

Pan-genotypic treatment regimens for hepatitis C virus: Advantages and disadvantages in high- and low-income regions

C. Hézode

Department of Hepatology, Hôpital Henri Mondor, Université Paris-Est, Créteil, France

Correspondence

Christophe Hézode, Service Hépatologie, Hôpital Henri Mondor, Créteil, France.
Email: christophe.hezode@aphp.fr

Summary

During the last 5 years, the availability of direct-acting antiviral (DAA) agents has revolutionized the treatment of hepatitis C virus (HCV). Compared with interferon/ribavirin—the previous standard of care—DAA combination regimens offer improved sustained virological response (SVR) rates, shorter treatment durations of 8–24 weeks, convenient once-daily single-tablet formulations and more favourable tolerability profiles. HCV treatment is complex, and the choice of therapy must consider a complex range of factors, including baseline viral load, fibrosis stage, the HCV genotype and subgenotype, and the presence of resistance-associated substitutions at baseline. Globally, HCV genotype 1 predominates, and there are extensive data and various treatment options available for this genotype. Genotypes 2–6 are prevalent and may even predominate in different geographical regions, reflecting diverse factors including human migration patterns and unsafe use of injection drugs and blood products. Such factors are themselves influenced by socio-economic factors, and poor regions often have the greatest unmet need for effective HCV therapies. The latest pan-genotypic DAA combination regimens provide the potential to eradicate HCV around the globe, regardless of genotype, hence minimizing the need for virological testing services, which often are unavailable in poorer regions. Economics inevitably remain a barrier to access, and extensive cooperation will be required between clinical organisations and pharmaceutical manufacturers to agree appropriate pricing policies, especially in poorer economic regions. This review considers key data and treatment guidelines for DAA therapies, including pan-genotypic combination regimens, in the context of regional differences in HCV genotype and socio-economic factors.

KEYWORDS

direct-acting antiviral, hepatitis C virus, low-income regions, pan-genotypic

1 | CURRENT BURDEN OF HEPATITIS C VIRUS

It is estimated that 130–180 million people worldwide suffer from chronic hepatitis C virus (HCV) infection.¹ HCV infection ranges in

severity from a mild illness of several weeks duration to a serious, lifelong illness, with a significant proportion of chronically infected individuals developing liver cirrhosis or liver cancer and approximately 700 000 people dying annually from HCV-related liver disease.¹

Developing countries and areas of low social and economic development face particular challenges relating to HCV. As a blood-borne virus, common routes of infection include unsafe injection practices, such as sharing contaminated needles, reuse of medical equipment

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; SVR, sustained virological response.

without adequate sterilization and transfusion of un-screened blood products. Currently, despite the availability of antiviral medicines which cure HCV infection in the majority of patients and thereby reduce the risk of death from liver cancer and cirrhosis,¹ access to diagnosis and treatment remains limited by socio-economic factors.

2 | GEOGRAPHICAL AND GENOTYPIC DIVERSITY

Considerable global diversity exists in terms of both the total prevalence of HCV infection and distribution of different HCV genotypes. Figure 1 summarizes the global prevalence of viraemic HCV by geographical region. Thirty-one countries account for 80% of total global viraemic infections, with China, Pakistan, Nigeria, Egypt, India and Russia accounting for >50% of total infections.²

Current analyses consider six major HCV genotypes, which are further classified into subtypes. Genotype 1, which is the most prevalent worldwide, constitutes 40%-50% of all HCV infections; it is seen as subtype 1a or 1b in almost all cases (99% overall; 31% and 68%, respectively).³ The next most prevalent genotype is genotype 3 (~30%), followed by genotypes 2 and 4 (~10% each), genotype 6 (~5%) and genotype 5 (<1%). A small proportion of patients may even have mixed

genotype infections. Subtypes 1a, 1b, 2a and 3a are globally distributed and are considered “epidemic subtypes”; these subtypes account for a considerable proportion of HCV infections in high-income regions. Other “endemic strains” are relatively rare, and their geographical distribution is more limited: approximately 75% of genotype 3 infections occur in South Asia, most genotype 2 and 6 infections occur in East Asia, genotype 4 infections are most common in North Africa and the Middle East, and genotype 5 infections are seen in southern and eastern sub-Saharan Africa.³ Such geographical variation reflects a wide range of factors, including historical migration patterns and, more recently, use of injected drugs and blood products (Figure 2).

3 | OVERVIEW OF CURRENT TREATMENT OPTIONS FOR THE SIX HCV GENOTYPES

Recent progress has led to improved understanding of HCV and the identification of a number of therapeutic targets to interrupt viral replication and polyprotein processing. Accordingly, dramatic developments in direct-acting antiviral (DAA) therapies have resulted in SVR12 rates (sustained virological response at 12 weeks, recognized as the measure of treatment success, defined as undetectable HCV RNA in the blood at the end of treatment and again 12 weeks

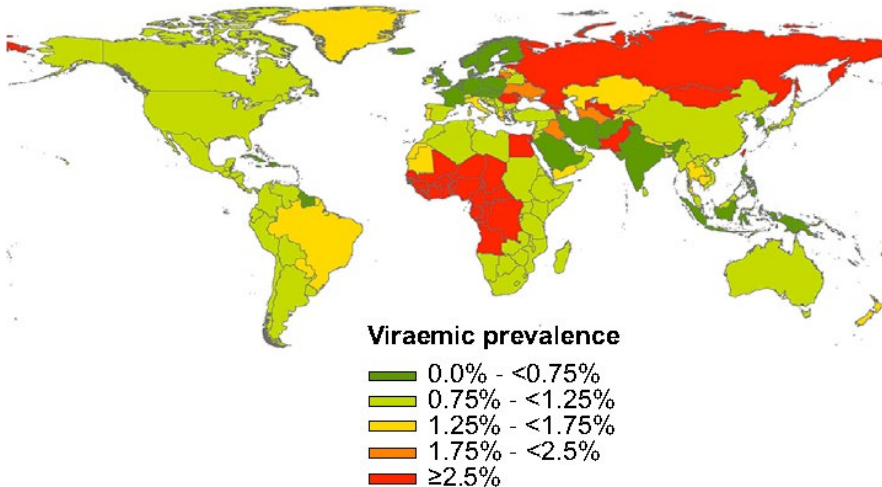


FIGURE 1 Viraemic prevalence of HCV: reproduced from Gower et al. 2014²

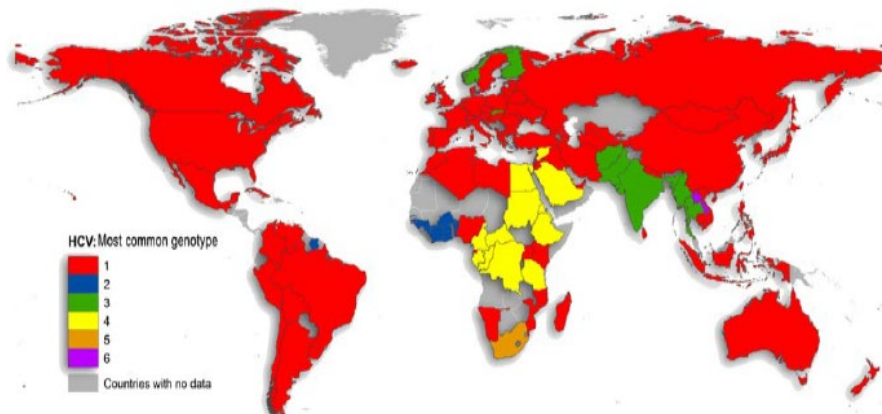


FIGURE 2 Countries by the majority genotype: reproduced from Messina et al. 2015³

following treatment end) in excess of 90% in many patients with HCV infection. In addition, more favourable adverse event profiles are seen with these new treatment combinations compared with PEGylated interferon/ribavirin-based therapies, the previous standard of care. However, the high degree of genetic diversity of HCV presents a significant challenge, and few treatment regimens are effective against all major genotypes. However, data are generally more limited for the less common genotypes, which are often more prevalent in poorer economic regions of the world where extensive baseline virological testing for genetic polymorphisms may not be available. The recent availability and ongoing development of pan-genotypic therapeutic options provide optimism in such settings.

4 | DEVELOPMENT OF DIRECT-ACTING ANTIVIRALS

The second wave of DAAs achieves significantly improved SVR rates, is better tolerated, has more convenient, once-daily dosing regimens and shorter treatment schedules (12 weeks for the majority of patients, or in some cases, duration of only 8 weeks) than the previously common PEGylated interferon/ribavirin-based therapies. Four classes of DAAs are available and target the function of nonstructural (NS) HCV proteins involved in the viral lifecycle. The NS3/4A protease inhibitors inhibit viral protein processing, nucleotide analogues of the NS5B RNA-dependent RNA polymerase directly block HCV replication, non-nucleosides inhibit the same NS5B RNA-dependent RNA polymerase, and NS5A phosphoprotein inhibitors block HCV replication by disorganizing the replication complex and inhibiting viral particle assembly and release.

Combination regimens, including two, three or even four new generation, oral agents, without peginterferon- α , are the new standard of care for HCV. The requirement to add ribavirin depends on the genotype to be treated, degree of cirrhosis and prior treatment failure. The individual DAAs have different characteristics; many are dependent on HCV genotype, genotypic subtype and disease severity (eg cirrhosis). Therefore, to optimize SVR rates, physicians need to choose the most appropriate combination of DAA agents and the appropriate duration of treatment and also must consider the potential need for adjuvant ribavirin in harder-to-treat cases. Treatment recommendations^{4,5} for initial treatment of chronic HCV are summarized in Table 1.

5 | PAN-GENOTYPIC COMBINATION REGIMENS

An increasing amount of data is now available for DAAs, including pan-genotypic regimens.

5.1 | Ledipasvir plus sofosbuvir

The combination of the NS5A inhibitor ledipasvir plus sofosbuvir, as a fixed-dose, once-daily single-tablet regimen, approaches but

does not achieve pan-genotypic status, with efficacy demonstrated against HCV genotype 1, 4, 5 and 6 infections. Evidence is lacking for this regimen in genotype 2, and it has only limited activity against genotype 3 without the addition of ribavirin, as such ledipasvir plus sofosbuvir is not recommended for use in genotypes 2 and 3.^{4,5}

A pooled analysis of 2108 patients with genotype 1a or b infection included in trials with sofosbuvir plus ledipasvir indicates that, overall, in patients with genotype 1b, there is no significant effect of baseline resistance-associated substitutions (RASs) in NS5A on SVR12, with only a small effect reported in patients with HCV genotype 1a.⁶ RASs in NS5A that increased the half-maximal effective concentration to ledipasvir by more than 100-fold reduced the rate of SVR12 in treatment-naïve patients treated for 8 weeks (SVR12: 82.8%; $P=0.011$), but not in patients treated for 12 weeks (SVR12: 95.7%). In treatment-experienced patients with baseline RASs conferring less than 100-fold resistance to ledipasvir, SVR rates are similar to those without baseline RASs (97%-100%). Treatment-experienced patients with baseline NS5A RASs with more than 100-fold resistance to ledipasvir who were treated for only 12 weeks had a significantly lower SVR12 rate (64.7%) compared with those without baseline RASs (97.4%) or, most notably, those with high-level RASs treated for 24 weeks (100%, although there were only six patients in this group). This analysis indicates that if you wish to truly personalize treatment to individuals, then baseline resistance testing is needed, although it is not recommended by The European Association for the Study of the Liver (EASL) as such requirements may limit treatment access.⁵

The Phase 2 SOLAR-1 trial tested 12 or 24 weeks of treatment with ledipasvir plus sofosbuvir and ribavirin in 337 patients with advanced liver disease and almost exclusively (99%) genotype 1 HCV infection.⁷ SVR12 rates varied with the degree of liver disease, ranging from 98% in patients with no cirrhosis or compensated cirrhosis, to 86% in post-transplant patients with decompensated cirrhosis. Lower SVR12 rates (60% and 75%, in patients receiving 12 and 24 weeks of treatment, respectively) were reported in nine patients with Child-Pugh Class C disease post-transplantation. A total of 13 (4%) patients discontinued study treatment due to adverse events, and there were 10 (3%) deaths, due mainly to complications related to hepatic decompensation. A further Phase 2 trial included treatment-naïve and previously treated patients (N=44) with genotype 4 who received ledipasvir plus sofosbuvir for 12 weeks.⁸ The SVR12 rate was 93% overall, 95% for treatment-naïve and 91% for previously treated patients. In the SOLAR-1 trial, described above, 3 of 5 genotype 4 patients achieved SVR12.⁷ In Trial 1119, ledipasvir plus sofosbuvir was administered for 12 weeks to treatment-naïve or previously treated subjects with genotype 5 HCV infection, with or without cirrhosis.¹⁰ The overall SVR12 rate was 93%, with similar results regardless of prior HCV treatment or cirrhosis status. The ELECTRON-2 trial included some patients with genotype 6 who achieved an SVR12 rate of 96% (24/25 patients) when treated with ledipasvir plus sofosbuvir (without ribavirin) for 12 weeks.¹¹ The combination of ledipasvir-sofosbuvir has been well tolerated with most commonly reported adverse effects being fatigue and headache.

TABLE 1 Therapeutic options for initial treatment of chronic hepatitis C virus

Names	Mechanism of action	Recommended for use in HCV genotypes	AASLD/IDSA guidelines ⁴	EASL guidelines ⁵
Sofosbuvir + velpatasvir	Sofosbuvir—HCV nucleotide analogue NS5B polymerase inhibitor Velpatasvir—HCV NS5A inhibitor	Pan-genotypic—1, 2, 3, 4, 5 and 6	Recommended for treatment-naïve patients with HCV genotype 1a, 1b, 2, 3, 4, 5 or 6 infection, including patients with compensated cirrhosis (12 wk)	Recommended for treatment-naïve patients with HCV genotype 1a, 1b, 2, 3, 4, 5 or 6 infection, including patients with compensated cirrhosis (12 wk)
Sofosbuvir + daclatasvir	Sofosbuvir—HCV nucleotide analogue NS5B polymerase inhibitor Daclatasvir—HCV NS5A replication complex inhibitor	Pan-genotypic—1, 2, 3, 4, 5 and 6	Recommended for treatment-naïve patients with HCV genotype 3 infection (12 wk in patients without cirrhosis, or for 24 wk with or without ribavirin in patients who have compensated cirrhosis) Alternative: can be given with or without to treatment-naïve patients with HCV genotype 1a and 1b infection who have compensated cirrhosis (24 wk) Alternative: can be given to treatment-naïve patients with HCV genotype 2 infection, including patients with compensated cirrhosis (24 wk)	Recommended for treatment-naïve patients with HCV genotype 1a, 1b, 2, 3, 4, 5 or 6 infection, including patients with compensated cirrhosis (12 wk)
Sofosbuvir + ledipasvir	Ledipasvir—HCV NS5A inhibitor Sofosbuvir—HCV nucleotide analogue NS5B polymerase inhibitor	1, 4, 5 and 6	Recommended for treatment-naïve patients with HCV genotype 1a, 1b, 4, 5 or 6 infection, including patients with compensated cirrhosis (12 wk)	Recommended for treatment-naïve patients with HCV genotype 1a, 1b, 4, 5 or 6 infection, including patients with compensated cirrhosis (8–12 wk for genotypes 1a and 1b; 12 wk for genotypes 4, 5 and 6)
Elbasvir + grazoprevir	Elbasvir—HCV NS5A inhibitor Grazoprevir—HCV NS3/4A protease inhibitor	1 and 4	Recommended for treatment-naïve patients with HCV genotype 1a or 1b infection and in whom no baseline NS5A RAVs for elbasvir are detected, including patients with compensated cirrhosis (12 wk). Alternative: can be given with ribavirin for treatment-naïve patients with HCV genotype 1a infection in whom baseline NS5A RAVs for elbasvir are detected, including patients with compensated cirrhosis (16 wk) Recommended for treatment-naïve patients with HCV genotype 4 infection, including patients with compensated cirrhosis (12 wk)	Recommended for treatment-naïve patients with HCV genotype 1a, 1b and 4, including patients with compensated cirrhosis: Genotype 1a—12 wk without ribavirin if HCV RNA \leq 800 000 (5.9 log) IU/mL or 16 wk with ribavirin if HCV RNA $>$ 800 000 (5.9 log) IU/mL in patients with resistance to elbasvir confirmed by baseline RAS testing, if available Genotypes 1b and 4—12 wk without ribavirin
Sofosbuvir + simeprevir	Sofosbuvir—HCV nucleotide analogue NS5B polymerase inhibitor Simeprevir—HCV NS3/4A protease inhibitor	1 and 4	Recommended for treatment-naïve patients with HCV genotype 1a and 1b (12 wk) Alternative: can be given with or without ribavirin for treatment-naïve patients with HCV genotype 1a and 1b infection and compensated cirrhosis in whom no Q80K polymorphism is detected for genotype 1a	Recommended for treatment-naïve patients with HCV genotype 4 infection, including patients with compensated cirrhosis (12 wk)
Ombitasvir + paritaprevir + ritonavir	Ombitasvir—HCV NS5A inhibitor Paritaprevir—HCV NS3/4A protease inhibitor Ritonavir—a CYP3A inhibitor	4	Recommended with ribavirin for treatment-naïve patients with HCV genotype 4 infection, including patients with compensated cirrhosis (12 wk)	Recommended with ribavirin for treatment-naïve patients with HCV genotype 4 infection, including patients with compensated cirrhosis (12 wk)
Ombitasvir + paritaprevir + dasabuvir + ritonavir	Ombitasvir—HCV NS5A inhibitor Paritaprevir—HCV NS3/4A protease inhibitor Ritonavir—CYP3A inhibitor Dasabuvir—HCV non-nucleoside NS5B palm polymerase inhibitor	1	Recommended with ribavirin for treatment-naïve patients with HCV genotype 1a or 1b infection, including patients with compensated cirrhosis (12 wk) Alternative: recommended with ribavirin for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis (24 wk)	Recommended with for treatment-naïve patients with HCV genotype 1 infection, including patients with compensated cirrhosis (12 wk with ribavirin for genotype 1b)

5.2 | Sofosbuvir and daclatasvir

The combination of sofosbuvir plus daclatasvir, administered once daily in a two-tablet regimen, has demonstrated efficacy across all HCV genotypes in Phase 3 trials. In ALLY-1, 103 patients with advanced cirrhosis or postliver transplantation recurrence achieved SVR12 rates ranging from 76% to 100% across genotypes 1, 2, 3, 4 and 6.¹² In the open-label, ALLY-2 trial, 203 patients co-infected with HCV genotypes 1, 2, 3 or 4 and HIV were treated with 8 or 12 weeks of sofosbuvir plus daclatasvir.¹³ Patients treated for 12 weeks achieved SVR12 rates of 96%-98% across all genotypes, but the SVR12 rates were only ~76% after 8 weeks of treatment. In ALLY-3, 152 patients with HCV genotype 3 were treated with 12 weeks of sofosbuvir plus daclatasvir.¹⁴ In noncirrhotic patients, SVR12 rates of 94%-97% were achieved. However, this combination was considered suboptimal in cirrhotic genotype 3 patients, who achieved SVR12 rates of only 58%-69%. In the ALLY-3+ study, the addition of ribavirin to sofosbuvir plus daclatasvir over 12 weeks increased SVR12 rates for patients with HCV genotype 3 and advanced fibrosis or compensated cirrhosis (N=50) to 88%, 92% if treated for 16 weeks.¹⁵ Treatment duration appears to be important in patients with advanced disease. Patients with HCV genotype 3 and cirrhosis treated for 24 weeks in the French early access programme achieved SVR12 rates of 91% when receiving sofosbuvir plus daclatasvir, and 92% when receiving sofosbuvir plus daclatasvir and ribavirin.¹⁶ We have limited data on the impact of baseline RASs on SVR with sofosbuvir plus daclatasvir. However, we could probably extrapolate and apply data reported for the ledipasvir plus sofosbuvir combination. The most common adverse effects seen with sofosbuvir plus daclatasvir were headache, nausea and fatigue.

5.3 | Sofosbuvir and velpatasvir

The combination of sofosbuvir and velpatasvir has been shown to have activity against all six major HCV genotypes in four, Phase 3 trials.

In ASTRAL-1, 12 weeks of treatment with sofosbuvir plus velpatasvir in previously treated and untreated patients infected with HCV genotype 1, 2, 4, 5 or 6, including patients with compensated cirrhosis, provided SVR rates of at least 97% for each individual genotype.¹⁷ Similar SVR12 rates were recorded in patients with HCV genotype 2 or genotype 3 treated for 12 weeks with sofosbuvir plus velpatasvir in ASTRAL-2 and ASTRAL-3 (99% and 95%, respectively).¹⁸ Without velpatasvir, in the comparator arms of the same studies, patients treated for 24 weeks with sofosbuvir plus ribavirin achieved lower SVR12 rates of 94% and 80%, respectively. In patients with cirrhosis, SVR12 rates reduced to 93% and 89% for genotypes 2 and 3 treated with sofosbuvir plus velpatasvir, and 73% and 58% for genotypes 2 and 3 treated with sofosbuvir plus ribavirin. In the ASTRAL-4 trial, patients with decompensated cirrhosis were treated with sofosbuvir plus velpatasvir (12 weeks), sofosbuvir plus velpatasvir plus ribavirin (12 weeks) or sofosbuvir plus velpatasvir (24 weeks) and achieved overall SVR12 rates of 83%, 94% and 86%, respectively.¹⁹ HCV genotype 1 patients with decompensated cirrhosis achieved SVR12 rates of 88%, 96% and 92%, respectively, by treatment. Patients with genotype 3 HCV

achieved SVR rates of 50%, 85% and 50%, respectively, although patient numbers were small. Although there were few patients, all those with genotypes 2, 4 and 6 achieved SVR12, with the exception of one patient with genotype 2 who died of liver failure after completing only 28 days of sofosbuvir plus velpatasvir treatment. A pooled deep sequencing analysis of the ASTRAL studies reported no impact of NS5A RASs on SVR (SVR12 rates in patients with baseline NS5A RASs: 97%-100% in genotypes 1, 2, 4, 5 and 6, 88% in genotype 3).⁹ Of the genotype 3 patients who relapsed, six of ten had Y93H emerge and four of ten maintained/enriched this baseline variant. The most common adverse events reported for sofosbuvir plus velpatasvir were headache, fatigue and nausea. Overall, these findings suggest that this combination (without ribavirin) may not be ideal for all genotype 3 patients when given for 12 weeks. It may be necessary to adapt the regimen (by adding RBV) according to fibrosis score, patient status or baseline resistance testing.⁵

6 | PAN-GENOTYPIC COMBINATION REGIMENS BEING EVALUATED

6.1 | Glecaprevir plus pibrentasvir

A new pan-genotypic combination of "next-generation" DAAs is currently being developed, with results from the Phase 2b SURVEYOR-1 and SURVEYOR-2 trials published recently.²⁰ In these studies, the NS3/4A protease inhibitor glecaprevir (ABT-493) and the NS5A inhibitor pibrentasvir (ABT-530) were administered once daily for 8 or 12 weeks to various populations of patients, including all major HCV genotypes, a range of prior treatment experiences and presence or absence of liver cirrhosis. In patients without cirrhosis, 8 weeks of treatment with glecaprevir plus pibrentasvir resulted in 97% of patients with genotype 1 and 98% of patients with genotype 2 achieving SVR12. Twelve weeks of treatment resulted in an SVR rate of 97%-100% in noncirrhotic patients with genotype 3, 4, 5 or 6. Based on the Phase 2 data available to date, there does not appear to be an impact of baseline RASs on the efficacy of glecaprevir plus pibrentasvir. Treatment was well tolerated, with no treatment-related serious adverse events, discontinuations due to adverse events or grade 2 or higher laboratory abnormalities. The most common adverse events were mild fatigue and headache. Phase 3 studies are ongoing to test 8 and 12 weeks of treatment with glecaprevir plus pibrentasvir in a larger number of patients with and without cirrhosis, including all six major HCV genotypes.

7 | PAN-GENOTYPIC COMBINATION REGIMENS—OUTLOOK

The purpose of a pan-genotypic regimen is to allow for considerable simplification of treatment and disease testing and offer the possibility that one or two regimens could meet the needs of all patients with HCV, regardless of genotype. First-generation pan-genotypic regimens do not completely fulfil this need. Ledipasvir plus sofosbuvir is not suitable for genotype 3 infection, and the regimen of sofosbuvir plus

daclatasvir needs to be tailored according to genotype, subtypes, patient status, fibrosis stage and, if available, baseline resistance profile. Thus, treatment is still complicated and not optimal for poor countries. Second-generation pan-genotypic combinations offer further improvements. Sofosbuvir plus velpatasvir appears to be effective in all but genotype 3 infections, and although confirmation is needed in Phase 3 studies, there appears to be minimal impact of genotype, subtype and baseline resistance with glecaprevir plus pibrentasvir. However, fibrosis stage needs to be determined to identify the appropriate regimen.

These pan-genotypic regimens somehow address the need for simplified HCV treatment and could offer considerable benefits in particular for lower-income regions where access to HCV testing services is limited and compliance with longer treatment regimens may be poor. However, the cost of these new treatment regimens provides a particular challenge in such regions.

8 | OTHER DIRECT-ACTING ANTIVIRAL COMBINATIONS WITH ACTIVITY ACROSS SOME GENOTYPES

A number of other DAA combination regimens are available or in development, but their activity is more selective than that of the pan-genotypic regimens considered above. The choice of agents and the schedule of therapy is complicated as it is dependent on a number of different factors including HCV genotype and subtype, viral load, fibrosis stage and resistance testing. Therefore, different regimens are required in different situations, and pretreatment virological testing is essential to maximize the chance of cure in accordance with treatment guidelines.

A number of combinations have demonstrated activity in patients with genotype 1 infections, the most common HCV genotype globally. The activity of the combination, simeprevir plus sofosbuvir, was demonstrated against genotype 1 in the OPTIMIST trial (SVR12 after 12 weeks of treatment: 97%).²¹ SVR12 with the combination of ombitasvir, paritaprevir, dasabuvir, ritonavir and ribavirin is 92%-96% in treatment-naïve and previously treated patients.^{22,23} Removal of ribavirin from this regimen had little effect on SVR in patients with genotype 1 HCV in the PEARL-III and PEARL-IV trials.²⁴ Ombitasvir, paritaprevir, ritonavir and ribavirin in treatment-naïve and treatment-experienced, noncirrhotic patients with genotype 4 HCV infection achieved SVR12 rates of 95%-100%.²⁵ The combination of the NS3/4A protease inhibitor grazoprevir plus the HCV NS5A inhibitor elbasvir, administered once daily as a single tablet, has demonstrated activity against HCV genotype 1, 4, and 6 infections (SVR12: 80%-100%).²⁶⁻²⁸ No drug-related serious adverse events were reported, and the most common adverse events were headache, fatigue and nausea.

9 | TREATMENT FAILURE AND DRUG RESISTANCE

Treatment failure may occur as a result of one or more factors related to disease virology (eg HCV genotype and subtype, and the presence

and fitness of viral variants resistance to treatments such as NS5A inhibitors), treatment regimen (eg choice of DAAs used and their metabolism, requirement for concomitant use of ribavirin, duration of treatment and pre-treatment status), or host-related factors (eg *IL28B* status, severity of liver disease and fibrosis stage, portal hypertension, immune function and patients' lack of adherence to the therapeutic regimen).^{29,30} Although patients can be retreated after an initial failure,³¹ efforts should be made to optimize first-line treatment and to minimize the chance of failure due to resistance. In poorer economic regions where healthcare resources are limited, it is particularly important to "get it right first time" wherever possible.

As a result of the multifactorial nature of treatment failure, routine drug-resistance testing is not recommended in the major US or European HCV guidelines.^{4,5} To reduce the incidence of treatment failure, based on the disease characteristics (ie genotype and extent of liver damage), we need to identify those patients who require the addition of ribavirin or extended treatment duration. However, it is likely that the increasing use of pan-genotypic combination regimens will resolve many of the incidences of treatment failure associated with resistance. After initial failure, there are two options: conduct resistance testing and adjust the treatment regimen accordingly or retreat with sofosbuvir plus other DAAs.

10 | PAN-GENOTYPIC OPTIONS FOR RETREATMENT AFTER PREVIOUS TREATMENT FAILURE

Current treatment guidelines^{4,5} provide detailed guidance on which DAA combinations to use in patients where previous therapy has failed (Table 2). Sofosbuvir is an attractive option for use in retreatment of all HCV genotypes due to its high genetic barrier for resistance. Indeed, the combinations of sofosbuvir plus velpatasvir and sofosbuvir plus daclatasvir have shown activity in the retreatment of all six HCV genotype infections.

Other sofosbuvir combinations are active against some of the genotypes; sofosbuvir plus ledipasvir has demonstrated efficacy against HCV genotype 1, 4, 5 and 6 infections, and sofosbuvir plus simeprevir is recommended for retreatment of HCV genotype 1 and 4 infections. The combinations of sofosbuvir plus ombitasvir/paritaprevir/dasabuvir/ritonavir or grazoprevir/elbasvir have also demonstrated activity in retreatment of HCV genotype 1 and 4 infections.^{32,33}

11 | SCREENING AND ACCESS TO SPECIALIST TREATMENT CENTRES

In the World Health Organization 2014 guidelines for screening, care and treatment for HCV infection, it is reported that the global prevalence of HCV is high, most individuals with HCV infection remain undiagnosed, and few have access to HCV treatment services.³⁴ Even when diagnosed, treatment often remains unavailable even though cure rates for patients in low- and middle-income

TABLE 2 Therapeutic options for retreatment of chronic hepatitis C virus

Names	Mechanism of action	Recommended for use in genotypes	AASLD/IDSA guidelines ⁴	EASL guidelines ⁵
Sofosbuvir + velpatasvir	Sofosbuvir—HCV nucleotide analogue NS5B polymerase inhibitor Velpatasvir—HCV NS5A inhibitor	Pan-genotypic—1, 2, 3, 4, 5 and 6	Recommended for treatment-experienced patients with HCV genotype 1a, 1b and 2 infection, including patients with compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed (12 wk) Recommended for patients with HCV genotype 3 infection, regardless of cirrhosis state, in whom prior sofosbuvir and ribavirin treatment has failed (24 wk with ribavirin) Recommended with ribavirin for patients with HCV genotype 4, 5 or 6 infection, including patients with compensated cirrhosis, in whom prior interferon/ribavirin has failed (12 wk)	Recommended for treatment-experienced patients with HCV genotype 1a, 1b, 2, 3, 4, 5 or 6 infection, including patients with compensated cirrhosis (12 wk without ribavirin for all genotypes except genotype 3 : 12 wk with ribavirin in patients with NS5A RAS Y93H at baseline if RAS testing is available, or 24 wk without ribavirin)
Sofosbuvir + daclatasvir	Sofosbuvir—HCV nucleotide analogue NS5B polymerase inhibitor Daclatasvir—HCV NS5A replication complex inhibitor	Pan-genotypic—1, 2, 3, 4, 5 and 6	Recommended for patients with HCV genotype 1a, 1b , infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed (12 wk), and in patients with genotype 2 infection regardless of cirrhosis state (16 wk with or without ribavirin) <i>Alternative:</i> recommended with or without ribavirin in treatment-experienced patients with HCV genotype 1a or 1b infection, who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed (24 wk for genotype 1a and 1b) Recommended for patients with HCV genotype 3 infection, regardless of cirrhosis state, in whom prior sofosbuvir and ribavirin treatment has failed (24 wk with ribavirin).	Recommended for treatment-experienced patients with HCV genotype 1a, 1b, 2, 3, 4, 5 or 6 infection, including patients with compensated cirrhosis: Genotype 1a —12 wk with ribavirin (in patients with RASs that confer high-level resistance to NS5A inhibitors at baseline if RAS testing available) or 24 wk without ribavirin Genotype 1b and 2 —12 wk without ribavirin Genotype 3 —12 wk with ribavirin (in patients with NS5A RAS Y93H at baseline if RAS testing available) or 24 wk without ribavirin in patients who do not have cirrhosis; 24 wk with ribavirin in patients with compensated cirrhosis Genotype 4, 5 and 6 —12 wk with ribavirin or 24 wk without ribavirin
Sofosbuvir + ledipasvir	Sofosbuvir—HCV nucleotide analogue NS5B polymerase inhibitor Ledipasvir—HCV NS5A inhibitor	1, 4, 5 or 6	Recommended with ribavirin for treatment-experienced patients with HCV genotype 1a or 1b infection, including patients with compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed (12 wk) <i>Alternative:</i> recommended for treatment-experienced patients with HCV genotype 1a, 1b or 4 who have compensated cirrhosis (24 wk) Recommended for patients with HCV genotype 4, 5 or 6 infection, including patients with compensated cirrhosis, in whom prior PEG-IFN/RBV has failed (12 wk)	Recommended for treatment-experienced patients with HCV genotype 1a, 1b, 4, 5 or 6 infection, including those with compensated cirrhosis: Genotype 1a —12 wk with ribavirin in patients with RASs that confer high-level resistance to NS5A inhibitors at baseline if RAS testing available or 24 wk without ribavirin Genotype 1b —12 wk without ribavirin Genotype 3, 4, 5 and 6 —12 wk with ribavirin or 24 wk without ribavirin
Elbasvir + grazoprevir	Elbasvir—HCV NS5A inhibitor Grazoprevir—HCV NS3/4A protease inhibitor	1 and 4	Recommended for treatment-experienced patients with HCV genotype 1a or 1b infection and in whom no baseline NS5A RAVs for elbasvir are detected who do not have cirrhosis or have compensated cirrhosis (12 wk). <i>Alternative:</i> can be given with ribavirin for treatment-experienced patients with HCV genotype 1a infection in whom prior PEG-IFN/ribavirin treatment has failed, and in whom baseline NS5A RAVs for elbasvir are detected, including patients with compensated cirrhosis (16 wk) Recommended with ribavirin for patients with HCV genotype 4 infection, including patients with compensated cirrhosis, who experienced viral relapse after prior PEG-IFN/ribavirin (16 wk)	Recommended for treatment-experienced patients with HCV genotype 1a, 1b and 4 infection, including those with compensated cirrhosis: Genotype 1a —12 wk without ribavirin if HCV RNA $\leq 800\ 000$ (5.9 log) IU/mL or 16 wk with ribavirin if HCV RNA $> 800\ 000$ (5.9 log) IU/mL in patients with resistance to elbasvir confirmed by baseline RAS testing, if available Genotype 1b —12 wk without ribavirin Genotype 4 —12 wk without ribavirin if HCV RNA $\leq 800\ 000$ (5.9 log) IU/mL or 16 wk with ribavirin if HCV RNA $> 800\ 000$ (5.9 log) IU/mL

(Continues)

TABLE 2 (Continued)

Names	Mechanism of action	Recommended for use in genotypes	AASLD/IDSA guidelines ⁴	EASL guidelines ⁵
Sofosbuvir + simeprevir	Simeprevir—HCV NS3/4A protease inhibitor Sofosbuvir—HCV nucleotide analogue NS5B polymerase inhibitor	1 and 4	Recommended regimen for treatment-experienced patients with HCV genotype 1a or 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed (12 wk) Alternative: Recommended with or without ribavirin for treatment-experienced patients with HCV genotype 1a and 1b infection, including patients with compensated cirrhosis, who are negative for the Q80K variant by commercially available resistance assay, in whom prior PEG-IFN/ribavirin treatment has failed. Other recommended or alternative regimens should be used for patients with compensated cirrhosis and HCV genotype 1a infection in whom the Q80K variant is present (24 wk) Recommended with or without weight-based ribavirin for treatment-experienced patients with HCV genotype 1b infection who have compensated cirrhosis. (24 wk)	Recommended for treatment-experienced patients with HCV genotype 4 infection, including those with compensated cirrhosis (12 wk with ribavirin or 24 wk without ribavirin)
Ombitasvir + paritaprevir + ritonavir	Ombitasvir—HCV NS5A inhibitor Paritaprevir—HCV NS3/4A protease inhibitor Ritonavir—CYP3A inhibitor	4	-	Recommended for treatment-experienced patients with HCV genotype 4 infection, including those with compensated cirrhosis (12 wk with ribavirin)
Ombitasvir + paritaprevir + dasabuvir + ritonavir	Ombitasvir—HCV NS5A inhibitor Paritaprevir—HCV NS3/4A protease inhibitor Ritonavir—CYP3A inhibitor Dasabuvir—HCV non-nucleoside NS5B polymerase inhibitor	1 and 4	Recommended with ribavirin for treatment-experienced patients with HCV genotype 1a infection who do not have cirrhosis, or with HCV genotype 1b with compensated cirrhosis (12 wk) Alternative: recommended with weight-based ribavirin for treatment-experienced patients with HCV genotype 1a infection who have compensated cirrhosis (24 wk). Recommended with ribavirin for patients with HCV genotype 4 infection, including patients with compensated cirrhosis, in whom prior PEG-IFN/RBV/ribavirin has failed (12 wk)	Recommended for treatment-experienced patients with HCV genotype 1a and 1b, including patients with compensated cirrhosis: Genotype 1a—12 wk without cirrhosis or 24 wk with cirrhosis, with ribavirin in both cases Genotype 1b—12 wk without ribavirin

regions are similar to those in high-income regions. These guidelines state that their aim is to facilitate the introduction and expansion of treatment services for persons with HCV infection, particularly in low- and middle-income countries. It is acknowledged that technical, logistical and financial challenges must be overcome if this is to become a reality.³⁴

Diagnosis and clinical management of HCV infection require sophisticated and expensive laboratory capacity to determine HCV genotype and subtype, detect specific resistance mutations and measure HCV viral load (see Tables 1 and 2 for details by regimen). Clearly, virological and genetic testing can maximize the chance of selecting the most effective regimen for a certain individual, but such services are often unavailable in low-income countries. The requirement for testing can be minimized by selecting pan-genotypic DAA regimens that will work regardless of the genotype. However, even with pan-genotypic DAA regimens, resistance testing may be helpful to improve treatment outcomes. For example, in treatment-experienced patients with genotype 1a or 3, it is recommended to add ribavirin to sofosbuvir plus daclatasvir on the basis of baseline resistance testing (see Table 2). Although treatment can be optimized for groups of patients by selecting the most likely successful regimen for a certain geographical region on the basis of the most prevalent genotype, without resistance testing, the risk remains that resistance-associated variants present at baseline will reduce response to therapy in individuals and potentially drive further resistance within the community.

12 | ACCESS TO PAN-GENOTYPIC TREATMENTS AND ADDITIONAL FUTURE CHALLENGES

The greatest challenge for managing patients with HCV now is the high pricing of HCV drugs. Although PEGylated interferon/ribavirin—perhaps the first pan-genotypic treatment regimen for HCV—is no longer recommended in current treatment guidelines, regional differences in per capita incomes and health insurance systems result in the continued use of this regimen (with or without DAAs) in poorer regions. Even in high-income countries, the high cost of the latest DAA regimens has a significant impact on uptake. This problem is exacerbated in lower-income countries where high prevalence of HCV presents a particular challenge. World Health Organization guidelines call for national governments, the pharmaceutical industry and other relevant organisations, to work together to make HCV treatments affordable and accessible globally to those in need. They also suggest a move away from treatment in specialist HCV centres and towards primary-care clinics to improve access to HCV treatment. The simplicity of pan-genotypic regimens is likely to be of future benefit in such environments.

Although there have been some discount negotiations (eg sofosbuvir was provided to Egypt [where genotype 4 predominates] at a 99% discounted rate),³⁵ modern treatment regimens remain unaffordable for the majority. Consequently, physicians operating within fixed

budgets are faced with a dilemma of who to treat. Priority should be given to patients with the greatest immediate need (eg those with advanced liver fibrosis or cirrhosis), but if we are to provide more comprehensive access to HCV therapy, a significant drop in HCV drug prices is essential. It has been suggested that, within the next 15 years, large-scale manufacture of two or three drug combinations of HCV DAAs could be feasible, with target prices of \$100–\$250 per 12-week treatment course.³⁶ If this could be achieved for some of the pan-genotypic regimens, such prices could make widespread access to effective HCV treatments a realistic goal in low- and middle-income countries. It is hoped that up-to-date recommendations will guide reimbursement and discounting of drug costs and harmonize treatments across different regions.⁵

Even if suitable pricing agreements are negotiated to allow for greater access, a number of other challenges still exist in the management of HCV infection. The burden of HCV-related complications is expected to rise over the next 20 years, with most people infected with HCV being from resource-limited countries where unsafe medical procedures remain a risk factor and access to HCV testing is limited. Additionally, as many patients are unaware of their HCV infection status, treatment may not have such a profound effect on the burden as would be hoped. Population movement from countries with high HCV prevalence is another confounding factor. If these challenges are to be met, it will be imperative to initiate appropriate HCV screening programmes and use very simple treatment options, especially in resource-limited countries, this is where affordable pan-genotypic regimens will be vital.

13 | CONCLUSIONS

The last few years have witnessed a remarkable transformation in treatment for HCV infection, with the development of DAA therapies that target specific HCV proteins. Treatment with combinations of DAAs has now removed the need to use PEGylated interferon and has reduced the requirement for ribavirin. However, the selection of therapeutic regimen, the duration of treatment and the need for adjuvant ribavirin with DAA therapies are still dependent on HCV genotype and, in some cases, also on baseline resistance polymorphisms. Therefore, the development of regional and national treatment strategies for the use of DAA therapies requires a detailed understanding of relative HCV genotype prevalence to tailor treatment paradigms and work within the bounds of local economic constraints.

Despite all the recent, positive developments, affordable access to DAA treatment is needed to provide the broad availability required to decrease the prevalence and burden of HCV globally, particularly in poorer economic regions. Therefore, the future goal for treatment must be the development and widespread availability of pan-genotypic DAA combinations that are equally effective against all viral genotypes, which will simplify treatment options and mean that resource-intensive viral genotyping becomes a thing of the past.

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