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Treatment of hepatitis C virus infection for adults and children: Updated Swedish consensus recommendations

Martin Lagging[a]*, Rune Wejstål[a,b], Gunnar Norkrans[a], Olle Karlström[c], Soo Aleman[d], Ola Weiland[d], Maria Castedal[e], Filip Josephson[c]; for the Swedish Consensus Group*

[a]Department of Infectious Medicine, Institute of Biomedicine at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [b]Swedish Reference Group for Antiviral Therapy (RAV), Sweden; [c]Medical Products Agency, Uppsala, Sweden; [d]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; [e]Transplant Institute, Sahlgrenska University Hospital and Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

ABSTRACT

In a recent expert meeting, Swedish recommendations for the treatment of HCV infection were updated. An interferon-free combination of direct-acting antiviral agents was recommended as the first line standard-of-care treatment for chronic HCV infection. Interferon-based therapy should be considered as a second line option after an individual benefit-risk assessment. Treatment is strongly recommended for HCV infected patients with bridging fibrosis or cirrhosis (Metavir stages F3–4), before and after liver transplantation, and in the presence of extra-hepatic manifestations. Additionally, patients with moderate liver fibrosis (stage F2) as well as women in need of *in vitro* fertilisation should be prioritised for therapeutic intervention. Treatment indications for people who inject drugs, children, chronic kidney disease and HIV co-infection are also discussed.

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Introduction

The World Health Organisation (WHO) estimates that globally there are ~170 million infected with hepatitis C virus (HCV). In Sweden, the estimated prevalence is $\leq$0.5%, corresponding to 45 000 individuals. Approximately 2000 new cases are reported annually in accordance with the Swedish Infectious Diseases Act. Currently, intravenous drug use is the predominant route of infection in the western world. An estimated 75% of those infected with HCV develop a chronic infection, which generally has a slow progression rate to advanced liver disease.[1,2] However, an estimated 20% of those with chronic HCV infection progress to cirrhosis within 20 years from onset of infection [3] and this proportion tends to increase over time. HCV-induced cirrhosis entails a substantial risk of serious complications such as liver decompensation, including portal hypertension with oesophageal varices, ascites and hepatic encephalopathy. Furthermore, HCV cirrhosis entails an annual 1–4% risk of developing hepatocellular carcinoma (HCC) [4] and chronic HCV infection is the underlying cause of approximately a quarter of the liver transplants performed in Sweden.

Acute HCV infection

Previously, selected patients with acute HCV infection were recommended treatment with pegylated interferon-α (peg-IFN) for 24 weeks.[5] This is no longer advocated, as the treatment of chronic infection has become highly efficacious and, therefore, anti-viral therapy can be deferred to a later time-point if spontaneous resolution does not occur during the acute phase (recommendation grade A1; recommendation grading scale adapted from the GRADE system used by EASL) Table 3.[6]

Chronic HCV infection

The ultimate goal of the HCV treatment is to prevent cirrhosis, as this entails an increased risk of HCC and/or decompensated

CONTACT Martin Lagging, MD, PhD martin.lagging@medfak.gu.se Department of Infectious Diseases, Institute of Biomedicine at Sahlgrenska Academy, University of Gothenburg, Guldhedsgatan 10B, SE-413 46 Göteborg, Sweden

*Additional participants in the Swedish Consensus Group: Kristina Aggefors, Stockholm Healthcare Administration, Per Björkman, Department of Infectious Diseases, Skåne University Hospital, Malmö, Ann-Sofi Duberg, Department of Infectious Diseases, Örebro University Hospital, Örebro, Björn Fischler, Astrid Lindgren Children's Hospital, Stockholm, Henrik Gjertsen, Department of Transplant Surgery, Karolinska University Hospital, Stockholm, Martin Kåberg, Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Lisa Landerholm, The Dental and Pharmaceutical Benefits Agency, TLV, Stockholm, Karin Lindahl, Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Magnus Lindh, Department of Infectious Medicine, Institute of Biomedicine at Sahlgrenska Academy, Gothenburg, Peter Rosenberg, Medical Products Agency, Uppsala, Elisabeth Rubbetoft, Medical Products Agency, Uppsala, Robert Schvarz, Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Stephan Stenmark, Department of Communicable Disease Control Västerbotten, Umeå, Hans Verbaan, Department of Gastroenterology, Skåne University Hospital, Malmö, Johan Westin, Department of Infectious Diseases, Sahlgrenska University Hospital, Göteborg, Anja Wikström, The Dental and Pharmaceutical Benefits Agency, TLV, Stockholm, and Pernilla Örtqvist, Medical Products Agency, Uppsala.

liver disease. The immediate virologic therapeutic objective is defined as sustained virologic response (SVR), i.e. undetectable plasma HCV RNA 12–24 weeks after discontinuation of treatment, which likely corresponds to a cured infection.

Among HCV infected cirrhotic patients, the annual risk of developing HCC can be reduced from ~4% to 1% if SVR is achieved. Fibrosis stage F3 (bridging fibrosis) also entails an increased risk of HCC and the transition from fibrosis stage F3 to F4 (cirrhosis), as well as the progression from F2 (moderate fibrosis) to F3, often is difficult to accurately diagnose. Therefore, treatment should not be delayed for patients with fibrosis stages F3–4 and, if possible, should be initiated before stage F3 is reached. Consequently, it is recommended that treatment not be deferred for patients with fibrosis stage F2 or higher.

For patients with extrahepatic manifestations, e.g. cryoglobulin induced vasculitis, porphyria cutanea tarda or glomerulonephritis, antiviral therapy also is warranted, as it generally improves these immune mediated diseases.

In addition to reducing or abolishing the risk of HCV-induced serious liver disease and/or extrahepatic manifestations, successful treatment also eliminates the risk of transmission, for example from mother to child during pregnancy or delivery (1–5% risk), through sex or secondary to sharing injection paraphernalia among people who inject drugs (PWIDs).

In each individual case it is important to evaluate whether the patient is in immediate need of treatment or if therapy can be deferred. Aside from the degree of liver damage, other factors also should be considered, such as the patient's age, general health, overall life expectancy, own wishes and the ability to adhere to the treatment. In patients with ongoing substance abuse, where compliance problems may be anticipated, supportive care is particularly important before initiation of anti-viral treatment.

Assessment of fibrosis stage

Evaluation of the fibrosis stage should be performed in all patients with chronic HCV infection (recommendation grade A1). Formerly this was accomplished by means of a liver biopsy. Presently non-invasive methods such as a combination of validated blood biomarkers and liver elasticity measurement (e.g. FibroScan®) are considered to provide a sufficient estimate.[7,8] With these methods, in particular with liver elasticity measurement, the absence of fibrosis as well as the presence of cirrhosis can be diagnosed with reasonably high accuracy. Non-invasive fibrosis evaluations utilise the same stages as a liver biopsy, e.g. the protocols suggested by Batts and Ludwig [9] and the Metavir,[10] from F0 (normal liver without fibrosis) to F4 (liver cirrhosis). However, these methods are less accurate than a liver biopsy, particularly when differentiating fibrosis stages F2 and F3. By including patients with stage F2 (moderate fibrosis) among those recommended for treatment, the risk is reduced of delaying therapy for those whose fibrosis stage has been under-estimated.

It should be noted that a liver biopsy may provide more information than simply an estimation of fibrosis stage and can be useful if non-invasive methods render questionable results or fail and when other causes of liver disease are suspected. An experienced liver pathologist, who can judge whether or not the material is sufficient, should perform the evaluation of the liver biopsy and the risk of sampling error must always be considered.

Regular, biannual liver ultrasound for the surveillance of possible HCC development is recommended for cirrhotic patients, both before and after treatment (recommendation grade B2) and an endoscopy should be performed to evaluate the presence of varices. For patients with HCV-induced cirrhosis lacking varices, it is probably not necessary to perform additional gastroscopies if SVR is achieved. If and when additional gastroscopies are needed should be evaluated on an individual basis, taking into account other risk factors for progression of cirrhosis (recommendation grade C2).

Treatment prioritisation

All patients with chronic HCV infection are eligible for treatment and recently the Icelandic government announced that all HCV infected there will be provided free medication in addition to education and follow-up, thereby initiating the first national HCV elimination programme.[11]

If prioritisation is necessary, disease severity and the risk of disease progression should be considered. Patients who meet one or more of the following four criteria should be prioritised for treatment:

- Patients with fibrosis stage 2–4 (F2–4). If bridging fibrosis (stage F3) or cirrhosis (F4) is present, the patient should be treated at the earliest appropriate opportunity. To avoid progression to fibrosis stage F3, patients with moderate fibrosis (F2) also should be prioritised (recommendation grade A1).
- Liver-transplant recipients should be treated as soon as possible (recommendation grade A1). Other solid organ and stem cell transplant recipients should be treated similarly, because of an increased fibrosis progression rate induced by immunosuppressive therapy (recommendation grade A1).
- If extra-hepatic manifestations are present, e.g. cryoglobulin induced vasculitis, porphyria cutanea tarda or glomerulonephritis, treatment is recommended irrespective of fibrosis stage (recommendation grade A1).
- Women waiting for *in vitro* fertilisation (IVF).

Other specific factors to be considered are:

- Women who wish to become pregnant should be treated before pregnancy to avoid the risk of transmission during delivery, if this is not inappropriate for some reason (recommendation grade A1). If possible, ribavirin should be avoided in these cases (recommendation grade A1). Due to limited experience, treatment during pregnancy is not recommended.
- In selected patients whose HCV infection has a strong negative impact on their quality-of-life or psychosocial situation, treatment may be considered regardless of fibrosis stage (recommendation grade B2).

Fibrosis stages F0–1 indicate the absence of or non-significant fibrosis and for these patients treatment may be

deferred with continued monitoring for disease progression (recommendation grade B2). If a patient is not treated due to mild liver fibrosis stage, re-assessment of fibrosis should be performed within 1–2 years (recommendation grade A2).

When prioritising treatment, it is also reasonable to consider the continued risk of transmission caused by ongoing substance abuse, as this is not a contraindication for HCV therapy.

Assessment of factors influencing treatment options and the likelihood of achieving SVR

With currently available treatment options, the probability of SVR is high, regardless of baseline demographic, clinical and virological characteristics, provided that an appropriate regimen and duration is given.

Viral genotype and the presence or absence of cirrhosis are the principal factors governing treatment recommendations:

- HCV genotype should be determined before initiating therapy because it affects the choice and duration of treatment as well as the likelihood of achieving SVR. Additionally, HCV genotype should be re-evaluated before re-treatment after a prior relapse to rule out (i) an initial undetected co-infection with multiple HCV genotypes, of which not all were eradicated, and (ii) a re-infection with a different genotype.
- Fibrosis stage impacts on treatment duration and for some regimens, whether or not ribavirin should be added.

Other factors that may impact the likelihood of achieving SVR following therapy with direct-acting antiviral agents (DAAs), especially if treatment duration is sub-optimal, include male gender (lower chance for SVR), baseline plasma viral load (greater likelihood of SVR at lower levels), indicators of more advanced cirrhosis (e.g. low platelets and low albumin) and host genetic factors,[12–14] e.g. *IL28B* genotype (higher likelihood of SVR among patients with *IL28B* CC than CT/TT). However, the currently available treatments are so effective that these baseline characteristics are diminishing in clinical importance.

Naturally occurring virus variants that entail reduced sensitivity to NS5A inhibitors or NS3/4A protease inhibitors may also impact the likelihood of achieving SVR.[15] However, routine susceptibility testing currently is not recommended.

Prior to treatment of chronic HCV infection

Before initiating therapy, it is important that patients are well informed and fully understand the importance of compliance as well as the necessity of close monitoring. A careful review of concomitant medications is essential to avoid potential drug–drug interactions. Ribavirin is a potential teratogen and, if prescribed, the need for contraception is vital, regardless of gender. Pregnancy should be avoided with all HCV treatment regimens, as experience of treatment during pregnancy is limited.

Sampling

A basic evaluation, including assessment of other causes of transaminase elevations, must be performed in accordance with local practices before initiating treatment. Prior to starting HCV therapy, the following sampling is recommended: plasma HCV RNA quantification, HCV genotyping, haemoglobin, platelet count, serum albumin, serum bilirubin, PK-INR, AST, ALT, serum creatinine to calculate creatinine-clearance, pregnancy test and evaluation of fibrosis stage.

Treatment of chronic HCV infection

Because of the relatively high cost of DAA regimens and limited therapeutic experience outside tertiary care centres, treatment should presently be administered by specialised clinics. The following recommendations apply to patients with compensated liver disease and Table 1 provides an overview of registered DAAs active against HCV infection.

Combination therapy including interferon is not recommended as first line therapy due to an inferior safety profile as compared to DAA-based treatment (recommendation grade A1). However, interferon-α is still approved as a second line therapy for the treatment of HCV infection and selected HCV genotype 2 or 3 infected patients have a high likelihood of achieving SVR with as little as 12 weeks of interferon-based therapy, e.g. if age is below 40 years or HCV RNA below 1000 IU/mL is achieved by day 7.[16–19] Thus, interferon-based therapy should only be given after an individual benefit risk assessment.

Genotype 1

The following recommendations apply for patients not previously treated with DAA.

Non-cirrhosis—fibrosis stage $\leq$ F3

One of the following treatment options is recommended (recommendation grade A1):

- Ombitasvir/paritaprevir/ritonavir (fixed combination) + dasabuvir 12 weeks. Ribavirin should be added for genotype 1a, but not for genotype 1b.[20–22]
- Sofosbuvir + daclatasvir 12 weeks.[23]
- Sofosbuvir/ledipasvir (fixed combination) for 12 weeks.[24–28] Treatment for 8 weeks may be considered in patients with favourable prognostic factors for achieving SVR, e.g. fibrosis stage $<$F3, lower HCV RNA levels, etc.[28] In the ION-3 study, 8 weeks of treatment with sofosbuvir/ledipasvir resulted in a slightly higher relapse rate as compared to 12 weeks.
- Sofosbuvir + simeprevir 12 weeks.[29]

Compensated cirrhosis—fibrosis stage F4

- Ombitasvir/paritaprevir/ritonavir (fixed combination) + dasabuvir + ribavirin for 12 weeks for genotype 1b.[30] For genotype 1a this treatment should be given for 24 weeks (recommendation grade B1).[31,32] In treatment-naive patients with normal platelet count and normal serum albumin, 12 weeks of therapy should be considered also for genotype 1a (recommendation grade B1).

Table 1. Direct-acting antiviral pharmaceuticals against HCV infection approved for use in interferon-free therapy within the EU.

Substance class	Generic substance	Brand name	Genotype specificity	Barrier to resistence
NS5B polymerase inhibitor (nucleotide analogue)	Sofosbuvir	Sovaldi Harvoni	High activity against genotype 1–6	Very high
NS5B polymerase inhibitor (non-nucleotide analogue)	Dasabuvir	Exviera	Relevant activity only for genotype 1	Low
NS3/4A protease inhibitor	Simeprevir	Olysio	High activity against genotype 1 and 4 No activity against genotype 3	Low
NS3/4A protease inhibitor	Paritaprevir	Viekirax	High activity against genotype 1 and 4	Low
NS5A inhibitor	Daclatasvir	Daklinza	High activity against genotype 1 and 4 Clinical relevant activity also against other genotypes	Low
NS5A inhibitor	Ledipasvir	Harvoni	High activity against genotype 1 and 4 Clinical relevant activity also against genotypes 3–6	Low
NS5A inhibitor	Ombitasvir	Viekirax	High activity against genotype 1 and 4	Low

- Sofosbuvir + daclatasvir 12 weeks (± ribavirin) or 24 weeks (without ribavirin) (recommendation grade B1).
- Sofosbuvir/ledipasvir (fixed combination) for 12 weeks (± ribavirin) or 24 weeks (without ribavirin) (recommendation grade A1).[33,34]
- Sofosbuvir + simeprevir for 12 weeks (± ribavirin) or 24 weeks (without ribavirin) (recommendation grade B1).[35]

For the three latter treatment options, the following applies:

- For patients lacking negative predictive factors for SVR (low platelets, low albumin and/or previous non-response to interferon-based treatment), 12 weeks of treatment without the addition of ribavirin is recommended.
- For patients with negative predictive factors regarding the likelihood of achieving SVR, 12 weeks of treatment with the addition of ribavirin or 24 weeks of treatment without ribavirin is recommended.

Additionally it should be noted that grazoprevir (NS3/4A protease inhibitor) and elbasvir (NS5A inhibitor) recently have completed several registration trials for HCV genotypes 1, 4 and 6 infection [36–38] and likely will be licensed in the near future. Similarly, sofosbuvir/velpatasvir (GS-5816) (fixed combination) for 12 weeks has demonstrated promising results in phase 3 trials for HCV genotypes 1–6.[39]

Genotype 2

Non-cirrhosis—fibrosis stage ≤ F3

- Sofosbuvir + ribavirin administered for 12 weeks (recommendation grade A1).[40]
- If the patient is ribavirin-intolerant, sofosbuvir + daclatasvir may be given for 12 weeks (recommendation grade B2).[41]

Compensated cirrhosis—fibrosis stage F4

- Increased relapse-rate has been reported in patients with cirrhosis and, hence, sofosbuvir + ribavirin for 16 weeks is recommended (recommendation grade C2).[40]
- If the patient is ribavirin-intolerant, contact with an expert is advised.

Genotype 3

The present options regarding re-treatment are more limited for HCV genotype 3 as compared to other genotypes. Therefore, the risk of relapse must be minimised by means of adequate treatment duration and by the addition of ribavirin in patients with more advanced fibrosis.

Non-cirrhosis—fibrosis stage ≤ F3

- sofosbuvir + daclatasvir for 12 weeks is primarily recommended (recommendation grade A1).[41] Addition of ribavirin should be considered for patients with fibrosis stage F3 (recommendation grade B1).
- An alternative interferon-free therapy is sofosbuvir + ribavirin for 24 weeks (recommendation grade A1).[40] However, this regime recently has been reported to result in a lower likelihood of achieving SVR as compared to sofosbuvir + peg-IFN + ribavirin given for 12 weeks in the BOSON study.[42]

Compensated cirrhosis—fibrosis stage F4

sofosbuvir + daclatasvir + ribavirin for 24 weeks is primarily recommended (recommendation grade B1).

Genotype 4

Non-cirrhosis—fibrosis stage ≤ F3

One of the following treatments is recommended:

- Ombitasvir/paritaprevir/ritonavir (fixed combination) + ribavirin for 12 weeks (recommendation grade A1).[43]
- Sofosbuvir + daclatasvir 12 weeks (recommendation grade B1).
- Sofosbuvir/ledipasvir (fixed combination) for 12 weeks (recommendation grade A1).[44,45]
- Sofosbuvir + simeprevir for 12 weeks (recommendation grade B1).

Compensated cirrhosis—fibrosis stage F4

One of the following treatments is recommended (recommendation grade B1):

- Ombitasvir/paritaprevir/ritonavir (fixed combination) + ribavirin for 24 weeks. For genotype 4 infections, this regime has only been studied in non-cirrhotic patients, where 12 weeks of treatment yielded a high likelihood of achieving SVR. The recommended 24-week duration hinges on a conservative extrapolation based on results among cirrhotic genotype 1a infected patients.
- Sofosbuvir + daclatasvir 12 weeks (± ribavirin) or 24 weeks (without ribavirin).
- Sofosbuvir/ledipasvir (fixed combination) for 12 weeks (± ribavirin) or 24 weeks (without ribavirin).
- Sofosbuvir + simeprevir for 12 weeks (± ribavirin) or 24 weeks (without ribavirin).

For the three latter above treatment options, the following applies:

- For patients lacking negative predictive factors for achieving SVR (low platelets, low albumin and/or previous non-response to interferon-based treatment) 12 weeks of treatment without the addition of ribavirin is recommended.
- For patients with negative predictive factors for achieving SVR, 12 weeks of treatment with the addition of ribavirin or 24 weeks of treatment without ribavirin is recommended.

Genotypes 5 and 6

sofosbuvir/ledipasvir (fixed combination) for 12 weeks is recommended (recommendation grade B1).[46,47] In patients with cirrhosis, the addition of ribavirin and/or prolonged duration of treatment should be considered (recommendation grade B1).

Pharmacokinetic drug–drug interactions during treatment with direct-acting antivirals

The risk of interactions differs considerably between DAAs. This applies to their impact on the exposure to other drugs, as well as the effect on their own pharmacokinetic profile. Thus, prior to therapy, careful review of the patient's current medication should be undertaken, including assessment of non-prescription medicines, dietary supplements, as well as healthcare products.

Contraindications and side-effects

Contraindications regarding direct-acting antivirals

Contraindications are few and vary slightly between DAAs.

Contraindications to ribavirin

Pregnancy, breastfeeding or a history of or on-going heart disease.

Side-effects of direct-acting antivirals

Side-effect profiles vary between DAAs, but those reported thus far are few and mostly mild. In general, the proportion of pre-mature termination of therapy secondary to adverse events has been very low in clinical trials (< 1%), often compatible with placebo.

Side-effects of ribavirin

The major side-effect of ribavirin is haemolytic anaemia, with a mean decrease in haemoglobin of ~20 g/L during treatment. Additionally, ribavirin can cause itching and rash. Cough and neuropsychiatric side-effects, such as insomnia, are more common in patients treated with ribavirin when compared to ribavirin-free treatment.

Monitoring during treatment

The following should be monitored during therapy:

- HCV RNA quantification (the limit of detection should be ≤ 10–15 IU/ml): At the start of therapy, week 4, at the end-of-treatment, and at two occasions ≥ 12 weeks after the end-of-treatment. If HCV RNA is detectable at week 4, a new sample should be analysed after 2 weeks. If clinically motivated, closer monitoring of HCV RNA should be performed.
- Complete blood count (CBC), serum bilirubin, ALT, serum albumin, serum creatinine: weeks 2 and 4, and thereafter every 4th week.

Adherence is crucial in order to achieve a favourable therapeutic outcome and, therefore, should be discussed at each visit.

Management of ribavirin-induced anaemia

The dose of ribavirin should be reduced at haemoglobin concentrations below 100 g/L and should be temporarily discontinued at levels below 85 g/L. Reduction of ribavirin has not been associated with reduced efficacy of DAA-based treatment.

Follow-up after treatment

HCV RNA in plasma should be analysed when discontinuing treatment and ≥ 12 weeks after termination of treatment, as well as at one additional later time-point. The positive predictive value of SVR12 for SVR24 is > 99% and, therefore, undetectable HCV RNA at a sampling at least 3 months after termination of treatment may be considered as equivalent to cure.

In spite of achieving SVR, patients will continue to have antibodies directed against HCV and, thus, may not donate blood or organs. However, organs from HCV-positive donors may be accepted if the recipient is HCV infected. Patients achieving SVR should be advised that they are not immune to the re-infection with HCV.

The annual risk of developing HCC is reduced from ~4% to 1% after achieving SVR in patients with compensated cirrhosis.[4] Until more data are generated, continued surveillance

with a bi-annual liver ultrasound investigation is recommended in patients with cirrhosis because of the residual risk of HCC (recommendation grade B2).

Re-treatment of patients who have failed direct acting antiviral treatment

During failure of DAA-based therapy, selection of resistance-associated variants (RAVs) with reduced susceptibility to one or more drugs occurs commonly. Sofosbuvir, however, appears to be an exception as NS5B RAVs only transiently have been observed in isolated cases. Sofosbuvir is, thus, the only DAA documented to retain full effect upon re-treatment.

Selected NS3/4A RAVs tend to revert back to fully sensitive wild-type virus over a period of 1–3 years. Although still not formally studied, NS3/4A protease inhibitors likely may be re-used in subsequent re-treatment regimens, provided sufficient time has passed to allow for reversion to wild-type virus.

In contrast, reversion appears less likely if selection of NS5A RAVs occurs, as these variants seem more persistent. However, NS5A inhibitors might retain partial activity, even in the presence of resistant variants and may, thus, possibly contribute to re-treatment.

Patients having failed DAA-based therapy comprise a heterogeneous group and data concerning re-treatment is limited. Therefore, such patients should be handled individually in consultation with an expert, with the following factors being considered:

- A new genotyping should be performed prior to re-treatment, as discussed previously.
- Patients failing DAA-containing regimen, regardless of the presence or absence of RAVs, are by definition difficult-to-cure. This must be considered when re-treatment is planned, by prolonging duration and/or increasing the overall anti-viral activity of the new regimen, e.g. by adding ribavirin.
- At present, all re-treatment regimens should include sofosbuvir, regardless of whether the patient previously has been treated with sofosbuvir or not (recommendation grade B1).
- If possible, the re-treatment regimen should consist of a combination of sofosbuvir with a new DAA class to which the patient has not been exposed, e.g. a NS3/4A protease inhibitor if the patient previously received the NS5A inhibitor and vice versa (recommendation grade A1).
- If switching DAA class is not possible or if RAVs against multiple classes of DAAs may be suspected, resistance testing may be of value prior to re-treatment.
- Peg-IFN should be considered as part of a re-treatment regimen if multiple class RAVs are expected, e.g. after failure of ombitasvir/paritaprevir/ritonavir combination therapy. This also applies for relapse after combination sofosbuvir and daclatasvir for genotype 3 infections, where NS5A resistance was observed in most patients with relapse in the ALLY-3 study. Treatment with sofosbuvir, peg-IFN and ribavirin for 12 weeks for genotype 3 infections resulted in a high likelihood of achieving SVR in the BOSON study (recommendation grade A1).[42]

Treatment of patients with decompensated liver cirrhosis

These patients should be treated in the same manner, whether or not they are on the transplant waiting list. The choice of treatment selection should be based on HCV genotype.

Genotype 1 or 4

One of the following treatment options is primarily recommended:

- Sofosbuvir/ledipasvir (fixed combination) + ribavirin for 12 weeks (recommendation grade A1).
- Sofosbuvir + daclatasvir + ribavirin for 12 weeks (recommendation grade B1).

For ribavirin-intolerant patients, 24 weeks of treatment with either of the above DAA combinations is an alternative (recommendation grade C2).

Genotype 2

- Sofosbuvir + ribavirin for 16–24 weeks (recommendation grade B1).For ribavirin intolerant patients, sofosbuvir + daclatasvir for 16–24 weeks may be considered (recommendation grade B2).

Genotype 3

- Sofosbuvir + daclatasvir + ribavirin for 24 weeks (recommendation grade B1).For ribavirin-intolerant patients, sofosbuvir + daclatasvir for 24 weeks may be considered (recommendation grade C2).

Dosing of ribavirin in decompensated cirrhosis

As stated above, the addition of ribavirin is recommended in all regimens for patients with decompensated cirrhosis, in spite of poorer tolerance of ribavirin. If anaemia is present at baseline, a starting daily dose of 600 mg should be considered, which, if tolerated, may be increased to the normal weight-based dosing (1000 or 1200 mg). If standard dosing of ribavirin is used at the initiation of therapy, rapid dose reductions should be performed in the event of anaemia.

Treatment of patients with compensated or decompensated cirrhosis accepted for liver transplant

These patients should be managed in collaboration with a liver specialist affiliated with a transplant centre and there is an immediate indication for therapy. If possible, all patients with HCV infection who are on the waiting list for liver transplantation should receive antiviral treatment.

These patients can be divided into two groups: (i) patients with compensated cirrhosis and HCC, where the tumour is the main indication for liver transplantation; and (ii) patients with

decompensated cirrhosis, where severe hepatic impairment motivates transplantation. If HCV treatment needs to be continued after the transplant, paritaprevir/ritonavir-based treatment should be avoided due to the risk of drug interactions with immunosuppressive drugs. This also may apply for simeprevir-containing regimens if cyclosporine use is planned.

Recommendation for sampling while on the waiting list

During HCV therapy

- HCV RNA quantification at the start of therapy and, thereafter, once weekly until the week after the first sample with undetectable HCV RNA.
- Thereafter, HCV RNA quantification should be performed every 4th week until the transplantation.

After completion of HCV treatment

- HCV RNA quantification at 1, 2, 3 and 4 weeks post-treatment.
- Thereafter, HCV RNA quantification every 4th week until the transplant has been performed.In the event of relapse after treatment while on the waiting list, possible re-treatment before liver transplantation should be discussed with a specialist at the transplant centre. An alternative approach is to postpone re-treatment until the first appropriate time-point after transplantation.

Information regarding HCV RNA levels must be continuously reported to the transplant clinic, as this impacts on whether the HCV treatment should continue to be administered in the peri- and post-operative phase.

Considerations at the time of transplantation

If the patient has been virus-free for $\geq$4 weeks before transplantation

Discontinue treatment when the transplantation is performed, even if the full intended treatment duration has not been given.

If the patient has been virus-free <4 weeks before transplantation

Continue treatment, without interruption, for 12 weeks after transplantation. Consider discontinuing or reducing ribavirin dosing if renal impairment occurs post-transplant.

Treatment after liver transplantation

All patients who are viremic at the time of transplantation will relapse upon reperfusion of the transplanted liver. Furthermore, HCV-associated liver disease progresses more rapidly in liver transplant recipients than non-transplanted patients. Thus, HCV infected liver transplant recipients should be offered treatment, regardless of fibrosis stage at the earliest appropriate time-point after transplantation.

The choice of therapy follows the same principles as in non-transplanted patients, taking into account HCV genotype and fibrosis stage. Because of potential drug interactions, regimens including paritaprevir/ritonavir should not be prescribed as a first line therapy. If cyclosporine is included in the immunosuppressive regimen, simeprevir concentrations likely will increase and, thus, may require monitoring. If, prior to transplantation, the patient has relapsed despite a full DAA-based treatment course, this should be considered before initiation of re-treatment.

Dose adjustments of tacrolimus, cyclosporine or everolimus/sirolimus are not needed before the start of concomitant sofosbuvir in combination with ledipasvir, daclatasvir or simeprevir. Secondary to potential drug interactions and expected improvements in liver function, including increased metabolism, close monitoring of immunosuppressive drug concentrations during antiviral therapy is recommended.

On the basis of clinical experience at the transplantation units at the Karolinska and Sahlgrenska University Hospitals,[48] the dose of ribavirin given twice daily can be calculated using the following formula:

$$\text{Ribavirin dose (mg)} = 0.244 \times \text{target concentration} \times T \times (0.122 \times \text{Creatinine clearance} + 0.0414 \times \text{body weight})$$

Creatinine clearance is calculated as Cockroft-Gault formula based on serum creatinine, body weight, sex and age and the target through concentration of ribavirin is 10 μmol/L. The dosage interval (T) is 12 h, so that the calculated ribavirin dose is given twice daily.

Monitoring of laboratory parameters during treatment is similar to that recommended for non-transplanted patients.

Treatment before or after other solid organ or stem cell transplantation

Patients undergoing evaluation for transplantation of organs other than the liver should be treated in the same manner as all other patients with treatment choice based on HCV genotype and liver fibrosis stage.

Potential drug interaction with immunosuppressive medication used in recipients of organ transplantations other than the liver should be handled as described above.

Treatment of patients with renal insufficiency

DAA use in patients with renal impairment

For patients with mild-to-moderate renal impairment, the same treatment options apply as for patients with normal renal function.

- Exposure to the virologic inactive major metabolite of sofosbuvir (GS331007) increases with decreasing renal function. Despite this, sofosbuvir dosing does not need adjustment in the presence of mild-to-moderate renal impairment.

- Currently there is limited experience of sofosbuvir in patients with severe renal impairment (creatinine clearance < 30 mL/min) or haemodialysis, although it recently has been reported that among six patients with severe renal insufficiency receiving a full dose of sofosbuvir for 12–24 weeks, only one patient experienced worsening of renal function, possibly secondary to lupus.[49] Depending on the infecting genotype and severity of liver disease, a suitable sofosbuvir-free regimen, thus, is recommended if possible, e.g. treatment with ombitasvir/paritaprevir/ritonavir with or without ribavirin may be given if glomerular filtration rate (GFR) is below 30 mL/min.[50] Grazoprevir/elbasvir (fixed combination) without the addition of ribavirin reportedly resulted in high SVR rates among genotype 1 infected patients with chronic kidney disease.[51]
- If an appropriate sofosbuvir-free regimen currently does not exist, treatment should only be given if urgently needed. Sofosbuvir treatment of patients with renal impairment should only be given with careful monitoring and in close consultation with a nephrologist.

Ribavirin use in renal impairment

Previously ribavirin was contraindicated in patients with renal impairment (creatinine clearance < 50 mL/min) secondary to the risk of accumulation and, thus, toxic side-effects, in particular severe anaemia. These patients should be treated in collaboration with a physician with extensive experience with such therapy.

Treatment of patients with renal failure and/or ongoing haemodialysis with interferon and ribavirin has been reported.[52] A pre-requisite for the use of ribavirin in this setting is the initiation of therapy with a reduced dose, dependent upon the degree of kidney impairment and that monitoring of plasma ribavirin concentrations is performed. Additionally, haemoglobin should be closely monitored and erythropoietin and iron substitution should be given if needed.

The optimal target trough concentration of ribavirin remains unclear, but the toxicity increases dramatically at concentrations exceeding 15 μmol/L. In this context it should be noted that reduced ribavirin dosing has not been associated with a decreased likelihood of achieving SVR with the new interferon-free treatments.

At steady state, which occurs after more than 4 weeks in patients with normal renal function treated with normal weight-based ribavirin dosing, i.e. 1000 or 1200 mg daily, trough ribavirin concentrations of ~8–12 μmol/L (2000–3000 ng/mL) generally are achieved. In subjects with renal impairment the half-life of ribavirin is prolonged and, thus, also the time before achieving steady state. In severe renal impairment, this may take several months, which must be considered when interpreting the plasma concentrations. In addition, monitoring of ribavirin concentration may be useful in the event of a serious decline in haemoglobin.

In patients with severe renal impairment, creatinine clearance is a better predictor of ribavirin clearance and, thus, also of ribavirin concentration than body weight. Ribavirin, therefore, should primarily be dosed according to renal function rather than solely based on body weight, see Table 2 (recommendation grade A1).

Table 2. Suggested starting dose of ribavirin for patients weighing 70 kg with renal insufficiency adjusted according to creatinine clearance.

Creatinine clearance (ml/min)	Starting dose of ribavirin (mg/dag)
80	800
60	600
40	400
20	400 three-times per week

Treatment of patients co-infected with HCV and HIV

Complications of chronic HCV infection are a major cause of morbidity and mortality in HIV infected patients. In Sweden, ~15% of HIV infected patients have antibodies against HCV.

The same recommendations regarding the indications for and contraindications to HCV treatment apply as for HCV mono-infected patients (recommendation grade A1). However, data supporting the use of shortened treatment duration, e.g. 8 weeks with sofosbuvir and NS5A inhibitors, currently is lacking and, therefore, is not recommended.

Studies among co-infected patients are still limited regarding number and sample size for many regimens. The SVR rates observed with the modern regimens studied, however, are similar to those achieved in HCV mono-infected patients.[53–55]

The most important factor to consider when treating co-infected patients is the potential risk of drug–drug interactions between HIV and HCV treatment regimens. For patients receiving a complex HIV treatment, it may be difficult to evaluate possible interactions, and in such cases contact with a specialist in the field is recommended. If the on-going HIV treatment needs modification, this should be performed prior to the initiation of the HCV treatment.

Patients with on-going HIV treatment should have stable virological control of their HIV infection prior to initiating HCV treatment. CD4 counts are not considered a significant predictor of the likelihood of achieving SVR.[53–55]

In the event of a newly-diagnosed HIV infection, treatment of the HIV infection should be prioritised before HCV therapy.

The same recommendations regarding sampling apply as for patients with HCV mono-infection and HIV monitoring may follow normal clinical routines.

Patients with ongoing or recently concluded substance abuse

Patients with current alcohol abuse or PWIDs should be offered contact with an addiction treatment centre, regardless of whether HCV treatment is indicated or not. Ongoing or recently concluded substance abuse is not an absolute or relative contraindication for HCV therapy if a treatment indication is present. Instead, focus should be placed on individually assessing adherence to HCV treatment and providing psychiatric and/or dependency support.

Table 3. Grading of recommendations regarding the strength and underlying evidence; adapted from the GRADE system used by EASL.

Evidence quality	Definition	
High	Further research is very unlikely to change the confidence in the estimate of effect	A
Moderate	Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate	B
Low	Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate	C
Any change of estimate is uncertain		
Recommendation		
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

Advanced alcohol abuse may negatively impact adherence to HCV treatment and, in addition to host genetic factors [56–59], also is a risk factor for deterioration of liver disease. Therefore, in order to reduce disease progression, the patient should be offered help to reduce or abolish alcohol intake. If a patient cannot abstain from alcohol, the initiation of HCV therapy should be based on the likelihood of adhering to treatment.

Patients who use illicit drugs may have an indication for HCV treatment. Also in this setting compliance problems can be present. In order to create optimal conditions for adherence to HCV therapy, a multidisciplinary approach is required. Thus, close contact with addiction, mental health and social services may be needed prior to initiating anti-viral therapy.

Studies have reported comparable therapeutic outcome among patients on opiate substitution therapy with methadone or buprenorphine [60,61]. Also in this setting, focus should be placed on a multidisciplinary approach in order to optimise adherence.

PWIDs achieving SVR should be offered appropriate supportive measures, including participation in needle exchange programmes, to prevent re-infection.

Children and adolescents (<18 years) with chronic HCV infection

The prevalence of chronic HCV infection is less than 0.5% among European children.[62] During the past decade, ~50 such cases have been reported annually to the Swedish Public Health Agency, with half being below 16 years of age. In light of the expected annual number of infections secondary to mother–child transmission,[63] as well as the number of children immigrating to Sweden from countries with higher HCV prevalence, this number is probably an under-estimate of the true incidence.

The risk of the development of chronicity in children appears to be equivalent (55–80%) to that seen in adults. Spontaneous resolution of infection after vertical transmission may occasionally occur until the age of 5 years and is reportedly related to the host *IL28B* genotype.[64] Among those developing a chronic HCV infection, progression of liver fibrosis may occur, and ~2–3% of teenagers infected early in life develop cirrhosis.

Evaluation and treatment decisions during childhood

In children with chronic HCV infection, the same sampling and monitoring as for adults should be performed. The interpretation of serological analyses in children born to infected mothers is complicated by the presence of residual maternal antibodies for up to 15 months of age. Serological screening at 18 months of age is recommended for babies born to HCV infected mothers and, if reactivity is noted in the screening antibody test, infection must be confirmed by HCV RNA analysis. Children with confirmed chronic HCV infection should be monitored annually by HCV RNA quantification and liver function tests. The need for antiviral therapy should be evaluated in collaboration with a specialist experienced with HCV treatment in paediatric patients.

Fibrosis stage in children can be measured by liver biopsy or elastography using an appropriate child probe. The relationship between histological fibrosis stage and elastography is less well documented in children. However, similar cut-off levels as for adults may probably be used.

Choice of treatment for children with chronic HCV

Currently there are no data on the efficacy and side-effects of DAA treatment in children. Thus, if possible, children should be primarily enrolled in clinical trials using interferon-free treatment. For patients older than 12 years, use of DAA-based regimens may be considered, with the same indications and doses as recommended for adults.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] 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.

[2] Seeff LB. The history of the "natural history" of hepatitis C (1968–2009). Liver Int. 2009;29(Suppl 1):89–99.

[3] Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2001;34:809–816.

[4] Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology. 2004;127(5 Suppl 1):S35–50. PMID: 15508101.
[5] Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology. 2003;125:80–88.
[6] EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol. 2015;63:199–236.
[7] Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology. 2012;142:1293–1302 e4. doi: 10.1053/j.gastro.2012.02.017.
[8] Sebastiani G, Halfon P, Castera L, et al. SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C. Hepatology. 2009;49:1821–1827.
[9] Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. Am J Surg Pathol. 1995;19:1409–1417.
[10] Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996;24:289–293.
[11] Free medication for Hepatitis C. Iceland Monitor. 2015. Iceland Monitor, © 2015 Árvakur hf., Iceland. Available online at: http://icelandmonitor.mbl.is/news/politics_and_society/2015/10/07/free_-medication_for_hepatitis_c/. Accessed 7 Oct 2015.
[12] Rembeck K, Lagging M. Impact of IL28B, ITPA and PNPLA3 genetic variants on therapeutic outcome and progression of hepatitis C virus infection. Pharmacogenomics. 2015;16:1179–1188.
[13] Waldenstrom J, Nystrom K, Lagging M. Do variations in the ITPA gene determine the risk of hepatitis C virus relapse? Future Microbiol. 2014;9:1009–1012.
[14] Rembeck K, Waldenstrom J, Hellstrand K, et al. Variants of the inosine triphosphate pyrophosphatase gene are associated with reduced relapse risk following treatment for HCV genotype 2/3. Hepatology. 2014;59:2131–2139.
[15] Sarrazin C. The importance of resistance to direct antiviral drugs in HCV infection in clinical practice. J Hepatol. 24 Sep 2015. [Epub ahead of print]
[16] Waldenstrom J, Farkkila M, Rembeck K, et al. Short interferon and ribavirin treatment for HCV genotype 2 or 3 infection: NORDynamIC trial and real-life experience. Scand J Gastroenterol. 2016, Mar;51(3):337–343. doi: 10.3109/00365521.2015.1087588.
[17] Lagging M, Langeland N, Pedersen C, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology. 2008;47:1837–1845.
[18] Lagging M, Langeland N, Pedersen C, et al. Weight-adjusted dosing of ribavirin and importance of hepatitis C virus RNA below 1000 IU/mL by day 7 in short-term peginterferon therapy for chronic genotype 2/3 hepatitis C virus infection. Hepatology. 2008;48:695. doi: 10.1002/hep.22450.
[19] Lagging M, Alsio S, Hellstrand K, Norkrans G. Is HCV RNA analysis at day 7 cost-effective in deciding the duration of therapy in chronic HCV genotype 2/3 infection? J Hepatol. 2011;54:835–836; author reply 6–7.
[20] Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370:1594–1603.
[21] Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014;370:1983–1992.
[22] Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370:1604–1614.
[23] Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370:211–221.
[24] Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014;383:515–523.
[25] Mizokami M, Yokosuka O, Takehara T, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. Lancet Infect Dis. 2015;15:645–653.
[26] Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370:1889–1898.
[27] Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370:1483–1493.
[28] Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014;370:1879–1888.
[29] Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014;384: 1756–1765.
[30] Kumada H, Chayama K, Rodrigues L Jr, et al. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. Hepatology. 2015;62:1037–1046.
[31] Lawitz E, Makara M, Akarca US, et al. Efficacy and Safety of Ombitasvir, Paritaprevir, and Ritonavir in an Open-Label Study of Patients With Genotype 1b Chronic Hepatitis C Virus With and Without Cirrhosis. Gastroenterology. 2015;149:971–980.
[32] Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014;370:1973–1982.
[33] Bourliere M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis. 2015;15:397–404.
[34] Reddy KR, Bourliere M, Sulkowski M, et al. Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: An integrated safety and efficacy analysis. Hepatology. 2015;62:79–86.
[35] Pearlman BL, Ehleben C, Perrys M. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related Child's class A cirrhosis. Gastroenterology. 2015;148:762–770 e2; quiz e11–12.
[36] Lagging M, Brown A, Mantry PS, et al. Grazoprevir plus peginterferon and ribavirin in treatment-naive patients with hepatitis C virus genotype 1 infection: a randomized trial. J Viral Hepat. 2015, Sep 10. [Epub ahead of print]. doi: 10.1111/jvh.12464.
[37] Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385:1075–1086.
[38] Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial. Ann Intern Med. 2015;163:1–13.
[39] Gilead Sciences, Inc. Gilead announces svr12 rates from four phase 3 studies evaluating a once-daily, fixed-dose combination of Sofosbuvir (SOF) and Velpatasvir (VEL) (GS-5816) for the treatment of all six Hepatitis C Genotypes. 2015. Available online at: http://www.gilead.com/news/press-releases/2015/9/gilead-announces-svr12-rates-from-four-phase-3-studies-evaluating-a-oncedaily-fixed-dose-combination-of-sofosbuvir-sof-and-velpatasvir-vel-gs5816-for-the-treatment-of-all-six-hepatitis-c-genotypes/. Accessed Sep 21, 2015.
[40] Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370:1993–2001.
[41] Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus

genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61:1127–1135.
[42] Foster GR, Pianko S, Brown A, et al. Efficacy of Sofosbuvir plus Ribavirin with or without Peginterferon-alfa in patients with HCV Genotype 3 Infection and treatment-experienced patients with Cirrhosis and HCV Genotype 2 Infection. Gastroenterology. 2015;149:1462–70. doi: 10.1053/j.gastro.2015.07.043.
[43] Hezode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet. 2015;385:2502–2509.
[44] Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. Lancet Infect Dis. 2015;15:1049–1054.
[45] Smith MA, Mohammad RA. Ledipasvir-sofosbuvir for hepatitis C genotype 4 infection. Lancet Infect Dis. 2015;15:993–995.
[46] Abergel A, Loustaud-Ratti V, Metivier A. Ledipasvir/sofosbuvir treatment results in high SVR rates in patients with chronic genotype 4 and 5 HCV infection. J Hepatol. 2015;62:S219.
[47] Gane EJ, Hyland RH, An D, et al. Efficacy of Ledipasvir and Sofosbuvir, with or without Ribavirin, for 12 weeks in patients with HCV Genotype 3 or 6 Infection. Gastroenterology. 2015;149:1454–1461.e1. doi: 10.1053/j.gastro.2015.07.063.
[48] Ackefors M, Castedal M, Dahlgard O, et al. Peg-IFN and ribavirin treatment for recurrence of genotype 2 and 3 hepatitis C after liver transplantation. Infect Dis (Lond). 2015;47:209–217.
[49] Hundemer GL, Sise ME, Wisocky J, et al. Use of sofosbuvir-based direct-acting antiviral therapy for hepatitis C viral infection in patients with severe renal insufficiency. Infect Dis (Lond). 2015;47:924–929.
[50] Pockros PJ, Reddy KR, Mantry PS, et al. Safety of ombitasvir/paritaprevir/ritonavir plus dasabuvir for treating HCV gt1 infection in patients with severe renal impairment or end-stage renal disease: the RUBY-I study. J Hepatol. 2015;62:S257.
[51] Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386:1537–1545. doi: 10.1016/S0140-6736(15)00349-9.
[52] Bruchfeld A, Lindahl K, Schvarcz R, Stahle L. Dosage of ribavirin in patients with hepatitis C should be based on renal function: a population pharmacokinetic analysis. Ther Drug Monit. 2002;24:701–708.
[53] Naggie S, Cooper C, Saag M, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med. 2015;373:705–713.
[54] Wyles DL, Ruane PJ, Sulkowski MS, et al. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med. 2015;373:714–725.
[55] Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. JAMA. 2015;313:1223–1231.
[56] Lagging M. Impact of IL28B SNPs on therapeutic outcome and liver histology differs between hepatitis C virus genotypes. Pharmacogenomics. 2012;13:847–849.
[57] Rembeck K, Alsio A, Christensen PB, et al. Impact of IL28B-related single nucleotide polymorphisms on liver histopathology in chronic hepatitis C genotype 2 and 3. PLoS One. 2012;7:e29370.
[58] Rembeck K, Maglio C, Lagging M, et al. PNPLA 3 I148M genetic variant associates with insulin resistance and baseline viral load in HCV genotype 2 but not in genotype 3 infection. BMC Med Genet. 2012;13:82.
[59] Ydreborg M, Westin J, Rembeck K, et al. Impact of Il28b-related single nucleotide polymorphisms on liver transient elastography in chronic hepatitis C infection. PLoS One. 2013;8:e80172.
[60] Puoti M, Panzeri C, Rossotti R, Baiguera C. Efficacy of sofosbuvir-based therapies in HIV/HCV infected patients and persons who inject drugs. Dig Liver Dis. 2014;46(Suppl 5):S206–211.
[61] Lalezari J, Sullivan JG, Varunok P, et al. Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. J Hepatol. 2015;63:364–369.
[62] Dominguez A, Bruguera M, Vidal J, et al. Community-based seroepidemiological survey of HCV infection in Catalonia, Spain. J Med Virol. 2001;65:688–693.
[63] Thomas SL, Newell ML, Peckham CS, et al. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection. Int J Epidemiol. 1998;27:108–117.
[64] Ruiz-Extremera A, Munoz-Gamez JA, Salmeron-Ruiz MA, et al. Genetic variation in interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children. Hepatology. 2011;53:1830–1838.