genotype 1. *Gut* 2012;61:1473–1480.
- [107] Harrison SA, Hamzeh FM, Han J, Pandya PK, Sheikh MY, Vierling JM. Chronic hepatitis C genotype 1 patients with insulin resistance treated with pioglitazone and peginterferon alpha-2a plus ribavirin. *Hepatology* 2012;56:464–473.
- [108] Thevenot T, Cadranet JF, Di Martino V, Pariente A, Causse X, Renou C, et al. A national French survey on the use of growth factors as adjuvant treatment of chronic hepatitis C. *Hepatology* 2007;45:377–383.
- [109] Stickel F, Helbling B, Heim M, Geier A, Hirschi C, Terziroli B, et al. Critical review of the use of erythropoietin in the treatment of anaemia during therapy for chronic hepatitis C. *J Viral Hepat* 2012;19:77–87.
- [110] Alavian SM, Tabatabaei SV, Behnava B. Impact of erythropoietin on sustained virological response to peginterferon and ribavirin therapy for HCV infection: a systematic review and meta-analysis. *J Viral Hepat* 2012;19:88–93.
- [111] Poordad F, Lawitz EJ, Reddy KR, Afdhal NH, Hézode C, Zeuzem S, et al. A randomized trial comparing ribavirin dose reduction vs. erythropoietin for anemia management in previously untreated patients with chronic hepatitis C receiving boceprevir plus peginterferon/ribavirin. *J Hepatol* 2012;56:S559.
- [112] Tandon P, Doucette K, Fassbender K, Vandermeer B, Durec T, Dryden DM. Granulocyte colony-stimulating factor for hepatitis C therapy-associated neutropenia: systematic review and economic evaluation. *J Viral Hepat* 2011;18:e381–e393.
- [113] McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bourliere M, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007;357:2227–2236.
- [114] Homeida S, Ebdon C, Batty P, Jackson B, Kolade S, Bateman C, et al. New thrombopoietin receptor agonists for platelet disorders. *Drugs Today (Barc)* 2012;48:293–301.
- [115] Schaefer M, Capuron L, Friebe A, Diez-Quevedo C, Robaegs G, Neri S, et al. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. *J Hepatol* 2012;57:1379–1390.

# Clinical Practice Guidelines

- [116] Dalgard O. Follow-up studies of treatment for hepatitis C virus infection among injection drug users. *Clin Infect Dis* 2005;40:S336–S338.
- [117] Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. *Clin Infect Dis* 2004;39:1540–1543.
- [118] Currie SL, Ryan JC, Tracy D, Wright TL, George S, McQuaid R, et al. A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus. *Drug Alcohol Depend* 2008;93:148–154.
- [119] Grebely J, Pham ST, Matthews GV, Petoumenos K, Bull RA, Yeung B, et al. Hepatitis C virus reinfection and superinfection among treated and untreated participants with recent infection. *Hepatology* 2012;55:1058–1069.
- [120] Grebely J, Knight E, Ngai T, Genoway KA, Raffa JD, Storms M, et al. Reinfection with hepatitis C virus following sustained virological response in injection drug users. *J Gastroenterol Hepatol* 2010;25:1281–1284.
- [121] Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1207–1217.
- [122] Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011;364:2417–2428.
- [123] Flamm SL, Lawitz E, Jacobson I, Bourliere M, Hezode C, Vierling JM, et al. Boceprevir with peginterferon alfa-2a-ribavirin is effective for previously treated chronic hepatitis C genotype 1 infection. *Clin Gastroenterol Hepatol* 2013;11:81, [e84; quiz e85].
- [124] Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol* 2010;8:280–288, [288 e281].
- [125] van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012;308:2584–2593.
- [126] Schmid M, Kreil A, Jessner W, Homoncik M, Datz C, Gangl A, et al. Suppression of haematopoiesis during therapy of chronic hepatitis C with different interferon alpha mono and combination therapy regimens. *Gut* 2005;54:1014–1020.
- [127] Garcia-Retortillo M, Forns X, Feliu A, Moitinho E, Costa J, Navasa M, et al. Hepatitis C virus kinetics during and immediately after liver transplantation. *Hepatology* 2002;35:680–687.
- [128] Forns X, Garcia-Retortillo M, Serrano T, Feliu A, Suarez F, de la Mata M, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. *J Hepatol* 2003;39:389–396.
- [129] Carrion JA, Martinez-Bauer E, Crespo G, Ramirez S, Perez-del-Pulgar S, Garcia-Valdecasas JC, et al. Antiviral therapy increases the risk of bacterial infections in HCV-infected cirrhotic patients awaiting liver transplantation: a retrospective study. *J Hepatol* 2009;50:719–728.
- [130] Everson GT, Trotter J, Forman L, Kugelmas M, Halprin A, Fey B, et al. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. *Hepatology* 2005;42:255–262.
- [131] Prieto M, Berenguer M, Rayon JM, Cordoba J, Arguello L, Carrasco D, et al. High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. *Hepatology* 1999;29:250–256.
- [132] Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002;122:889–896.
- [133] Berenguer M, Palau A, Aguilera V, Rayon JM, Juan FS, Prieto M. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. *Am J Transplant* 2008;8:679–687.
- [134] Neumann UP, Berg T, Bahra M, Seehofer D, Langrehr JM, Neuhaus R, et al. Fibrosis progression after liver transplantation in patients with recurrent hepatitis C. *J Hepatol* 2004;41:830–836.
- [135] Blasco A, Forns X, Carrion JA, Garcia-Pagan JC, Gilibert R, Rimola A, et al. Hepatic venous pressure gradient identifies patients at risk of severe hepatitis C recurrence after liver transplantation. *Hepatology* 2006;43:492–499.
- [136] Samuel D, Bizollon T, Feray C, Roche B, Ahmed SN, Lemonnier C, et al. Interferon-alpha 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study. *Gastroenterology* 2003;124:642–650.
- [137] Carrion JA, Navasa M, Garcia-Retortillo M, Garcia-Pagan JC, Crespo G, Bruguera M, et al. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: a randomized controlled study. *Gastroenterology* 2007;132:1746–1756.
- [138] Berenguer M. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. *J Hepatol* 2008;49:274–287.
- [139] Selzner N, Guindi M, Renner EL, Berenguer M. Immune-mediated complications of the graft in interferon-treated hepatitis C positive liver transplant recipients. *J Hepatol* 2011;55:207–217.
- [140] Garg V, van Heeswijk R, Lee JE, Alves K, Nadkarni P, Luo X. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. *Hepatology* 2011;54:20–27.
- [141] Hulskotte E, Gupta S, Xuan F, van Zutven M, O'Mara E, Feng HP, et al. Pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and cyclosporine and tacrolimus in healthy volunteers. *Hepatology* 2012;56:1622–1630.
- [142] Coilly A, Roche B, Botta-Fridlund D, Leroy V, Pageaux P, Si-Ahmed S, et al. Efficacy and safety of protease inhibitors for severe hepatitis C recurrence after liver transplantation: a first multicentric experience. *J Hepatol* 2012;56:S21.
- [143] Qurishi N, Kreuzberg C, Luchters G, Effenberger W, Kupfer B, Sauerbruch T, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet* 2003;362:1708–1713.
- [144] Solas C, Pambrun E, Winnock M, Salmon D, Poizat-Martin I, Dominguez S, et al. Ribavirin and abacavir drug interaction in HIV-HCV coinfecting patients: fact or fiction? *AIDS* 2012;26:2193–2199.
- [145] Alberti A, Clumeck N, Collins S, Gerlich W, Lundgren J, Palu G, et al. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005;42:615–624.
- [146] Opravil M, Rodriguez-Torres M, Rockstroh J, Snoeck E, Chung RT, Tietz A, et al. The dose-response relationship of peginterferon alfa-2a and ribavirin in the treatment of patients coinfecting with HIV-HCV. *HIV Clin Trials* 2012;13:33–45.
- [147] Rodriguez-Torres M, Slim J, Bhatti L, Sterling R, Sulkowski M, Hassanein T, et al. Peginterferon alfa-2a plus ribavirin for HIV-HCV genotype 1 coinfecting patients: a randomized international trial. *HIV Clin Trials* 2012;13:142–152.
- [148] Dieterich D, Soriano V, Sherman K, Girard P-M, Rockstroh J, Adiwijaya B, et al. Telaprevir in combination with pegylated interferon-alfa-2a+RBV in HCV/HIV-co-infected patients: a 24-week treatment interim analysis. In: 19th conference on retroviruses and opportunistic infections, seattle, WA, March 5–8; 2012 [abstract 46].
- [149] Sulkowski M, Pol S, Mallolas J, Fainboim H, Cooper C, Slim J, et al. Boceprevir vs. placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomized, double-blind, controlled phase 2 trial. *Lancet Infect Dis* 2013;13:597–605.
- [150] Kiser JJ, Burton JR, Anderson PL, Everson GT. Review and management of drug interactions with boceprevir and telaprevir. *Hepatology* 2012;55:1620–1628.
- [151] European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel. Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. *AIDS* 2011;25:399–409.
- [152] Potthoff A, Wedemeyer H, Boecker WO, Berg T, Zeuzem S, Arnold J, et al. The HEP-NET B/C co-infection trial: A prospective multicenter study to investigate the efficacy of pegylated interferon-alpha2b and ribavirin in patients with HBV/HCV co-infection. *J Hepatol* 2008;49:688–694.
- [153] Potthoff A, Berg T, Wedemeyer H. Late hepatitis B virus relapse in patients co-infected with hepatitis B virus and hepatitis C virus after antiviral treatment with pegylated interferon-a2b and ribavirin. *Scand J Gastroenterol* 2009;44:1487–1490.
- [154] Fabrizi F, Dulai G, Dixit V, Bunnapradist S, Martin P. Meta-analysis: interferon for the treatment of chronic hepatitis C in dialysis patients. *Aliment Pharmacol Ther* 2003;18:1071–1081.
- [155] Liu CH, Liang CC, Lin JW, Chen SI, Tsai HB, Chang CS, et al. Pegylated interferon alpha-2a vs. standard interferon alpha-2a for treatment-naive dialysis patients with chronic hepatitis C: a randomised study. *Gut* 2008;57:525–530.
- [156] Peck-Radosavljevic M, Boletis J, Besisik F, Ferraz ML, Alric L, Samuel D, et al. Low-dose peginterferon alfa-2a is safe and produces a sustained virologic response in patients with chronic hepatitis C and end-stage renal disease. *Clin Gastroenterol Hepatol* 2011;9:242–248.
- [157] Liu CH, Liang CC, Liu CJ, Tsai HB, Hung PH, Hsu SJ, et al. Pegylated interferon alpha-2a plus low-dose ribavirin for the retreatment of dialysis chronic hepatitis C patients who relapsed from prior interferon monotherapy. *Gut* 2009;58:314–316.

- [158] Treitel M, Marbury T, Preston RA, Triantafyllou I, Feely W, O'Mara E, et al. Single-dose pharmacokinetics of boceprevir in subjects with impaired hepatic or renal function. *Clin Pharmacokinet* 2012;51:619–628.
- [159] van Heeswijk R, Vandevoorde A, Boogaerts G, De Paepe E, van Solingen-Riste R, Garg V, et al. The effect of severe renal impairment on the pharmacokinetics of the investigational HCV protease inhibitor telaprevir. *J Hepatol* 2011;54:S492.
- [160] Basu PP, Siriki R, Shah NJ, Farhat S, Mittimani K, Atluri S, et al. Telaprevir with adjusted dose of ribavirin in naïve CHC-G1: efficacy and treatment in CHC in hemodialysis population. Target C (RCT). *J Hepatol* 2013;58:S30–S31.
- [161] Scott DR, Wong JK, Spicer TS, Dent H, Mensah FK, McDonald S, et al. Adverse impact of hepatitis C virus infection on renal replacement therapy and renal transplant patients in Australia and New Zealand. *Transplantation* 2010;90:1165–1171.
- [162] Gane E, Pilmore H. Management of chronic viral hepatitis before and after renal transplantation. *Transplantation* 2002;74:427–437.
- [163] Van Wagner LB, Baker T, Ahya SN, Norvell JP, Wang E, Levitsky J. Outcomes of patients with hepatitis C undergoing simultaneous liver-kidney transplantation. *J Hepatol* 2009;51:874–880.
- [164] Martin P, Fabrizi F. Hepatitis C virus and kidney disease. *J Hepatol* 2008;49:613–624.
- [165] Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, et al. International guidelines for the selection of lung transplant candidates: 2006 update – a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2006;25:745–755.
- [166] Grebely J, Raffa JD, Lai C, Kerr T, Fischer B, Krajden M, et al. Impact of hepatitis C virus infection on all-cause and liver-related mortality in a large community-based cohort of inner city residents. *J Viral Hepat* 2011;18:32–41.
- [167] Darke S, Kaye S, Duflou J. Comparative cardiac pathology among deaths due to cocaine toxicity, opioid toxicity and non-drug-related causes. *Addiction* 2006;101:1771–1777.
- [168] Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005;5:558–567.
- [169] Hagan H, Pouget ER, Des Jarlais DC, Lelutiu-Weinberger C. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. *Am J Epidemiol* 2008;168:1099–1109.
- [170] Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 2011;378:571–583.
- [171] Pybus OG, Cochrane A, Holmes EC, Simmonds P. The hepatitis C virus epidemic among injecting drug users. *Infect Genet Evol* 2005;5:131–139.
- [172] van Asten L, Verhaest I, Lamzira S, Hernandez-Aguado I, Zangerle R, Boufassa F, et al. Spread of hepatitis C virus among European injection drug users infected with HIV: a phylogenetic analysis. *J Infect Dis* 2004;189:292–302.
- [173] de Bruijne J, Schinkel J, Prins M, Koekkoek SM, Aronson SJ, van Ballegooijen MW, et al. Emergence of hepatitis C virus genotype 4: phylogenetic analysis reveals three distinct epidemiological profiles. *J Clin Microbiol* 2009;47:3832–3838.
- [174] van den Berg CH, Smit C, Bakker M, Geskus RB, Berkhout B, Jurriaans S, et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. *Eur J Epidemiol* 2007;22:183–193.
- [175] Mehta SH, Astemborski J, Kirk GD, Strathdee SA, Nelson KE, Vlahov D, et al. Changes in blood-borne infection risk among injection drug users. *J Infect Dis* 2011;203:587–594.
- [176] Patrick DM, Tyndall MW, Cornelisse PG, Li K, Sherlock CH, Rekart ML, et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. *CMAJ* 2001;165:889–895.
- [177] Maher L, Li J, Jalaludin B, Chant KG, Kaldor JM. High hepatitis C incidence in new injecting drug users: a policy failure? *Aust N Z J Public Health* 2007;31:30–35.
- [178] Kim C, Kerr T, Li K, Zhang R, Tyndall MW, Montaner JS, et al. Unstable housing and hepatitis C incidence among injection drug users in a Canadian setting. *BMC Public Health* 2009;9:270.
- [179] Roy E, Alary M, Morissette C, Leclerc P, Boudreau JF, Parent R, et al. High hepatitis C virus prevalence and incidence among Canadian intravenous drug users. *Int J STD AIDS* 2007;18:23–27.
- [180] Bruneau J, Daniel M, Kestens Y, Abrahamowicz M, Zang G. Availability of body art facilities and body art piercing do not predict hepatitis C acquisition among injection drug users in Montreal, Canada: results from a cohort study. *Int J Drug Policy* 2010;21:477–484.
- [181] Aitken C, Lewis J, Hocking J, Bowden D, Hellard M. Does information about IDUs' injecting networks predict exposure to the hepatitis C virus? *Hepat Monthly* 2009;9:17–23.
- [182] Turner KM, Hutchinson S, Vickerman P, Hope V, Craine N, Palmateer N, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. *Addiction* 2011;106:1978–1988.
- [183] Rehm J, Frick U, Hartwig C, Gutzwiller F, Gschwend P, Uchtenhagen A. Mortality in heroin-assisted treatment in Switzerland 1994–2000. *Drug Alcohol Depend* 2005;79:137–143.
- [184] Kreek MJ, Dodes L, Kane S, Knobler J, Martin R. Long-term methadone maintenance therapy: effects on liver function. *Ann Intern Med* 1972;77:598–602.
- [185] Petry NM, Bickel WK, Piasecki D, Marsch LA, Badger GJ. Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine. *Am J Addict* 2000;9:265–269.
- [186] Andreu V, Mas A, Bruguera M, Salmeron JM, Moreno V, Nogue S, et al. Ecstasy: a common cause of severe acute hepatotoxicity. *J Hepatol* 1998;29:394–397.
- [187] Karch SB, Stephens BG, Ho CH. Methamphetamine-related deaths in San Francisco: demographic, pathologic, and toxicologic profiles. *J Forensic Sci* 1999;44:359–368.
- [188] Hezode C, Roudot-Thoraval F, Nguyen S, Grenard P, Julien B, Zafrani ES, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology* 2005;42:63–71.
- [189] Hezode C, Zafrani ES, Roudot-Thoraval F, Costentin C, Hessami A, Bouvier-Alias M, et al. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. *Gastroenterology* 2008;134:432–439.
- [190] Ostapowicz G, Watson KJ, Locarnini SA, Desmond PV. Role of alcohol in the progression of liver disease caused by hepatitis C virus infection. *Hepatology* 1998;27:1730–1735.
- [191] Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. *Hepatology* 2012;55:49–57.
- [192] Dore GJ, Hellard M, Matthews GV, Grebely J, Haber PS, Petoumenos K, et al. Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. *Gastroenterology* 2010;138:e121–e122.
- [193] Alvarez-Uria G, Day JN, Nasir AJ, Russell SK, Vilar FJ. Factors associated with treatment failure of patients with psychiatric diseases and injecting drug users in the treatment of genotype 2 or 3 hepatitis C chronic infection. *Liver Int* 2009;29:1051–1055.
- [194] Conway B, Grebely J, Tossonian H, Lefebvre D, de Vlaming S. A systematic approach to the treatment of HIV and hepatitis C virus infection in the inner city: a Canadian perspective. *Clin Infect Dis* 2005;41:S73–S78.
- [195] Grebely J, Genoway KA, Raffa JD, Dhadwal G, Rajan T, Showler G, et al. Barriers associated with the treatment of hepatitis C virus infection among illicit drug users. *Drug Alcohol Depend* 2008;93:141–147.
- [196] Doab A, Treloar C, Dore GJ. Knowledge and attitudes about treatment for hepatitis C virus infection and barriers to treatment among current injection drug users in Australia. *Clin Infect Dis* 2005;40:S313–S320.
- [197] Kramer JR, Kanwal F, Richardson P, Giordano TP, Petersen LA, El-Serag HB. Importance of patient, provider, and facility predictors of hepatitis C virus treatment in veterans: a national study. *Am J Gastroenterol* 2011;106:483–491.
- [198] Gidding HF, Law MG, Amin J, Macdonald GA, Sasadeusz JJ, Jones TL, et al. Predictors of deferral of treatment for hepatitis C infection in Australian clinics. *Med J Aust* 2011;194:398–402.
- [199] Bini EJ, Brau N, Currie S, Shen H, Anand BS, Hu KQ, et al. Prospective multicenter study of eligibility for antiviral therapy among 4084 U.S. veterans with chronic hepatitis C virus infection. *Am J Gastroenterol* 2005;100:1772–1779.
- [200] Kanwal F, Hoang T, Spiegel BM, Eisen S, Dominitz JA, Gifford A, et al. Predictors of treatment in patients with chronic hepatitis C infection – role of patient vs. nonpatient factors. *Hepatology* 2007;46:1741–1749.
- [201] Robaey G, Van Vlierberghe H, Mathel C, Van Ranst M, Bruckers L, Buntinx F. Similar compliance and effect of treatment in chronic hepatitis C resulting from intravenous drug use in comparison with other infection causes. *Eur J Gastroenterol Hepatol* 2006;18:159–166.
- [202] Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. *Clin Infect Dis* 2009;49:561–573.
- [203] Papadopoulos V, Gogou A, Mylopoulou T, Mimidis K. Should active injecting drug users receive treatment for chronic hepatitis C? *Arq Gastroenterol* 2010;47:238–241.

# Clinical Practice Guidelines

- [204] Manolakopoulos S, Deutsch MJ, Anagnostou O, Karatapanis S, Tiniakou E, Papatheodoridis GV, et al. Substitution treatment or active intravenous drug use should not be contraindications for antiviral treatment in drug users with chronic hepatitis C. *Liver Int* 2010;30:1454–1460.
- [205] Bruggmann P, Falcato L, Dober S, Helbling B, Keiser O, Negro F, et al. Active intravenous drug use during chronic hepatitis C therapy does not reduce sustained virological response rates in adherent patients. *J Viral Hepat* 2008;15:747–752.
- [206] Sasadeusz JJ, Dore G, Kronborg I, Barton D, Yoshihara M, Weltman M. Clinical experience with the treatment of hepatitis C infection in patients on opioid pharmacotherapy. *Addiction* 2011;106:977–984.
- [207] Sylvestre DL, Litwin AH, Clements BJ, Gourevitch MN. The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone. *J Subst Abuse Treat* 2005;29:159–165.
- [208] Mauss S, Berger F, Goelz J, Jacob B, Schmutz G. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. *Hepatology* 2004;40:120–124.
- [209] van Heeswijk R, Vandevoorde A, Verboven P, Boogaerts G, De Paepe E, van Solingen-Ristea R, et al. The pharmacokinetic interaction between methadone and the investigational HCV protease inhibitor telaprevir. *J Hepatol* 2011;54:S491–S492.
- [210] Luo X, Trevejo J, Van Heeswijk R, Garg V. No significant effect of the HCV protease inhibitor telaprevir on pharmacokinetics and pharmacodynamics of buprenorphine in HCV-negative volunteers. *Global Antivir J* 2011;7:116–117.
- [211] Hulskotte E, Feng H, Bruce R, Webster L, Xuan F, Lin W, et al. Pharmacokinetic interaction between HCV protease inhibitor boceprevir and methadone or buprenorphine in subjects on stable maintenance therapy. *J Gastroenterol Hepatol* 2012;27:169–170.
- [212] Burger D, Back D, Buggisch P, Buti M, Craxi A, Foster G, et al. Clinical management of drug-drug interactions in HCV therapy: challenges and solutions. *J Hepatol* 2013;58:792–800.
- [213] Van Heeswijk R, Boogaerts G, De Paepe E, Van Solingen-Ristea R, Garg V, Beumont M. The pharmacokinetic interaction between escitalopram and the investigational HCV protease inhibitor telaprevir. In: Fifth international workshop on clinical pharmacology of hepatitis therapy, Boston, MA, June 23–24; 2010 [abstract 12].
- [214] Hulskotte EGJ, Gupta S, Xuan F, van Zutven MGJA, O'Mara E, Galitz L, et al. Coadministration of the HCV protease inhibitor boceprevir has no clinically meaningful effect on the pharmacokinetics of the selective serotonin reuptake inhibitor escitalopram in healthy volunteers. In: Sixteenth annual meeting of HEP DART, Koloa, Hawaii, December 4–8; 2011 [poster 121].
- [215] Garg V, Chandorkar G, Smith F, Alves K, van Heeswijk R. The effect of telaprevir on the pharmacokinetics of midazolam and digoxin. In: Sixth International Workshop on Clinical Pharmacology of Hepatitis Therapy, Cambridge, MA, June 22–23; 2011 [abstract PK\_12].
- [216] Luo X, Van Heeswijk R, Alves K, Garg V. The effect of telaprevir on the pharmacokinetics of alprazolam and zolpidem in healthy volunteers. In: Sixth international workshop on clinical pharmacology of hepatitis therapy, Cambridge, MA, June 22–23; 2011 [abstract PK\_11].
- [217] Maurer HH, Sauer C, Theobald DS. Toxicokinetics of drugs of abuse: current knowledge of the isoenzymes involved in the human metabolism of tetrahydrocannabinol, cocaine, heroin, morphine, and codeine. *Ther Drug Monit* 2006;28:447–453.
- [218] Robaey G, Grebely J, Mauss S, Bruggmann P, Moussalli J, De Gottardi A, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. *Clin Infect Dis* 2013;57:S129–S137.
- [219] Mauss S, Klinker H. Drug-Drug interactions in the treatment of HCV among people who inject drugs. *Clin Infect Dis* 2013;57:S125–S128.
- [220] Robaey G, Nevens F, Starkel P, Colle I, Van Eyken P, Bruckers L, et al. Previous intravenous substance use and outcome of liver transplantation in patients with chronic hepatitis C infection. *Transplant Proc* 2009;41:589–594.
- [221] De Gottardi A, Hilleret MN, Gelez P, La Mura V, Guillaud O, Majno P, et al. Injection drug use before and after liver transplantation: a retrospective multicenter analysis on incidence and outcome. *Clin Transplant* 2010;24:564–571.
- [222] Miró JM, Laguno M, Moreno A, Rimola A. Management of end stage liver disease (ESLD): what is the current role of orthotopic liver transplantation (OLT)? *J Hepatol* 2006;44:S140–S145.
- [223] Ranney DN, Acker WB, Al-Holou SN, Ehrlichman L, Lee DS, Lewin SA, et al. Marijuana use in potential liver transplant candidates. *Am J Transplant* 2009;9:280–285.
- [224] Webb K, Shepherd L, Neuberger J. Illicit drug use and liver transplantation: is there a problem and what is the solution? *Transpl Int* 2008;21:923–929.
- [225] Kanchana TP, Kaul V, Manzarbeitia C, Reich DJ, Hails KC, Munoz SJ, et al. Liver transplantation for patients on methadone maintenance. *Liver Transpl* 2002;8:778–782.
- [226] Koch M, Banyas P. Liver transplantation and opioid dependence. *JAMA* 2001;285:1056–1058.
- [227] Liu LU, Schiano TD, Lau N, O'Rourke M, Min AD, Sigal SH, et al. Survival and risk of recidivism in methadone-dependent patients undergoing liver transplantation. *Am J Transplant* 2003;3:1273–1277.
- [228] Murray KF, Carrithers RL. AASLD practice guidelines: evaluation of the patient for liver transplantation. *Hepatology* 2005;41:1407–1432.
- [229] Harmatz P, Jonas MM, Kwiatkowski JL, Wright EC, Fischer R, Vichinsky E, et al. Safety and efficacy of pegylated interferon alpha-2a and ribavirin for the treatment of hepatitis C in patients with thalassemia. *Haematologica* 2008;93:1247–1251.
- [230] Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004;39:1147–1171.
- [231] Mondelli MU, Cerino A, Cividini A. Acute hepatitis C: diagnosis and management. *J Hepatol* 2005;42:S108–S114.
- [232] Dienstag JL. Reply. *Gastroenterology* 2006;131:332–333.
- [233] Kamal SM. Acute hepatitis C: a systematic review. *Am J Gastroenterol* 2008;103:1283–1297, [quiz 1298].
- [234] Santantonio T, Wiegand J, Gerlach JT. Acute hepatitis C: current status and remaining challenges. *J Hepatol* 2008;49:625–633.
- [235] Wiegand J, Jackel E, Cornberg M, Hinrichsen H, Dietrich M, Kroeger J, et al. Long-term follow-up after successful interferon therapy of acute hepatitis C. *Hepatology* 2004;40:98–107.
- [236] Deterding K, Gruner N, Buggisch P, Wiegand J, Galle PR, Spengler U, et al. Delayed vs. immediate treatment for patients with acute hepatitis C: a randomised controlled non-inferiority trial. *Lancet Infect Dis* 2013;13:497–506.
- [237] Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006;13:34–41.
- [238] Gerlach JT, Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterology* 2003;125:80–88.
- [239] Poynard T, Regimbeau C, Myers RP, Thevenot T, Leroy V, Mathurin P, et al. Interferon for acute hepatitis C. *Cochrane Database Syst Rev* 2002. <http://dx.doi.org/10.1002/14651858CD000369>.
- [240] Camma C, Licata A, Cabibbo G, Latteri F, Craxi A. Treatment of hepatitis C: critical appraisal of the evidence. *Expert Opin Pharmacother* 2005;6:399–408.
- [241] Hofer H, Watkins-Riedel T, Janata O, Penner E, Holzmann H, Steindl-Munda P, et al. Spontaneous viral clearance in patients with acute hepatitis C can be predicted by repeated measurements of serum viral load. *Hepatology* 2003;37:60–64.