



Editor's choice
Scan to access more
free content

Hepatitis C virus treatment in the real world: optimising treatment and access to therapies

Fabien Zoulim,¹ T Jake Liang,² Alexander L Gerbes,³ Alessio Aghemo,⁴ Sylvie Deuffic-Burban,^{5,6,7,8} Geoffrey Dusheiko,⁹ Michael W Fried,¹⁰ Stanislas Pol,¹¹ Jürgen Kurt Rockstroh,¹² Norah A Terrault,¹³ Stefan Wiktor¹⁴

For numbered affiliations see end of article.

Correspondence to

Professor Fabien Zoulim, Université Lyon 1, Cancer Research Center of Lyon (CRCL), INSERM U1052, Hospices Civils de Lyon 69003, France; fabien.zoulim@inserm.fr

Received 21 July 2015

Revised 2 September 2015

Accepted 3 September 2015

ABSTRACT

Chronic HCV infections represent a major worldwide public health problem and are responsible for a large proportion of liver related deaths, mostly because of HCV-associated hepatocellular carcinoma and cirrhosis. The treatment of HCV has undergone a rapid and spectacular revolution. In the past 5 years, the launch of direct acting antiviral drugs has seen sustained virological response rates reach 90% and above for many patient groups. The new treatments are effective, well tolerated, allow for shorter treatment regimens and offer new opportunities for previously excluded groups. This therapeutic revolution has changed the rules for treatment of HCV, moving the field towards an interferon-free era and raising the prospect of HCV eradication. This manuscript addresses the new challenges regarding treatment optimisation in the real world, improvement of antiviral efficacy in 'hard-to-treat' groups, the management of patients whose direct acting antiviral drug treatment was unsuccessful, and access to diagnosis and treatment in different parts of the world.

INTRODUCTION

The global burden of hepatitis is immense. Viral hepatitis kills 1.45 million people worldwide each year, which is as many as HIV and more than tuberculosis or malaria.¹ Yet, while deaths from HIV/AIDS have declined since 2010, hepatitis deaths have risen. Of the hepatitis viruses, HBV and HCV cause the vast majority of deaths, with hepatocellular carcinoma (HCC) and cirrhosis accounting for most of them. Since 1990, deaths from HBV have plateaued, while HCV deaths continue to rise and are expected to do so at least for the next decade.²

Against this gloomy backdrop, the treatment of HCV has undergone a revolution. In the past 5 years, the launch of direct acting antiviral drugs (DAAs) has seen sustained virological response (SVR) rates reach 95% and above for many patient groups. The new treatments are effective, well tolerated, allow for shorter treatment regimens and offer new opportunities for previously excluded groups. This therapeutic revolution has changed the rules for treatment of HCV, moving the field towards an interferon (IFN)-free era and raising the prospect of HCV eradication.^{3–4} Yet it raises further questions. How do we optimise outcomes in the real world? How can we improve results for 'hard-to-treat' groups? Is it better to treat HCV before or after liver transplant (LT)? How should we manage people whose DAA treatment is unsuccessful? And—given the high price of these new

treatments—how can we improve access to diagnosis and treatment for those patients who need them most?

Gut brought together some of the leading global experts in HCV to discuss these questions and point a way forward. The round table, held during the European Association for the Study of the Liver's International Liver Congress 2015, brought clarity to some of these issues and looked into the future pipeline of HCV treatment. This article aims to summarise that shared knowledge.

Treatment efficacy with currently available drugs

The development of new generation DAAs with much higher SVR rates has dramatically improved the prospects for people infected with HCV. SVR directly affects clinical outcomes and survival, lowering all cause mortality, as shown in cohort studies and meta-analysis.^{5–7} A recent meta-analysis found that mortality rates in those with SVR after IFN-containing regimens, compared with those without SVR, decreased by 62–84%, varying by cirrhosis and co-infection with HIV. The risk of HCC after 5 years was reduced from 9.3% to 2.9% in mono-infected patients, from 13.9% to 5.3% in patients with cirrhosis and from 10% to 0.9% in HIV co-infected patients. Risk of LT within 5 years for patients with cirrhosis reduced from 7.3% to 0.2%. SVR is also associated with a reduction in extrahepatic disease associated with HCV such as diabetes, kidney impairment, non-Hodgkin's lymphoma and cardiovascular complications.^{8,9}

It will be necessary to follow patients treated successfully with DAA-based therapy to establish the long-term clinical benefits. But even so, these data provide a strong argument for HCV treatment, given the high cost of treating liver cancer and of liver transplantation.

In 2011, the standard treatment regimen for HCV was pegylated IFN plus ribavirin (PR) for 24 weeks or 48 weeks. PR therapy resulted in an SVR in 45% of genotype 1 (G1) patients. The first generation of DAAs with protease inhibitors (PIs) used in combination with PR pushed SVR rates up to 75%, but with a substantially increased side effect burden⁴ which also limited eligibility to treatment.¹⁰ With the development of additional classes of DAAs (nucleotide and non-nucleotide inhibitors of NS5B polymerase, second wave PIs, and NS5A inhibitors), rates improved again. A combination of DAA drugs, used in the first non-IFN regimens with or without ribavirin, produce SVR rates of



CrossMark

To cite: Zoulim F, Liang TJ, Gerbes AL, et al. *Gut* 2015;64:1824–1833.

95% and above for (G1) patients. These new combinations have better efficacy across genotypes, are better tolerated thus improving treatment eligibility,⁵ allow a reduced treatment duration of 12 weeks or 24 weeks, and an easier dosing schedule with a reduced pill burden. See table 1 for a summary of the classes of new DAAs. While data exist for combinations of DAAs with PR,^{11–14} IFN therapy is increasingly difficult to use as patients are aware of the side effects and the existence of alternative drug regimens.

The combination of two DAAs (NS5B inhibitor sofosbuvir and NS5A inhibitor ledipasvir) cures >90% treatment-naïve patients without cirrhosis with G1 HCV in phase 3 studies. Studies suggest there is no need to add ribavirin in this group, or to extend beyond 12 weeks of treatment.^{15–16} It was even suggested that shortening to 8 weeks of sofosbuvir/ledipasvir might be sufficient to achieve cure in >90% naïve patients with G1 HCV, low viral load (<6 log IU/mL) and without cirrhosis;¹⁷ this suggests an opportunity for shorter duration therapy with even more potent antivirals, as discussed below. For patients with cirrhosis, SVR rates with this dual therapy drop to 90%, but addition of ribavirin and extension of treatment to 24 weeks raises rates to 95%.^{15–18–19} This DAA combination is successful even in patients with cirrhosis who had previously failed PR and then a PI plus PR.¹⁹ Success rates drop by around 10% with decompensated cirrhosis.²⁰ We consider the challenge of decompensated cirrhosis and treatment failure below.

Trials of the recently licensed three-dimensional (3D) combination (the PI paritaprevir boosted with ritonavir, combined with NS5A inhibitor ombitasvir and NS5B inhibitor dasabuvir) show similarly high SVR rates.^{21–24} For G1b, recent results suggest there is no need to use ribavirin or extend treatment beyond 12 weeks, whether patients have cirrhosis or not.²⁵ However, the current label recommends ribavirin in patients with G1b and cirrhosis. In contrast, patients with G1a appear to benefit from the addition of ribavirin, and patients with cirrhosis may require treatment extended to 24 weeks.^{22–26}

G2 infected patients can usually be treated with a combination of sofosbuvir and ribavirin for 12 weeks, giving high rates of SVR.^{27–31} Patients with cirrhosis, especially those who are treatment experienced, may require longer treatment (16–24 weeks) or the addition of an NS5A inhibitor to increase antiviral potency. HCV G3 is the new ‘hard-to-treat’ genotype, with lower SVR rates, and is considered in more detail below.

Recent data for non-IFN treatment of G4 comes from a study in mono-infected patients without cirrhosis, using the

combination of ombitasvir and paritaprevir with or without ribavirin, for 12 weeks. SVR was 100% with ribavirin, 91% without.³² In a recent study including 103 patients with G4, sofosbuvir and ribavirin gave an SVR rate of 90% in those treated for 24 weeks versus 77% with a 12 week course and patients with cirrhosis at baseline had lower rates of SVR12 (78%; 24 weeks of therapy) than those without cirrhosis (93%; 24 weeks of therapy).³³ In addition, real-world data of sofosbuvir plus simeprevir and sofosbuvir plus daclatasvir in G4-infected patients showed high rates of SVR4 across 12-week and 24 week regimens, with and without ribavirin.³⁴ The results of a recent single-centre, open-label cohort, phase 2a trial, in patients with HCV G4, who were treatment-naïve or IFN treatment-experienced and received sofosbuvir and ledipasvir combination for 12 weeks, showed that 20 (95%) of 21 patients completed 12 weeks of treatment and achieved SVR12 (95%) including 7 patients with cirrhosis.³⁵ These results give promise for IFN and ribavirin-free treatments for G4-infected patients. Few trials have included participants with G5 and G6. A trial including seven patients with G5 or G6 gave a 100% SVR rate for the combination of PR plus sofosbuvir in treatment-naïve patients.²⁹ Twenty-five patients with G6 treated with sofosbuvir and ledipasvir for 12 weeks had a 96% SVR rate, suggesting that this may be a good combination.³⁶

The advances in therapy over the last few years are reflected in clinical practice guidelines published by the European Association for the Study of the Liver in April 2015, which can be viewed at <http://www.easl.eu/research/our-contributions/clinical-practice-guidelines>³⁷ and by the American Association for the Study of Liver Diseases published in September 2015: at (<http://www.hcvguidelines.org/full-report-view>).³⁸ See summary box below.

Key points:

- ▶ In trials, all-oral DAA regimens are available for all genotypes and show remarkable efficacy with SVR rates consistently 90% or above
- ▶ From IFN-based treatments, SVR has a direct effect on important clinical outcomes
- ▶ In trials, shorter treatment regimes without ribavirin are suitable for some genotypes and stages of disease
- ▶ However, while SVR rates are improved across most populations, better treatment options are needed for patients with decompensated cirrhosis and cirrhosis with previous treatment failure, especially those with G3

Questions:

- ▶ Should HCV screening and treatment be more widely offered?

Optimal treatment in the real world

Translating clinical trial results into real-world practice provides important information for clinicians, patients and policy makers. While phase 3 trials include a relatively homogeneous population, utilisation of HCV medications in the real world often includes patients with more advanced liver disease or medical comorbidities who may have been excluded from registration trials. Thus, safety and efficacy may differ in the expanded population being treated with new agents.

Data from the HCV-TARGET cohort, an international longitudinal observational study, demonstrated that DAA regimens were generally safe and well tolerated in the real-world environment with low rates of serious adverse events or discontinuations due to side effects.³⁹ However, ongoing vigilance is warranted as a recent advisory from regulatory authorities suggested potentially serious interaction of sofosbuvir-containing

Table 1 Oral antivirals for hepatitis C: examples of drugs approved (at least in some countries) and in the pipeline of development

Class	Action	Examples
Protease inhibitors	Inhibits translation and polyprotein processing	Approved: telaprevir, boceprevir, asunaprevir, vaniprevir, simeprevir, paritaprevir In development: grazoprevir On hold: faldaprevir
NS5A inhibitors	Inhibits replication complex	Approved: daclatasvir, ledipasvir, ombitasvir In development: elbasvir, odalasvir, velpatasvir
NS5B inhibitors	Inhibits replication of viral RNA	Approved: sofosbuvir, dasabuvir In development: beclabuvir On hold: deleobuvir, valopicitabine

regimens with amiodarone that can result in severe, and even fatal, bradycardias.⁴⁰

Efficacy results from real-world studies are generally supportive of those found in clinical trials, although SVR rates are somewhat lower in the expanded population. The HCV-TARGET study of more than 700 patients with G1 treated with the combination of sofosbuvir and simeprevir reported an overall SVR rate of 87%. The study did not find a significant impact of adding ribavirin in this context.⁴¹ Other smaller studies gave similar results.⁴² The Hepather Cohort study with more than 400 patients, the majority of whom were cirrhotic, with G1 treated with sofosbuvir and daclatasvir reported higher SVR rates when used for 24 weeks or with the addition of ribavirin for 12 weeks.⁴³ Data for real-world experience of treating patients with G3 for 24 weeks with sofosbuvir and ribavirin demonstrated SVR rates of 65%, with 30% relapse rates.⁴⁴ Patients infected with G3 with cirrhosis and previous treatment failure are emerging as the new difficult-to-treat population.

Recently, investigators assessed clinical data from electronic medical records for 4026 patients with G1 or G2 HCV who started sofosbuvir-based therapy for the recommended 12-week duration through the US Department of Veterans Affairs, the largest integrated national provider of HCV care in the USA. A third of the patients were treatment-experienced. Among 3203 G1 patients, 1302 started sofosbuvir, peginterferon and ribavirin; 1559, sofosbuvir plus simeprevir; and 342, sofosbuvir +simeprevir+ribavirin. All 823 G2 patients started sofosbuvir +ribavirin. The SVR rate seemed to be significantly lower by 15–20% than what was observed in the registration trials and in patient cohorts followed in reference centres.⁴⁵

Current DAA regimens are highly effective with few contraindications to treatment such that the number of patients who are potential treatment candidates is daunting. Therefore, it is important to make the most of finite resources and to maximise the cost-effectiveness of therapy. Perhaps the most important factor in treatment success is adherence to treatment recommendations. The patient's commitment to therapeutic success should be assessed prior to embarking on therapy. Assessment should include factors that might interrupt treatment, such as travel plans, work schedule and unstable social environment un conducive to medication adherence. Patients who have been living with HCV for many years, treated unsuccessfully with various regimens, and who have been waiting for more effective all-oral regimen therapy are usually well known to their clinicians and have demonstrated great capacity to be adherent to even toxic regimens.

Pretreatment education is also important and may be the best strategy for maximising adherence. Stressing the importance of taking the medications each day and a discussion of the potential mild side effects will equip patients to self-manage their regimens. Newly diagnosed patients may need more time to process the consequences of HCV infection and the implications of therapy. Clinicians need to be alert for this changing patient profile as screening increases and treatment becomes more widespread. Regardless of duration of HCV infection, however, a patient's needs should be individually addressed to maximise adherence. The clinician needs to discuss adherence strategies relative to the patient's lifestyle, for example how to accommodate a pill regimen while working night shifts.

Before starting treatment, a comprehensive clinical and virological evaluation is needed, including staging of liver disease for the presence of cirrhosis, virological evaluation for HCV genotype and level of HCV RNA, and all current medications should be evaluated for potential drug-drug interactions (DDIs).

This information is needed to choose the right treatment regimen. For instance, many patients with HCV take acid-suppressant therapy, which can diminish absorption of ledipasvir. Drug interactions can be checked on websites such as (<http://www.hep-druginteractions.org/>).

Once treatment is underway, the clinician needs to put in place a specific programme of visits and/or scheduled telephone calls with a pharmacist or a nurse during treatment to monitor treatment adherence, antiviral efficacy, potential side effects and DDI. A challenge is to establish a practical intervention that improves adherence rates at low cost to the clinic with minimal inconvenience to the patient.

Five basic concepts apply when selecting the most appropriate regimen for an individual patient:

- ▶ Viral genotype
- ▶ Prior treatment experience
- ▶ Presence of cirrhosis
- ▶ Comorbidities (especially renal insufficiency)
- ▶ Concurrent medications that interact with HCV DAAs.

Data from the trials discussed above have been translated into guidelines for all-oral treatment of HCV infection. Organisations issuing guidance include the food and drug administration (FDA) via drug labels (ledipasvir and sofosbuvir pack, simeprevir pack, ombitasvir, paritaprevir and ritonavir, dasabuvir pack), the European Association for the Study of the Liver (EASL)³⁷ and the American Association for the Study of Liver Disease/Infectious Disease Society of America (AASLD/IDSA).³⁸

Key points:

- ▶ The DAA regimens have high cure rates across diverse populations in the real world
- ▶ Choice of optimal treatment regimen, duration and addition of ribavirin are well expressed in recent treatment guidelines
- ▶ Adherence to treatment is likely to be crucial for success

Questions:

- ▶ How can we optimise adherence in newly diagnosed patients?

Treatment of hard-to-treat groups

With the arrival of new therapies, the old rules about which patients are difficult to treat for HCV and should be deferred for future treatment have dramatically changed. Here we consider four key 'hard-to-treat' groups: G3, co-infection with HIV, renally impaired and those with drug and alcohol misuse. Treatment of patients with decompensated cirrhosis or liver transplantation who are in more urgent need for treatment is addressed separately in the following chapter.

When PR was the mainstay of treatment, G1 was the genotype least responsive to drug therapy. Since the introduction of DAAs, G3 has become the most difficult. Twenty-four weeks of sofosbuvir and ribavirin is required to achieve SVR rates of 90%, with a sharp drop-off in SVR rates among treatment-experienced patients with cirrhosis to only 60%,^{28 31} rising to 73% with the addition of ledipasvir for 12 weeks, also in treatment-experienced patients.⁴⁶ The combination of daclatasvir/sofosbuvir shows rates of approximately 95% for patients without cirrhosis, but SVR rates drop sharply when cirrhosis is present.⁴⁷ Other real-world experience in patients without cirrhosis with G3 infection showed SVR rates of approximately 90% with sofosbuvir/daclatasvir±ribavirin given for 24 weeks.⁴⁸ Thus, the recent European Association for the Study of the Liver (EASL) clinical practice guidelines and AASLD/IDSA HCV Guidance recommend that G3 patients with cirrhosis should be treated with sofosbuvir/daclatasvir and ribavirin for 24 weeks to

maximise the chance of SVR.^{37 38} This is based on evidence showing good efficacy of sofosbuvir/daclatasvir in compassionate use programme.⁴⁹ Currently, this is an argument to treat G3-infected patients before the stage of cirrhosis to improve the SVR rate based on sofosbuvir/daclatasvir for a shorter duration (12 weeks) without ribavirin. One of the current questions in the difficult-to-treat patients, especially those with G3 infection, liver cirrhosis and previous treatment failure, is the use of ribavirin in the DAA regimen.³⁷ Indeed, besides the results of cohort studies and trials,³⁷ ribavirin was shown to reset IFN-responsiveness in HCV-infected liver through epigenetic changes in the liver, which may explain the clinical observations in patients receiving IFN-free regimen via the action of endogenous IFN in the liver microenvironment.^{50 51} It was also interesting to see in a small study of ledipasvir/sofosbuvir given for 12 weeks in G3-infected patients that the SVR rate increased from 64% (16/25) to 100% (26/26) with the addition of ribavirin.³⁶

HIV co-infection is much less problematic than it was in the PR days. SVR rates have improved dramatically with the new therapies, to the extent that co-infected patients now achieve SVR rates similar to mono-infected patients. Recent studies showed high SVR rates of 96% in G1-infected or G4-infected patients treated with sofosbuvir/ledipasvir for 12 weeks,⁵² and 97% across G1–G4 in patients receiving sofosbuvir/daclatasvir for 12 weeks, but a decreased SVR rate to 76% when sofosbuvir/daclatasvir administration was shortened to 8 weeks.⁵³ This is reflected in the EASL³⁷ and AASLD/IDSA³⁸ recommendations for HCV treatment, which give identical treatment recommendations for co-infection and mono-infection. The main challenge with HCV treatment in co-infected patients is management of DDIs, especially with HCV regimens containing PIs. People who have been infected with HIV for decades are often on second line or salvage therapy, which frequently includes a boosted PI. HIV PIs and HCV PIs are metabolised by the same pathway and have severe interactions. The EASL guidelines recommend prioritisation of patients with HIV co-infection for treatment, regardless of fibrosis level, because of their higher risk of liver disease progression.³⁷ Rates of re-infection with HCV are considerably higher among the HIV co-infected population than in other high-risk groups, with a 5 year post-SVR re-infection rate of 21.7%. By comparison, 5 year post-SVR re-infection rates among intravenous drug users and prisoners are 13.2%, and among low-risk populations are 1.1%.⁵⁴ Besides antiviral treatment in HCV-HIV co-infection to reduce the pool of infected people, strategies for changing sexual behaviour are urgently needed to avoid re-infection and repeated treatments as traumatic sex practices with high risk for blood-blood contacts remaining the main transmission risk factor in HIV-seropositive men having sex with men (MSM).⁵⁴

Patients with renal insufficiency and on dialysis are a challenging population to treat, with high need but few treatment options. The toxicity of ribavirin is significantly increased by renal impairment. Sofosbuvir, now a mainstay of treatment, is contraindicated in patients with a glomerular filtration rate (GFR) below 30 mL/min. Recently, 28 patients without cirrhosis with severe renal insufficiency (creatinine clearance <30 mL/min/1.73 m², of whom 13 were on haemodialysis) were treated with paritaprevir/ritonavir+ombitasvir+dasabuvir for 12 weeks with (G1a) or without (G1b) ribavirin at 200 mg/day. Ten out of 10 patients achieved SVR4. Ribavirin was stopped in 8 out of 13 patients and 4 received erythropoietin (EPO).⁵⁵ This small study, while preliminary, suggests this combination may be a treatment option for this patient population. The grazoprevir

+elbasvir combination was evaluated in 116 G1-infected patients with end-stage renal insufficiency of whom 77% were on haemodialysis. Nineteen per cent achieved SVR12. One relapse was observed in a non-cirrhotic G1b patient. No dose adaptation and no treatment cessation were necessary during the study.⁵⁶ This study provided promising treatment options for this patient population.

There are very few data to assess how DAAs will affect clinical outcome in patients with extrahepatic manifestations of chronic hepatitis C.⁵⁷ While it is clear that the presence of mixed cryoglobulinaemia was a predictive factor of poor response to IFN-based therapy,⁵⁸ to what extent the use of DAAs may change treatment outcomes in this group of patients deserves further study.

There are little data to assess how DAAs will affect treatment of patients who misuse drugs and alcohol. Studies carried out in the PR era showed that patients on substitution therapies such as methadone or buprenorphine achieved SVR rates close to those seen in non-drug injecting populations,⁵⁹ suggesting that DAA therapy too will be feasible in this group. As IFN-free therapies promise fewer contraindications, many patients who would not have been considered for HCV therapy in the past because of psychological comorbidities will now become candidates for treatment. Adherence has always been a problem in this group and it is known that adherence declines after week 6 of treatment.⁶⁰ Shorter treatment regimens (<12 weeks) might be very helpful in this setting. As we have already discussed for the HIV co-infected patients, there is also a heightened risk of reinfection in this population.⁵⁴ However, it is reasonable to assume that treatment of HCV infection in this population should lead to a decreased burden of the virus and in turn in a decreased transmission of the infection. Antiviral treatment should be included in global programmes including lifestyle interventions and management of addictions.

Key points

- ▶ Some G3-infected patients remain hard to treat, especially those who are treatment-experienced with cirrhosis
- ▶ HIV co-infection is no longer a factor affecting SVR rates although DDIs add complexity to management
- ▶ Patients with renal insufficiency have limited treatment options, especially those on dialysis

Questions

- ▶ Does ribavirin add to efficacy of DAA treatment in G3?
- ▶ What is the effect of DAA on extrahepatic manifestations of HCV infection?
- ▶ How do we minimise the rates of re-infection in high-risk groups?
- ▶ Which interventions aid adherence to treatment for drug and alcohol users?

Treatment in patients with decompensated cirrhosis and LT

In the past, patients with decompensated cirrhosis were rarely offered treatment, as IFN based regimens were poorly tolerated and associated with significant risk of complications. All-oral DAA combinations offer the opportunity to treat these patients, although the only combinations licensed for patients with severe liver disease (Child-Pugh B or C) are sofosbuvir/ledipasvir or sofosbuvir/daclatasvir, with or without ribavirin.^{37 38} This should take into account that renal dysfunction typically accompanies advanced liver disease and the options are further limited, as sofosbuvir is not approved for use in patients with creatinine clearance <30 mL/min. However, patients with

decompensated cirrhosis have much to gain with successful therapy, including improvement in liver function and reversal of symptoms of decompensation. Since survival in persons with decompensated cirrhosis in the absence of treatment is on average only 2 years,⁶¹ there is a limited time period to intervene with treatment.

Results from treatment-experienced patients with compensated cirrhosis given sofosbuvir+ledipasvir, show that similar SVR results were achieved with the addition of ribavirin as a 12-week regimen or the extension of treatment to 24 weeks.¹⁹ In studies in decompensated cirrhosis treated with sofosbuvir+ledipasvir and ribavirin, ~85% of G1 patients with Child-Pugh B or C cirrhosis achieved SVR with 12 weeks of treatment.²⁰ Results of compassionate access studies report 80% SVR rates with sofosbuvir and daclatasvir with and without ribavirin for 12 weeks.⁶² Collectively, results show lower SVR rates in patients with decompensated cirrhosis than other treatment groups, and severity of liver dysfunction (Child-Pugh class) and portal hypertension (as indicated by platelet count) may identify patients with lower likelihood of achieving SVR.

While SVR is important, the additional goals of therapy in patients with decompensated cirrhosis are clinical stabilisation, reversal of decompensation, improved survival and reduced need for LT. Studies in patients with Child-Pugh B/C cirrhosis treated with ledipasvir+sofosbuvir for 12 weeks showed Model for End-Stage Liver Disease (MELD) scores improved in the majority of patients (17 of 30 with Child-Pugh class B; 13 of 23 with Child-Pugh class C).²⁰ However, some patients improved by only one or two points, some had no improvement and some deteriorated. Greater improvements may be evident with longer follow-up after SVR but whether the improvements obtained will be sufficient to reverse or prevent all complications of cirrhosis and avoid LT is unknown. Since access to LT is determined by MELD score and SVR may diminish MELD score, successful treatment may reduce the likelihood of getting a LT and this makes the timing of treatment a challenge. For some patients, having a LT is most important, and deferral of HCV treatment until after LT may be a better option.

The situation is different for people with cirrhosis listed for LT for HCC or other exceptions for whom access to LT is not dependent on severity of liver disease. In a study of treatment with sofosbuvir plus ribavirin up to the time of LT in Child-Pugh A patients with HCC, all patients achieved undetectable viral load on treatment, and among those who had a transplant, 70% were HCV-free post LT. The success of this approach increased to 96% if patients had HCV RNA levels below the lower limit of quantification for ≥ 4 weeks pre-transplant.⁶³ The treatment strategy works best in living donor transplants and for patients with exception status as treatment can be timed to LT. Even in those select patients, this strategy can be challenging since time to HCV RNA negativity varies and LT time is not always precisely predictable. To our knowledge, there are no data available regarding the impact of DAA therapy in patients with HCC outside the LT context, in terms of HCC recurrence or mortality. Currently, one might recommend DAA therapy in all patients undergoing a curative treatment for HCC.

Historically, transplant recipients were considered a difficult-to-treat group with low SVR rates and poor tolerability of therapy. This has changed completely with IFN-free DAA combinations. With current all oral HCV therapies, SVR rates in LT recipients appear comparable to non-transplant patients.^{23 63 64} Regimens that include a PI have added complexity due to DDIs with immunosuppressant therapy. Since

renal dysfunction is a frequent post-LT complication, recipients with concurrent disease and estimated glomerular filtration rate (eGFR) less than 30 mL/min have more limited treatment options.

Key points:

- ▶ Treatment options are more limited in decompensated cirrhosis
- ▶ Achievement of SVR can result in clinical improvement for patients with advanced disease, but this is not universal
- ▶ HCV therapies used post transplant appear to achieve rates of viral eradication similar to non-transplant patients but DDIs need to be considered.

Questions:

- ▶ Is it better to treat patients with advanced disease before or after liver transplantation?
- ▶ How does pre-transplant treatment failure affect post-transplant treatment success?
- ▶ What are the consequences of treatment failure (ie, drug resistance) post-transplant?

Management of DAA failure

One of the emerging questions is the management of patients who have failed a DAA-based treatment. Currently, most of these patients have been treated because of severe underlying liver disease. Therefore, rescue antiviral therapy seems mandatory in these patients, although the optimal antiviral regimen is not known. Should we re-treat with the same DAA class, or a different class? If we use the same DAA class, we might consider delaying treatment in the hope that acquired resistant mutations to treatment disappear. This is based on experience with the first generation of PIs, where the virus of G1 patients who failed treatment reverted to non-resistant wild type virus at a median of 1 year.⁶⁵ This may not be realistic for patients with advanced disease, and it may not be relevant to patients treated with IFN-free therapy and other DAA classes. Data about patients who failed on the NSSB inhibitor sofosbuvir show that resistant variants are uncommon and revert to wild type quickly, leaving the opportunity to re-treat early.⁶⁶ PI resistant variants selected after treatment failure tend to return to baseline levels rapidly and are detectable only in a minority of patients 48 weeks after treatment cessation. Conversely, NSSA inhibitor resistance tends to persist. Resistance-associated variants (RAVs) to ombitasvir were detected in 98% of patients who failed 3D therapy at 24 weeks, and in 96% at 48 weeks post treatment,⁶⁷ suggesting that patients who failed NSSA inhibitor containing regimens represent a challenging population.

Some data exists to assess the efficacy of re-treating with the same class of DAA. Patients who failed on a PI regime and were treated again with simeprevir+sofosbuvir with or without ribavirin showed a 4-week SVR of 81%, compared with 89% for patients who had not previously failed with a PI. This suggests SVR is likely to be slightly lower in these patients,³⁹ but is consistent with the kinetics of disappearance of PI-resistant variants described above. Further data on patients who had failed sofosbuvir and ribavirin and were then treated again with a combination of sofosbuvir+ledipasvir plus ribavirin show that 44 of 45 achieved an SVR on re-treatment, suggesting that re-treatment may be effective when associated with an NSSA inhibitor.⁶⁸

Few data are available for assessing retreatment of patients who have failed NSSA inhibitors, although a study showed that patients who have baseline RAVs associated with limited efficacy had a higher relapse rate (31%). This could be used as proxy data, although treatment duration was short (12 weeks) and ribavirin was not used (sofosbuvir/ledipasvir Summary of

Product Characteristics (SmPC)). The same finding was reported in a recent study investigating re-treatment with 24 weeks of sofosbuvir/ledipasvir in G1 patients who had failed the same combination for 8–12 weeks. Overall SVR rates were 71% but by stratifying patients on the presence of baseline RAVs in the NS5A region, the authors found that those with RAVs achieved an SVR in 60% of the cases compared with 100% in those without RAVs.⁶⁹ The question whether ribavirin could have increased SVR rates remains unanswered as it was not part of the studied regimen.

From a virological standpoint, the recommendation is to treat patients with another DAA class, to avoid cross-resistance issues. Data on re-treatment of people who had failed PI treatment, using a sofosbuvir/ledipasvir combination with or without ribavirin, showed the same SVRs as non-treatment-experienced patients.¹⁸ Another study of this combination, in people with compensated cirrhosis who had previously failed on PI, showed SVR of 96–97%.¹⁹ Changing the regimen looks to be a highly effective strategy. These data are reflected in the 2015 EASL guidelines, which suggest re-treatment of patients who have failed on a DAA-containing regimen with an IFN-free combination that includes a drug with a high barrier to resistance (currently sofosbuvir) and one or two other drugs without cross-resistance to the drugs already tried. The EASL committee suggests using a regimen suitable for ‘hard-to-treat’ patients, by extending the duration of treatment to 24 weeks and adding ribavirin.³⁷

The outstanding question is how to address the patient who fails on the 3D regimen of paritaprevir(r), ombitasvir and dasabuvir, which combines all available DAA classes. The option of returning to a combination with pegylated IFN is not attractive; sofosbuvir as a nucleotide NS5B inhibitor (different from the non-nucleoside inhibitor dasabuvir) might serve as a backbone to the rescue therapy with pegylated IFN.⁷⁰ However, unless new classes become available, it may be a last-resort therapeutic option. Another question to be addressed is the clinical relevance of testing for RAVs before starting re-treatment in patients who failed a previous DAA-containing regimen. Indeed, the different levels of drug resistance, viral fitness, and cross-resistance of the selected RAVs may affect treatment decisions, but this needs to be evaluated prospectively in the context of a rapidly evolving therapeutic field. By contrast, in treatment-naïve patients, detection of RAVs prior to therapy is not clinically useful because of the very high SVR rate in this situation.¹⁷

Key points:

- ▶ Limited data are available to guide ‘next’ treatment choices in patients who fail to achieve SVR with DAA combination therapy
- ▶ Deferral of treatment pending more data may be appropriate for patients who are not in need of immediate retreatment
- ▶ Currently, people who have failed DAA treatment are likely to have advanced disease and be in need of more immediate re-treatment
- ▶ Re-treatment including a different class of DAA without cross-resistance gives good results
- ▶ Patients who relapse after treatment with an all-oral combination have RAVs that will persist for a variable duration of time post treatment

Key questions:

- ▶ Should patients with milder disease wait before retreatment?
- ▶ How can we treat people who fail the 3D regimen and those who failed several lines of DAA-based therapy?
- ▶ Should ribavirin be considered in re-treatment of a DAA failure?

Future drug development

As noted above, while huge progress has been made over the past 5 years, HCV still presents challenges. Drug development continues for new therapies and combinations which may address some of these challenges. Priorities for next generation DAA combinations include regimens which:

- ▶ Are truly pan-genotypical, with high efficacy against all genotypes and subtypes
- ▶ Allow for shorter duration of treatment
- ▶ Include coformulated drugs and dispense with the need for ribavirin
- ▶ Have limited DDIs
- ▶ Result in an SVR for more than 95% of patients at all levels of fibrosis
- ▶ Treat prior DAA failures and have low resistance rates
- ▶ Treat special groups including people with HIV, post-transplant patients, people with end-stage renal disease and possibly children

Two new combinations expected in 2016 include sofosbuvir with the new NS5A inhibitor GS5816 (velpatasvir), and a double or triple regimen including the new PI grazoprevir and the new NS5A inhibitor elbasvir, possibly with the addition of an NS5B inhibitor.

Data for the sofosbuvir/GS5816 combination in treatment-naïve patients demonstrate good results across genotypes for 12 weeks of treatment at 100 mg dose of GS5816. Results from 8 weeks of treatment and lower doses were suboptimal.⁷¹ The study found ribavirin had no effect on SVR in this group of patients and there were no significant safety signals. In treatment-experienced patients, the combination also appeared safe and effective for 12 weeks without ribavirin. SVR rates were significantly lower in GT3 patients, especially those with cirrhosis, where higher dose (100 mg vs 25 mg) was clearly required.⁷² Overall, this combination seems to provide better results in the difficult-to-treat populations compared with sofosbuvir/ledipasvir.

Early proof-of-concept studies of triple therapy (sofosbuvir, ledipasvir and the non-nucleotide NS5B polymerase inhibitor GS9669 or the NS3 PI GS9451) showed high cure rates after 6 weeks of therapy. Particularly interesting was that some patients who finished the 6 week study with detectable HCV RNA levels went on to have an SVR within 14–21 days.⁷³ If this finding can be replicated, it could change the treatment paradigm with shorter duration treatments. How short can treatment regimes get? Interim data from a study of a nucleotide-based triple regimen (PI grazoprevir plus NS5A inhibitor elbasvir plus sofosbuvir) showed that some patients do respond within 4 weeks of treatment, but most need 8-week or 6 week regimens.⁷⁴ Identifying patients who will respond to shorter durations of treatment with some degree of certainty will be a challenge. An analysis of treatment outcomes by baseline resistance-associated variants demonstrated that patients with specific RAVs treated with this regimen had a lower SVR (38% vs 75%).⁷⁴

Results from another study of new generation NS5A inhibitor ACH-3102 combined with sofosbuvir (as a proxy for an NS5B inhibitor in development) in a phase 2 study showed 12 of 12 treatment-naïve G1 patients achieved SVR12, and that all of them had shown a viral load below the lower limit of quantification after 4 weeks of treatment.⁷⁵

One promising avenue for the new NS5A inhibitors is their use against different genotypes and subgenotypes. The NS5A inhibitor MK-8408 is pan-genotypical and demonstrates in vitro activity against known clinically relevant RAVs. The new

nucleoside MK-3682 demonstrates potency against G2 and G3, with significant reductions in viral load after only 7 days' dosing.⁷⁶

Finally, future treatment could use small-molecule entry inhibitors or monoclonal antibodies to prevent HCV from entering liver cells. Animal experiments demonstrate how this approach could prevent infection and reduce persistent infection.^{77–79} This route may be worth exploring for patients preparing for transplant, in order to prevent infection of the graft as well as in patients with RAVs to prevent their spread in association with other DAAs.

Key points:

- ▶ The DAA pipeline continues to deliver IFN-free treatments and most patients in future will not need ribavirin
- ▶ Treatment resistance may be a growing problem
- ▶ Drugs with pan-genotypical activity are in the pipeline

Questions:

- ▶ Can we identify patients who could benefit from short treatment regimens of 6 weeks or less with newer DAA combination therapies?

Access to treatment: high-income countries

DAAs are expensive and available resources are limited, even in high-income countries. We have to evaluate new treatment strategies to optimise the medical intervention and make the most of the resources available. While costs of treatment are 'upfront', the benefit expected from lower healthcare costs will be accrued over decades. One challenge is to find novel financing mechanisms to defray those upfront costs.

Cost-effectiveness analyses consider how effective a new technology is compared with existing technologies, and whether this additional benefit is worth the additional costs. This is often considered in terms of cost per quality-adjusted life year (QALY). Acceptable costs per QALY vary by country, although a benchmark of around US\$50 000 is often discussed.⁸⁰ Two recent publications compared sofosbuvir-based treatment regimens for HCV to the standard of care in the USA. The first showed an overall cost of US\$55 400 per QALY gained. However, the cost per QALY varies considerably in different populations: as low as US\$9700/QALY gained for G1 treatment-naïve patients with cirrhosis, rising to US\$410 500/QALY gained for G3 treatment-experienced patients without cirrhosis.⁸¹ A comparison of IFN-free regimens versus standard of care found that the costs per QALY varied by genotype and regimen: from US\$12 825/QALY gained for sofosbuvir/ledipasvir for G1 to US\$691 574/QALY gained for sofosbuvir/daclatasvir for G2. Overall the figures suggest that DAAs offer substantial public health benefits at a reasonable cost per treated patient, in selected groups.

Costs per QALYs are sensitive to the stage of fibrosis when treatment is initiated. The more advanced the fibrosis, the lower the cost per QALY. This can be seen across genotypes, and over several different treatment regimens. It may not be cost-effective to treat patients with G1 before they are at fibrosis stage 2.⁸² Age is also a factor; treating younger patients clearly saves more QALYs than older patients. By this analysis, treating patients over the age of 70 years does not result in a cost/QALY gained under \$50 000, for any genotype or treatment regimen. Treating patients over the age of 50 years may not be cost-effective in G2 or G3. This raises a fundamental question about how to treat older patients, who could benefit from improvements to quality of life. A threshold analysis evaluated treatment costs to cost-effectively treat patients at fibrosis stage F0, compared with treatment at stage F2, given a range of assumptions

and a cost-effectiveness threshold of \$100 000 per QALY.⁸³ It showed treatment costs could range from around \$20 000 for less effective drugs to around \$45 000 for highly effective drugs. Patients aged 40 years can be cost-effectively treated by a course costing around \$55 000, which drops to below \$20 000 for patients aged 70 years.

Even if the new DAA therapies are cost-effective in selected groups, they are not cost-saving and affordable at their current prices. Treating all eligible patients with HCV would have an immense impact on health service budgets, unless it is planned over a 10 year period, allowing progressive treatment for patients with lower fibrosis scores. Another issue will be how to identify the undiagnosed HCV carriers who are not seeking medical care. Therefore the current challenge in the HCV field is now treatment access. If these regimen prices remain at the current levels, the treatment of patients with HCV will require additional resources and value-based patient prioritisation. Limiting access to therapy, usually based on the severity of the disease, is one strategy to address the question of cost. However this generates some difficulties: it is difficult to accept for patients with less severe disease and will delay progress towards HCV elimination. It may also decrease the success rate as it was discussed for G3-infected patients. Attempting to convince patients with HCV and their advocates that cost-spreading via patient prioritisation is not discrimination but a way to make treatment for everyone more manageable in the long term, may be the most rational approach. However the simplest approach is probably to lower the costs of the drugs.⁸⁴

Key points

- ▶ DAAs are cost-effective in certain patient groups, but this varies by genotype, stage of fibrosis and age

Questions

- ▶ How do we prioritise treatment in cost-effective areas?
- ▶ How can clinicians explain the need to treat priority patients first, without failing lower-priority patients?
- ▶ How to lower drug costs to increase access to treatment?

Access to treatment: low-income and middle-income countries

Improving access to treatment for HCV-infected people in low-income and middle-income countries requires consideration of the burden of hepatitis C infection, knowledge of how many people require treatment, strategies to reduce the price of drugs and improved logistics to allow use of therapies.³ The task is hampered by missing data. There is no consensus on how many people are infected with HCV worldwide. WHO estimates between 130 million and 150 million people have chronic HCV infection. Prevalence is highest in Africa and Asia.⁸⁵ Most people with chronic HCV live in middle-income countries with the greatest numbers living in China, Pakistan, and Nigeria.⁸⁶ These are not countries that attract the interest of traditional aid donors. There are even less data to assess how many people need treatment. There are no population-based studies that assess the distribution of fibrosis stages. The numbers actually diagnosed and treated are low, but most of the results come from European countries.⁸⁷ Less than 5% of infected people in low-income countries know they are infected, and few of these have access to treatment.

Before considering the price of drug treatment, we should consider the obstacles for introducing wide-scale HCV treatment in low-income and middle-income countries. First, people need to be aware that they are at risk of infection, in order to come forward for testing. Confirming chronic HCV infection requires a nucleic acid test, which is not available everywhere.

Assessment for treatment eligibility then requires testing for degree of fibrosis, genotype and viral load. The health system requirements for this to happen are high including trained healthcare workers and well-equipped laboratories. At present, HCV treatment is the domain of hepatologists. To reach all those who need treatment, treatments have to be devolved to primary care doctors, which means that treatment needs to be standardised and simplified. One of the benefits of the newly emerging treatments is the hope for a dramatic simplification of the treatment cascade. Pan-genotypical drugs that are safe and effective regardless of fibrosis could remove the need for HCV genotyping and fibrosis assessment. We could foresee a treatment pathway that requires a rapid diagnostic test of HCV antigen to diagnose the disease, with a repeat antigen test after treatment to confirm success using point-of-care tests.

Price of drug treatment remains key. Prices have dropped quickly. Sofosbuvir has a list price of US\$84 000 for 12 weeks of treatment per patient in the USA, but this has dropped to US\$900 in Egypt. However, the manufacturing cost is estimated at US\$68 to US\$136 for sofosbuvir so lower costs should be possible and should become a reality with the introduction of generic formulations of DAAs.⁸⁸ Within the next 15 years, large-scale manufacture of two or three drug combinations of HCV DAAs is theoretically feasible, with minimum target prices of US\$100–250 per 12-week treatment course. These low prices could make widespread access to HCV treatment in low-income and middle-income countries a realistic goal.⁸⁸ The implementation of response guided therapy with IFN does not seem the best approach, as patients with the highest chance of achieving SVR usually can wait to have more affordable and even more effective treatments. Furthermore, the main issue as mentioned earlier will be to identify the undiagnosed patients; by that time, we can expect that DAA-based regimens will be more accessible. Antiretroviral treatment for HIV began with very high costs, which plummeted after the introduction of generic drugs. But the HIV story demonstrates what is lacking in HCV. Pressure on HIV drug pricing came from strong advocacy, initially driven by the MSM community in the USA and Europe. Large donors were active in low-income countries, and large-scale bulk purchases by donors such as the Global Fund created a large market for generics manufacturers, and through competition, significant price reductions. As HCV lacks a strong advocacy group, middle-income countries tend to be left to fend for themselves without these drivers.

There are several options to increase affordability of HCV drugs:

- ▶ Voluntary licensing agreements, whereby patent holders license their drugs to generic companies and provide technology transfer. However, medicines can only be marketed in specific, generally low-income, countries. An example of this is the voluntary licensing agreement announced by Gilead, which has issued voluntary licenses to 11 Indian generics manufacturers, which will be able to make their generic drugs available to 103 low-income and middle-income countries, excluding China.
- ▶ Differential pricing, where the patent holders negotiate a price reduction country by country. Prices tend to remain higher than those of generics and agreements are usually confidential.
- ▶ Patent oppositions, where countries take legal action to argue that a new drug does not demonstrate sufficient innovation

to qualify for a patent. This is usually a lengthy process. Patents for sofosbuvir have been declined in China, Egypt and India.

- ▶ Compulsory licensing, where a country decides based on its public health needs that drugs can be manufactured locally, or cheaper generic drugs can be imported. This approach is rarely used, as there is usually significant political opposition to compulsory licensing and local production of generics can be technically challenging. Bangladesh and Egypt are starting local manufacture of DAAs outside of the licensing agreements.

To speed access to treatment for low-income and middle-income countries, WHO is developing a global hepatitis strategy with a goal of eliminating HCV as a public health threat by 2030. It has included key HCV drugs on the Essential Medicines List and is producing updated treatment guidelines that will include preferred treatment regimens by the end of the year.

Key points

- ▶ The complexity of HCV diagnosis and treatment hamper access to therapy, even without high drug costs
- ▶ Simplified regimens may overcome this obstacle
- ▶ HCV lacks the strong advocacy and bulk purchasing through global-donor mechanisms that drove price decreases in HIV/AIDS

Questions

- ▶ Which of the current strategies for increasing access to HCV therapies in low-income or middle-income countries will work best?

CONCLUSION

Without doubt, the introduction of DAA therapies in HCV have transformed the treatment landscape and offer a brighter vista, which could even include eradication of this burdensome disease. With notable exceptions, most patient populations would now benefit from IFN-free therapy.

The expense of treatment, coupled with medical capacity, means that priority patients must be treated first. But once that job is underway, interesting questions arise about how and when to treat the remaining patients. More patients under treatment will mean more treatment failures, with the challenges that that brings. Resistance to therapy is likely to become a more significant problem, thus arguing for an optimisation of the current treatment management on an individual basis. Antiviral drugs currently under development may also address that question.

HCV therapy is undergoing a true medical revolution that still faces many challenges. The ongoing clinical research and the mobilisation of health stakeholders should hasten the path towards an eradication of the disease within the next decade.

Author affiliations

¹Université Lyon 1, Cancer Research Center of Lyon (CRCL), INSERM U1052, Hospices Civils de Lyon, Lyon, France

²Liver Diseases Branch, NIDDK, NIH, Bethesda, Maryland, USA

³Klinikum der LMU München-Grosshadern, Liver Center Munich, University Hospital Munich, Munich, Germany

⁴U O Gastroenterologia ed Epatologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

⁵InsERM, IAME, UMR 1137, Paris, France

⁶Univ Paris Diderot, Sorbonne Paris Cité, Paris, France

⁷InsERM, LIRIC-UMR995, Lille, France

⁸Univ Lille, Lille, France

⁹UCL Institute of Liver and Digestive Health, Royal Free Hospital London, London, UK

¹⁰UNC Liver Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

¹¹Université Paris Descartes, INSERM USM20, Institut Pasteur et Assistance Publique–Hôpitaux de Paris, Département d'Hépatologie, Hôpital Cochin, Paris, France

¹²Department of Medicine I, Jürgen Kurt Rockstroh: University Hospital Bonn, Bonn, Germany

¹³University of California San Francisco, San Francisco, California, USA

¹⁴World Health Organization, Geneva, Switzerland

Acknowledgements The authors thank Anna Sayburn for the contribution towards taking notes during the round-table discussion and drafting the first manuscript.

Contributors All authors contributed significantly to the manuscript by drafting the work or revising it critically for important intellectual content, and final approval of the submitted version was obtained from each author.

Competing interests AA received consulting and lecture fees from Gilead Sciences, Janssen, Merck, AbbVie, BMS, as well as grants and research support from Gilead Sciences. SD-B reports receiving research grants from Janssen and MSD; consultancy honoraria from AbbVie, Bristol-Myers Squibb, HEVA, Janssen, MSD and Public Health Expertise; and lecture fees from Bristol-Myers Squibb, Gilead and Janssen. GD acted as advisor to Gilead Sciences, Merck, Bristol Myers Squibb, Janssen and AbbVie. MWF reports research grant funding from AbbVie, Bristol-Myers Squibb, Gilead, Glaxo, Janssen, Merck, NIH and consultant funding from AbbVie, Bristol-Myers Squibb, Gilead, Glaxo, Janssen, Merck. ALG received grants from Gilead, MSD and Roche and advisory board fees from Bristol-Myers Squibb. SP has received consulting and lecturing fees from Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Vertex, Gilead, Roche, MSD, Novartis, Abbvie, Sanofi and Glaxo Smith Kline, and grants from Bristol-Myers Squibb, Gilead, Roche and MSD. JKR has received consulting and lecturing fees from Abbott laboratories, Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, Cipla, Gilead, Janssen, MSD, ViiV, and grants from NEAT-ID and Gilead. NAT received Grant support from Gilead, AbbVie, Eisai, Biotest, and consulting/advisory board fees from Bristol-Myers Squibb, MSD, Achillion, Janssen. FZ has received consulting and/or lecturing fees from Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Gilead Sc and MSD.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

- Murray CJ, Ortblad KF, Guinovart C, *et al.* Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014;384:1005–70.
- Thomas D, Zoulim F. New challenges in viral hepatitis. *Gut* 2012;61(Suppl 1):i1–5.
- Hill A, Cooke G. Medicine. Hepatitis C can be cured globally, but at what cost? *Science* 2014;345:141–2.
- Welsch C, Jesudian A, Zeuzem S, *et al.* New direct-acting antiviral agents for the treatment of hepatitis C virus infection and perspectives. *Gut* 2012;61(Suppl 1):i36–46.
- van der Meer AJ, Wedemeyer H, Feld JJ, *et al.* Life expectancy in patients with chronic HCV infection and cirrhosis compared with a general population. *JAMA* 2014;312:1927–8.
- van der Meer AJ, Veldt BJ, Feld JJ, *et al.* Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012;308:2584–93.
- Simmons B, Saleem J, Heath K, *et al.* Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. *Clin Infect Dis* 2015;61:730–40.
- Aghemo A, Lampertico P, Colombo M. Assessing long-term treatment efficacy in chronic hepatitis B and C: between evidence and common sense. *J Hepatol* 2012;57:1326–35.
- Hsu YC, Ho HJ, Huang YT, *et al.* Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut* 2015;64:495–503.
- Maasoumy B, Port K, Markova AA, *et al.* Eligibility and safety of triple therapy for hepatitis C: lessons learned from the first experience in a real world setting. *PLoS ONE* 2013;8:e55285.
- Hezode C, Hirschfield GM, Ghesquiere W, *et al.* Daclatasvir plus peginterferon alfa and ribavirin for treatment-naïve chronic hepatitis C genotype 1 or 4 infection: a randomised study. *Gut* 2015;64:948–56.
- Lawitz E, Lalezari JP, Hassanein T, *et al.* Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naïve patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis* 2013;13:401–8.
- Moreno C, Hezode C, Marcellin P, *et al.* Efficacy and safety of simeprevir with PegIFN/ribavirin in naïve or experienced patients infected with chronic HCV genotype 4. *J Hepatol* 2015;62:1047–55.
- Reddy KR, Zeuzem S, Zoulim F, *et al.* Simeprevir versus telaprevir with peginterferon and ribavirin in previous null or partial responders with chronic hepatitis C virus genotype 1 infection (ATTAIN): a randomised, double-blind, non-inferiority phase 3 trial. *Lancet Infect Dis* 2015;15:27–35.
- Afdhal N, Zeuzem S, Kwo P, *et al.* Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014;370:1889–98.
- Kowdley KV, Lawitz E, Poordad F, *et al.* Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med* 2014;370:222–32.
- 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;370:1879–88.
- Afdhal N, Reddy KR, Nelson DR, *et al.* Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014;370:1483–93.
- Bouliere 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.
- Charlton M, Everson GT, Flamm SL Jr, *et al.* Ledipasvir and Sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology* 2015;149:649–59.
- Andreone P, Colombo MG, Enejsa JV, *et al.* ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology* 2014;147:359–65.e1.
- 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;370:1594–603.
- Kwo PY, Mantry PS, Coakley E, *et al.* An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med* 2014;371:2375–82.
- 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;370:1604–14.
- Feld, *et al.* International Symposium on Viral Hepatitis and Liver Diseases. 2015.
- 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;370:1973–82.
- Gane EJ, Stedman CA, Hyland RH, *et al.* Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013;368:34–44.
- Jacobson IM, Gordon SC, Kowdley KV, *et al.* Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013;368:1867–77.
- Lawitz E, Mangia A, Wyles D, *et al.* Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013;368:1878–87.
- Omata M, Nishiguchi S, Ueno Y, *et al.* Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. *J Viral Hepat* 2014;21:762–8.
- 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.
- Hezode C, Asselah T, Reddy KR, *et al.* Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naïve and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-1): a randomised, open-label trial. *Lancet* 2015;385:2502–9.
- Doss W, Shih G, Hassany M, *et al.* Sofosbuvir plus ribavirin for treating Egyptian patients with hepatitis C genotype 4. *J Hepatol* 2015;63:581–5.
- Fontaine H, Hezode C, Zoulim F, *et al.* Efficacy of oral sofosbuvir-based combinations in HCV genotype 4 mono-infected patients from the French observational cohort ANRS C022 HEPATHER. *J Hepatol* 2015;62(Suppl):LP28.
- 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;15:1049–54.
- 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* Published Online First: 7 Aug 2015. doi:10.1053/j.gastro.2015.07.063
- European Association of Study of Liver. EASL recommendations on treatment of hepatitis C 2015. *J Hepatol* 2015;63:199–236.
- AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015;62:932–5.
- Jensen DM, O'Leary J, Pockros P, *et al.* Fried M for the HCV-TARGET Study Group. Safety and efficacy of sofosbuvir-containing regimens for hepatitis C: real-world experience in a diverse, longitudinal observational cohort. *Hepatology* 2014;60(Suppl 1):219A.
- Renet S, Chaumais MC, Antonini T, *et al.* Extreme Bradycardia After First Doses of Sofosbuvir and Daclatasvir in Patients Receiving Amiodarone: 2 Cases Including a Rechallenge. *Gastroenterology* 2015. in press.
- Sulkowski MS, Vargas HE, Di Bisceglie AM, *et al.*, for the HCV-TARGET Study Group. Simeprevir plus Sofosbuvir with or without ribavirin for the treatment of patients with HCV genotype 1 infection in real-world clinical practice: the HCV TARGET Study. *Hepatology* 2014;60(suppl 1):955 (abstract).
- Shiffman ML, James AM, Long AG, *et al.* Treatment of Chronic HCV With Sofosbuvir and Simeprevir in Patients With Cirrhosis and Contraindications to Interferon and/or Ribavirin. *Am J Gastroenterol* 2015;110:1179–85.

- 43 Pol S, Bourliere M, Lucier S, *et al.* Safety and efficacy of the combination Daclatasvir sofosbuvir in HCV genotype 1-mono-infected patients from the French Observational cohort ANRS CO22. *J Hepatol* 2015;62(Suppl 2):S258.
- 44 Alqahtani S, Zeuzem S, Manns MP, *et al.* Safety and effectiveness of sofosbuvir-based regimens for the treatment of hepatitis C genotype 3 & 4 infections: interim analysis of a prospective, observational study. *J Hepatol* 2015;62(Suppl 2):S652–3.
- 45 Backus LI, Belperio PS, Shahoumian TA, *et al.* Effectiveness of sofosbuvir-based regimens in genotype 1 and 2 hepatitis C virus infection in 4026 U.S. Veterans. *Aliment Pharmacol Ther* 2015;42:559–73.
- 46 Gane EJ, Hyland RH, An D, *et al.* High Efficacy of LDV/SOF Regimens for 12 Weeks for Patients with HCV Genotype 3 or 6 Infection. *Hepatology* 2014;60:1274A–5A.
- 47 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;61:1127–35.
- 48 Welzel T, Cornberg M, Petersen J, *et al.* Daclatasvir plus sofosbuvir with or without ribavirin in patients with chronic HCV infection: interim analysis of a multicenter compassionate use program. *J Viral Hepatitis* 2015;(Suppl 2):24–25.
- 49 Hezode C, de Ledinghen V, Fontaine H, *et al.* Daclatasvir plus sofosbuvir with or without ribavirin in patients with HCV genotype 3: interim analysis of a compassionate use program. *J Hepatol* 2015;62(Suppl 2):LP05.
- 50 Rotman Y, Noureddin M, Feld JJ, *et al.* Effect of ribavirin on viral kinetics and liver gene expression in chronic hepatitis C. *Gut* 2014;63:161–9.
- 51 Testoni B, Durantel D, Lebosse F, *et al.* Ribavirin restores IFN α responsiveness in HCV-infected livers by epigenetic remodeling at interferon stimulated genes. *Gut* Published Online First: 16 Jun 2015. doi:10.1136/gutjnl-2014-309011
- 52 Naggie S, Cooper C, Saag M, *et al.* Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med* 2015;373:705–13.
- 53 Wyles DL, Ruane PJ, Sulkowski MS, *et al.* Datasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med* 2015;373:714–25.
- 54 Hill AM, Simmons B, Saleem J, *et al.* Five-year risk of late relapse or reinfection with hepatitis C after sustained virological response: meta-analysis of 49 studies in 8534 patients. CROI 2015. February 23–26, 2015. Seattle, Washington. Abstract 654.
- 55 Pockros PJ, Reddy KR, Mantry P, *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-1 study. *J Hepatol* 2015;62(Suppl 2):S257.
- 56 Roth DA, Nelson D, Bruchfeld A, *et al.* LP02: C-surfer: grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease. *J Hepatol* 2015;62(Suppl 2):S264.
- 57 Carrier P, Jaccard A, Jacques J, *et al.* HCV-associated B-cell non-Hodgkin lymphomas and new direct antiviral agents. *Liver Int* Published Online First: 22 Jun 2015.
- 58 Gragnani L, Fognani E, Piluso A, *et al.* Long-term effect of HCV eradication in patients with mixed cryoglobulinemia: a prospective, controlled, open-label, cohort study. *Hepatology* 2015;61:1145–53.
- 59 Chossegros P, Melin P, Hezode C, *et al.* A French prospective observational study of the treatment of chronic hepatitis C in drug abusers. *Gastroenterol Clin Biol* 2008;32:850–7.
- 60 Petersen T GL, Townsend K, Calderon M, *et al.* Pill burden & treatment length reduce adherence to IFN-free hepatitis C therapy in an urban cohort. 21st Conference on Retroviruses and Opportunistic Infections; 3–6 March 2014:Abstract 667.
- 61 Gringeri E, Vitale A, Brolese A, *et al.* Hepatitis C virus-related cirrhosis as a significant mortality factor in intention-to-treat analysis in liver transplantation. *Transplant Proc* 2007;39:1901–3.
- 62 Foster GR, McLauchlan J, Irving W, *et al.* O002: treatment of decompensated HCV cirrhosis in patients with diverse genotypes: 12 weeks sofosbuvir and NS5A inhibitors with/without ribavirin is effective in HCV genotypes 1 and 3. *J Hepatol* 2015;62(Suppl 2):S190–1.
- 63 Charlton M, Gane E, Manns MP, *et al.* Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. *Gastroenterology* 2015;148:108–17.
- 64 Forns X, Charlton M, Denning J, *et al.* Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. *Hepatology* 2015;61:1485–94.
- 65 Sullivan JC, De Meyer S, Bartels DJ, *et al.* Evolution of treatment-emergent resistant variants in telaprevir phase 3 clinical trials. *Clin Infect Dis* 2013;57:221–9.
- 66 Svarovskaia ES, Dvory-Sobol H, Parkin N, *et al.* Infrequent development of resistance in genotype 1–6 hepatitis C virus-infected subjects treated with sofosbuvir in phase 2 and 3 clinical trials. *Clin Infect Dis* 2014;59:1666–74.
- 67 Krishnan P, Tripathi R, Schnell G, *et al.* Long-term follow-up of treatment-emergent resistance-associated variants in NS3, NS5A and NS5B with Paritaprevir/R-, Ombitasvir- and Dasabuvir-based regimens. *J Hepatol* 2015;62(Suppl 2):S220.
- 68 Wyles D, Pockros P, Morelli G, *et al.* Ledipasvir-sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens. *Hepatology* 2015;61:1793–7.
- 69 Lawitz E, Flamm S, Yang J, Pang P, *et al.* Retreatment of patients who failed 8 or 12 weeks of Ledipasvir/Sofosbuvir-based regimens with Ledipasvir/sofosbuvir for 24 weeks. *J Hepatol* 2015;62(Suppl 2):S192.
- 70 Pol S, Sulkowski MS, Hassanein T, *et al.* Sofosbuvir plus pegylated interferon and ribavirin in patients with genotype 1 hepatitis C virus in whom previous therapy with direct-acting antivirals has failed. *Hepatology* 2015;62:129–34.
- 71 Tran T, Morgan TR, Thuluvath PJ, *et al.* Safety and efficacy of treatment with sofosbuvir+GS 5816 plus/minus ribavirin for 8 or 12 weeks in treatment naïve patients with genotype 1–6 HCV infection. *Hepatology* 2014;60:237.
- 72 Pianko S, Flamm Steven L, Shiffman M, *et al.* High Efficacy of Treatment with Sofosbuvir+GS-5816 \pm Ribavirin for 12 Weeks in Treatment Experienced Patients with Genotype 1 or 3 HCV Infection. *Hepatology* 2014;60(Suppl 4):297A–8A.
- 73 Kohli A, Osinusi A, Sims Z, *et al.* Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study. *Lancet* 2015;385:1107–13.
- 74 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;385:1075–86.
- 75 Gane Edward J, Kocinsky Hetal, Schwabe Christian, *et al.* Interim sustained virologic response (SVR) safety and tolerability results of 8 week treatment with ACH-3102 and sofosbuvir in chronic hepatitis C (HCV) genotype 1 treatment naïve patients: a phase 2 “proxy” study. *Hepatology* 2014;60:1281A–2A.
- 76 Gane E, Sicard E, Popa A, Zhou X-J, *et al.* A phase 1/IIa study assessing 7 day dosing of IDX21437 in subjects infected with hepatitis C virus. *Hepatology* 2014;60:1161A.
- 77 Maily L, Xiao F, Lupberger J, *et al.* Clearance of persistent hepatitis C virus infection in humanized mice using a claudin-1-targeting monoclonal antibody. *Nat Biotechnol* 2015;33:549–54.
- 78 He S, Lin B, Chu V, *et al.* Repurposing of the antihistamine chlorcyclizine and related compounds for treatment of hepatitis C virus infection. *Sci Transl Med* 2015;7:282ra49.
- 79 Xiao F, Fofana I, Thumann C, *et al.* Synergy of entry inhibitors with direct-acting antivirals uncovers novel combinations for prevention and treatment of hepatitis C. *Gut* 2015;64:483–94.
- 80 Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the \$50,000-per-QALY threshold. *N Engl J Med* 2014;371:796–7.
- 81 Chhatwal J, Kanwal F, Roberts MS, *et al.* Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med* 2015;162:397–406.
- 82 Najafzadeh M, Andersson K, Shrank WH, *et al.* Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. *Ann Intern Med* 2015;162:407–19.
- 83 Leidner AJ, Chesson HW, Xu F, *et al.* Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. *Hepatology* 2015;61:1860–9.
- 84 Pawlotsky JM, Feld JJ, Zeuzem S, *et al.* From non-A, non-B hepatitis to hepatitis C virus cure. *J Hepatol* 2015;62(1 Suppl):S87–99.
- 85 Mohd Hanafiah K, Groeger J, Flaxman AD, *et al.* Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013;57:1333–42.
- 86 Cooke GS, Lemoine M, Thursz M, *et al.* Viral hepatitis and the Global Burden of Disease: a need to regroup. *J Viral Hepat* 2013;20:600–1.
- 87 Dore GJ, Ward J, Thursz M. Hepatitis C disease burden and strategies to manage the burden (Guest Editors Mark Thursz, Gregory Dore and John Ward). *J Viral Hepat* 2014;21(Suppl 1):1–4.
- 88 Hill A, Khoo S, Fortunak J, *et al.* Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. *Clin Infect Dis* 2014;58:928–36.