Challenges and perspectives of direct antivirals for the treatment of hepatitis C virus infection

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Summary
Treatment of chronic hepatitis C virus infection has been revolutionised by the development of direct-acting antivirals (DAAs). All-oral, once-daily, 8- to 12-week treatment regimens are now standard of care, with viral eradication possible in >95% of patients across different populations. Despite these advances, several unresolved issues remain, including treatment of patients with hepatitis C virus genotype 3, chronic kidney disease, and those in whom DAA therapy has previously failed. Glecaprevir/ pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir are the most recently approved DAA regimens. Given the overwhelming success of modern DAA-based therapies, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir are also likely to represent the last DAAs to be approved. Both are pangenotypic, once-daily, all-oral DAA combinations that have the potential to close the gaps in the current DAA treatment portfolio. Herein, we review the challenges associated with current DAAs and how these two regimens may be implemented in existing treatment algorithms.

Introduction
Hepatitis C virus (HCV) infection is a major global health concern, affecting approximately 70 million people or 1% of the world population according to recent estimates.¹ Moreover, chronic HCV infection is associated with substantial morbidity and mortality, with liver-related complications including cirrhosis, liver failure and hepatocellular carcinoma (HCC).² The goal of antiviral therapy is to prevent these complications by achieving viral eradication. This is defined as undetectable HCV RNA 12 weeks after treatment cessation, also called a sustained virologic response (SVR).²,³

The recent introduction of direct-acting antivirals (DAAs) has revolutionised HCV therapy and made viral cure, which is associated with improved quality of life, a reality in the vast majority of patients.⁴,⁵ Even in patients in whom interferon-based treatment has traditionally been difficult or contraindicated, including those with decompensated cirrhosis or severe kidney disease, HCV can now be eradicated with minimal toxicity and good overall tolerability.⁵-⁸ Moreover, large-scale post-marketing studies have shown that data from clinical trials can be replicated in the real-world setting with high overall efficacy and few safety concerns.⁹-¹¹

Finally, there is increasing evidence that viral eradication following DAA therapy is associated with a significant decrease in liver-related morbidity and mortality, and the adverse extrahepatic sequelae of HCV infection, while being associated with an increase in health-related quality of life.¹²-¹⁵ Despite these overwhelming advances, there remain challenges to eliminating HCV in some patient subgroups, including those in whom previous DAA-based therapies have failed.

Therapeutic challenges and limitations of DAA regimens prior to summer 2017
Genotype inclusivity of existing DAA regimens
There are eight major HCV genotypes and several dozens of subtypes that show a high degree of genetic variability.¹⁶,¹⁷ Worldwide, genotype 1 is the most prevalent HCV genotype, followed by genotypes 2 and 4.¹⁸ Interestingly, some genotypes show a high degree of endemicity, particularly genotype 3 in India and Pakistan and genotype 4 in Egypt and the Middle East.¹⁸,¹⁹ The natural course of HCV infection may vary among genotypes. For example, genotype 3 is associated with increased fibrosis progression and a higher risk of HCC development.²⁰,²¹ The variability among HCV genotypes is also reflected in their distinct response to interferon-based therapy, with HCV genotypes 2 and 3 showing superior response rates compared to HCV genotypes 1 and 4.²²

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Even today, in the era of interferon-free, pangenotypic DAA therapies, HCV genotype determination is still recommended before initiating antiviral therapy. This is mainly a consequence of the fact that DAA drug development was initially focussed on HCV genotype 1, partly because interferon showed the lowest efficacy in this genotype and partly because it is the most common genotype worldwide. Indeed, the first two DAs that were approved for the treatment of HCV, the NS3/4A protease inhibitors telaprevir and boceprevir, were specifically designed to mimic the natural substrate of the genotype 1 protease. These drugs marked an important step in the recent history of antiviral drug development. However, both telaprevir and boceprevir had to be combined with pegylated interferon and ribavirin and were associated with significant adverse effects. Moreover, both compounds had a relatively low barrier to resistance and were associated with the development of resistance within the HCV NS3/4A protease domain and subsequent treatment failure. Because of the genotype 1-specific drug design, telaprevir and boceprevir had to be combined with pegylated interferon and ribavirin and were associated with significant adverse effects. Moreover, both compounds had a relatively low barrier to resistance and were associated with the development of resistance within the HCV NS3/4A protease domain and subsequent treatment failure.

The introduction of the nucleotide analogue NS5B polymerase inhibitor SOF marked the next important milestone in DAA drug development. SOF binds to the active site of the HCV NS5B polymerase, which forms a highly conserved structure across all HCV genotypes. As a result, SOF has broad pangenotypic activity and a high barrier to resistance. In 2014, SOF became the first drug to replace interferon that could eradicate HCV. However, the ability to cure HCV with SOF plus ribavirin is confined to genotypes 2 and 3. To cure the other genotypes, a combination with another DAA from a different drug class is required.

**HCV genotype 1 and 4**

From 2014, when SOF first entered the market, to 2016, the standard of care for patients with HCV genotype 1 and 4 was either a combination of

| Table 1. Approved usage of GLE/PIB in DAA-naïve and DAA-experienced patients. |
|-------------------|-----------------|-----------------|
| **Treatment duration** | **No cirrhosis** | **Compensated cirrhosis** |
| Treatment-naive patients | | |
| HCV genotypes 1–6 | 8 weeks | 12 weeks |
| PegIFN/RBV-experienced patients | | |
| HCV genotypes 1,2,4–6 | 8 weeks | 12 weeks |
| HCV genotype 3 | 16 weeks | 16 weeks |
| NS3-experienced patients | | |
| HCV genotype 1 | 12 weeks | 12 weeks |
| NS5A-experienced patients | | |
| HCV genotype 1 | 16 weeks | 16 weeks |
| DAA, direct-acting antiviral; HCV, hepatitis C virus; NS3-exp., patients with prior HCV NS3/4A protease inhibitor failure; NS5A-exp., patients with prior HCV NS5A-inhibitor failure; P/R exp., patients with prior pegylated interferon and ribavirin failure; SOF/LDV, sofosbuvir/ledipasvir; SOF/VEL, sofosbuvir/velpatasvir; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; RBV, ribavirin. |
| Approved in the United States and Canada only; GLE/PIB is not recommended in patients with prior NS3-plus NS5A-exposure. |

| Table 2. Approved usage of SOF/VEL/VOX in DAA-naïve and DAA-experienced patients. |
|-------------------|-----------------|-----------------|
| **Treatment duration** | **No cirrhosis** | **Compensated cirrhosis** |
| Treatment-naive patients | | |
| HCV genotypes 1–6 | 8 weeks | 12 weeks |
| PegIFN/RBV-experienced patients | | |
| HCV genotypes 1–6 | 8 weeks | 12 weeks |
| NS5A-experienced patients | | |
| HCV genotypes 1–6 | 12 weeks | 12 weeks |
| DAA, direct-acting antiviral; HCV, hepatitis C virus; NS3-exp., patients with prior HCV NS3/4A protease inhibitor failure; NS5A-exp., patients with prior HCV NS5A-inhibitor failure; PEG-IFN, pegylated interferon; RBV, ribavirin. |
| 1 Includes patient with prior pegylated interferon/ribavirin and/or sofosbuvir-experience. |
| 2 Approved in Europe only. |
| 3 Includes patient with prior PEG-interferon/ribavirin-experience. |
| 4 8 weeks should only be considered in genotype 3 patients. |
HCV genotype 2

As the first NS5A inhibitors showed weak antiviral activity in patients with HCV genotype 2, the standard of care has long been a 12-week combination of SOF plus ribavirin. However, in addition to retaining the adverse effects associated with ribavirin, this combination proved less effective in the real-world setting than expected following registration trials. Moreover, SOF plus ribavirin is particularly ineffective in patients who are infected with the so-called “St. Petersburg” genotype 2 k/1b recombinant strain.

The development of the second-generation NS5A inhibitor VEL with potent activity against all major genotypes has overcome treatment constraints associated with HCV genotype 2 and the 2 k/1b chimera. Twelve weeks of SOF/VEL was superior to SOF/ribavirin and resulted in a 99% SVR rate in the pivotal ASTRAL-2 study.

HCV genotype 3

Genotype 3 appears to be more difficult to cure with DAAAs than other genotypes, but the underlying mechanisms are not fully understood. Twenty-four weeks of SOF plus ribavirin was the first interferon-free regimen available for the treatment of this genotype. However, this regimen had inferior efficacy in patients with cirrhosis, particularly in those who had failed prior treatment with (pegylated) interferon and ribavirin, with SVR rates in the range of 50–60%.

Daclatasvir was the first approved HCV NS5A inhibitor with potent antiviral activity against HCV genotype 3. Twelve weeks of daclatasvir plus SOF is highly effective in treatment-naive and -experienced patients without cirrhosis. However, as with SOF/ribavirin, SVR rates are significantly lower in patients with cirrhosis, ranging from 57–63%.

The pangenotypic, second-generation NS5A inhibitor VEL has potent in vitro activity against HCV genotype 3, even in the presence of NS5A resistance associated substitutions (RASs) that are known to decrease antiviral activity of various NS5A inhibitors. Today, 12 weeks of SOF/VEL is standard of care in patients with HCV genotype 3 in countries where this regimen is available. However, addition of ribavirin may still play a role in some of these patients, including those with cirrhosis and baseline Y93H which is associated with decreased VEL activity.

Chronic kidney disease

Renal impairment is frequently observed in patients infected with HCV. The HCV seroprevalence among European patients on chronic haemodialysis programmes has been estimated to be 13.5%. While SOF is highly effective and well tolerated in patients with decompensated liver disease, its efficacy and safety in patients with chronic kidney disease is not fully established. Exposure to the active metabolite of SOF, GS-331007, is increased in patients with renal impairment. Thus, SOF is not approved for patients with a glomerular filtration rate below 30 ml/min. Moreover, ribavirin, which is still being used as part of DAA regimens, is often poorly tolerated in patients with renal insufficiency, with dose adjustments or even drug discontinuation frequently required.

A significant step forward in the quest to eradicate HCV has been the development of DAA combinations that are primarily cleared via the liver with little or no renal excretion. Currently, three SOF-free drug combinations are approved for use in patients with severe or end-stage kidney failure. Combinations of grazoprevir/elbasvir and ombitasvir/paritaprevir ± dasabuvir were found to be effective in phase III clinical trials. However, both regimens are only approved in HCV genotypes 1 and 4, which left patients with other

Key points

Glecaprevir and pibrentasvir have limited to no renal excretion, making glecaprevir/pibrentasvir a promising combination for patients with chronic kidney disease.

SOF plus a protease inhibitor (simeprevir) or SOF plus an NS5A inhibitor (ledipasvir or daclatasvir) or a non-nucleoside inhibitor of the HCV NS5B polymerase (dasabuvir) in combination with an HCV NS3/4A protease inhibitor (paritaprevir with low-dose ritonavir boosting) and an HCV NS5A inhibitor (ombitasvir). With the exception of daclatasvir plus SOF in certain instances, all of these regimens were less active in other HCV genotypes than in genotypes 1 and 4. Thus, reliable genotype determination remained crucial for selection of the optimal DAA regimen, with genotype misclassification frequently resulting in treatment failure.

In patients with HCV genotype 1, treatment duration was mostly confined to 12 weeks. However, shortening treatment to 8 weeks was shown to be feasible in treatment-naive non-cirrhotic patients, with HCV genotype 1 and a baseline HCV RNA of less than 6 million IU/ml, who were treated with ledipasvir/SOF, as well as in treatment-naive patients with ≤F2 fibrosis and HCV genotype 1b who were treated with paritaprevir/ombitasvir plus dasabuvir or grazoprevir/elbasvir.

Although few head-to-head studies have been performed to date, regimens containing NS5A inhibitors appeared to be superior to simeprevir/sof in several large-scale real-world registries and quickly came to dominate the standard of care has long been a 12-week combination of SOF plus ribavirin. However, in addition to retaining the adverse effects associated with ribavirin, this combination proved less effective in the real-world setting than expected following registration trials. Moreover, SOF plus ribavirin is particularly ineffective in patients who are infected with the so-called “St. Petersburg” genotype 2 k/1b recombinant strain.

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genotypes without treatment options until more recently, when GLE/PIB became available.

DAA treatment failure
Despite the availability of highly potent DAAs and the excellent overall tolerability of these new anti-HCV regimens, treatment failure is frequently observed across different patient populations. Reasons for treatment failure are not always clear. However, recent data suggest that non-adherence and/or early treatment discontinuation may be common outside clinical trials. Moreover, the role of re-infection and impact on subsequent treatment options of selected variants with RASs requires further investigation.

Sofosbuvir experienced patients
The NS5B polymerase inhibitor SOF confers a high genetic barrier to resistance. So far, only one NS5B substitution (S282T) that is situated close to the enzyme’s active site has been associated with SOF resistance in vitro, while the role of other polymorphisms within the NS5B gene (e.g. C316N, L159F) remain unclear. In clinical practice, the S282T substitution has very rarely been detected, both before and after SOF-based treatment failure, mainly because it seems to be a highly unfit substitution that is usually only detectable for very short periods of time. Its impact on SOF-based treatment failure has not been fully established.

Retreatment with an NS5A inhibitor-based regimen has been recommended for HCV genotype 1 patients in whom SOF plus ribavirin or SOF plus pegylated interferon/ribavirin had failed. This recommendation was based on small pilot studies of ledipasvir/SOF, with and without ribavirin, where high SVR rates were achieved following 12 weeks of treatment in patients with a prior SOF failure. More recently, the phase III, open-label, randomised clinical trial POLARIS-4 compared a 12-week course of SOF/VEL/VOX to 12 weeks of SOF/VEL in non-NS5A inhibitor DAA-experienced patients, most of whom had received SOF. While the efficacy of SOF/VEL/VOX will be discussed below, it is interesting to note that patients treated in the SOF/VEL arm had a lower overall SVR rate, which was primarily driven by treatment failure among patients infected with HCV genotypes 1a and 3. Among patients infected with HCV genotypes 1b and 2, SVR rates were 95% and 97%, respectively, while no genotype 4 patients were treated with SOF/VEL. Interestingly, there was only a single HCV genotype 2 patient with virologic breakthrough in whom the S282T substitution was detectable at the time of treatment failure.

HCV NS3/4A inhibitor experienced patients
Failure of simeprevir-containing regimens has been associated with the emergence of resistant substitutions within the HCV NS3/4A protease that also show a high degree of cross-resistance with other HCV NS3/4A inhibitors. The most prevalent treatment-emergent RASs in patients with HCV subtype 1a were found at position D168 of the NS3/4A protein. In patients with HCV genotype 1b, common high-level RASs include R155K and D168E. Despite the fact that NS3/4A RASs tend to disappear within months of DAA failure, retreatment strategies for simeprevir failures have included a switch to NS5A-based regimens, which has led to high overall SVR rates in real-world studies.

HCV NS5A inhibitor experienced patients
Most NS5A inhibitors are active across different HCV genotypes but have a relatively low barrier to resistance. Importantly, NS5A resistance may occur even after very short courses of antiviral therapy. In patients with HCV genotype 1a in whom ledipasvir or daclatasvir has failed, the most prevalent treatment-emergent RASs in NS5A include Q30H/R, L31M and Y93H whereas in HCV genotype 1b, L31M and Y93H are commonly observed.

The most prevalent RAS in genotype 3 is Y93H, which is commonly detected following daclatasvir failure but not in ledipasvir pretreated patients, most likely because of its lack of antiviral activity in genotype 3. Most NS5A RASs are known to persist for several months to years after treatment failure and may significantly impact retreatment options. A combination of SOF/VEL plus ribavirin given for 24 weeks was the first DAA regimen to be approved for retreatment of patients with prior NS5A failure in Europe, although there were no clinical data to support this regimen at the time. Therefore, SOF/VEL for 24 weeks was only deemed suitable for patients at high risk of clinical disease progression. However, this recommendation was later supported by data from a phase II study of SOF/VEL plus ribavirin for 24 weeks in VEL-experienced patients that yielded an overall SVR of 91% (n = 63/69).

Glecaprevir/pibrentasvir clinical trials
Both glecaprevir and pibrentasvir (GLE/PIB) have very limited metabolic activity in the liver or kidney, and have potent antiviral activity in vitro against all major HCV genotypes. PIB has a high barrier to common RASs identified for other NS5A inhibitors, including those at key amino acid positions 28, 30, 31, and 93 of the NS5A gene.

A number of phase III trials evaluated an 8–16-week treatment duration in non-cirrhotic patients across genotypes 1–6. In the ENDURANCE-1 study, 8 or 12 weeks of treatment in 703 patients with HCV genotype 1 yielded SVR rates of 99.1% and 99.7%, respectively. Of the four patients with treatment failure in both groups, only one had virologic failure in the 8-week treatment arm. In the ENDURANCE-2 and -4 studies, 202 genotype 2
patients and 121 genotype 4–6 patients each had SVR rates of 99% with 12 weeks of GLE/PIB. The SURVEYOR-2, part 4 study showed that 8-week GLE/PIB treatment was similarly effective in genotypes 2, 4, 5 and 6, with SVR rates of 98%, 93%, 100% and 90% in 145, 45, 2, and 10 patients, respectively. There were no virologic failures in HCV genotypes 4–6 and only two virologic failures among patients with HCV genotype 2.

The GLE/PIB regimen was also evaluated in two studies of patients with HCV genotype 3 infection. In the ENDURANCE-3 trial, 505 non-cirrhotic patients with genotype 3 received 8 or 12 weeks of GLE/PIB, or 12 weeks of the previously approved regimen of daclatasvir and SOF, in one of the very few DAA head-to-head studies to date. The corresponding SVR rates were 95%, 95% and 97%, respectively. Both GLE/PIB arms were statistically noninferior to the 12-week daclatasvir/SOF regimen. The virologic failure rates were not statistically different (≤1%) although, numerically, there were more cases of virologic relapse in the 8-week GLE/PIB arm. In part 3 of SURVEYOR-2, a total of 44 pegylated interferon–experienced HCV genotype 3 infected patients with or without cirrhosis were randomised to 12 or 16 weeks of GLE/PIB with SVR rates of 91% and 96%, respectively. This finding led to the approval of 16 weeks of GLE/PIB therapy in treatment-experienced patients with HCV genotype 3 infection. There was a somewhat lower SVR rate in patients with the baseline A30K RAS.

The EXPEDITION-1 study evaluated 146 patients with HCV genotypes 1, 2, and 4–6 with compensated cirrhosis treated for 12 weeks. The corresponding SVR rates were 99–100%. In this study, no patients had significant elevations in alanine aminotransferase levels and no cases of hepatic decompensation were noted.

EXPEDITION-4 was a critical study in the GLE/PIB programme encompassing patients with all major HCV genotypes and chronic kidney disease (CKD) stages 4 and 5 treated for 12 weeks. Like the previous regimens of paritaprevir/ombitasvir plus dasabuvir and grazoprevir/elbasvir, which were approved for HCV genotypes 1 and 4, this regimen was considered attractive for the CKD population because of its components' lack of renal excretion and the added feature of pan-genotypic coverage. Over 80% of the trial participants were on haemodialysis. Of the 104 patients in the study, 98% achieved SVR, with only one virologic failure in a patient.

MAGELLAN-1 was a phase II, open-label study that evaluated the efficacy and safety of GLE/PIB with or without ribavirin for 12 weeks in 50 non-cirrhotic genotype 1 patients with prior DAA failure. The SVR rates were 100%, 95%, and 86% in three different dose arms: 200 mg GLE/80 mg PIB, 300 mg GLE/120 mg PIB plus 800 mg ribavirin, or 300 mg GLE/120 mg PIB, respectively. Only two out of 50 patients experienced virologic failure. These promising results could not be confirmed in the MAGELLAN-1, part 2, phase III extension in patients with prior NSSA and/or NS3/4A failure, with or without compensated cirrhosis. A total of 91 patients (95% with HCV genotype 1) were randomised to 12 or 16 weeks of GLE/PIB. SVR was 100% in NS3/4A-experienced patients, regardless of the retreatment duration. However, among patients who had previously received an NSSA inhibitor, SVR rates were only 88% and 94% in the 12-week and 16-week treatment arms, respectively. Moreover, a total of 30 patients had prior DAA failure on dual NSSA inhibitor and NS3/4A protease inhibitor treatment, and SVR rates were only 79% and 81% in the 12-week and 16-week treatment arms, respectively.

These findings were the basis for the United States and Canadian approval of GLE/PIB in patients with HCV genotype 1 for 12 weeks if there has been prior NS3/4A inhibitor exposure, 16 weeks if there has been NSSA inhibitor exposure, but not if patients had been exposed to both classes of DAA.

Sofosbuvir/velpatasvir/voxilaprevir clinical trials
The SOF/VEL/VOX regimen is approved in Europe, Canada and the United States for the treatment of patients with chronic HCV infection without cirrhosis or with compensated cirrhosis who have previously been treated with an NSSA inhibitor. The recommended treatment duration is 12 weeks. In Europe, 8–12 weeks of SOF/VEL/VOX is also approved for DAA-naïve patients, with and without compensated cirrhosis. As with the major GLE/PIB trials, the four POLARIS phase III trials, which evaluated the safety and efficacy of SOF/VEL/VOX, were entirely ribavirin-free.

The POLARIS-1 and -4 trials were conducted in patients who had previously received a DAA-containing regimen. In POLARIS-1, patients with HCV genotype 1 infection and prior NSSA inhibitor experience received SOF/VEL/VOX for 12 weeks or matching placebo. In addition, 114 patients who were infected with other HCV genotypes also received 12 weeks of SOF/VEL/VOX. Overall SVR rates were 96% (n = 97/101) for HCV genotype 1a, 100% (n = 45/45) for genotype 1b, 100% (n = 5/5) for genotype 2, 95% (n = 74/78) for genotype 3, 91% (n = 20/22) for genotype 4, and 100% for genotypes 5 and 6 (n = 7/7). There were six
patients with virologic relapse (four had HCV genotype 3) after the end of treatment, and one virologic breakthrough during treatment in a patient with low plasma levels of the main SOF metabolite, suggesting poor study adherence. Of note, all six patients that relapsed had cirrhosis. Baseline RASs were found in 83% of patients, although SVR rates were not statistically different in these patients compared to those without baseline RASs. Only one of the six patients to relapse had a treatment-emergent RAS (Y93H) during follow-up.

In POLARIS-4, genotype 1, 2, or 3 HCV infected patients who had previously received a DAA regimen excluding an NSSA inhibitor received SOF/VEL/VOX (n = 163) or SOF/VEL (n = 151) for 12 weeks. An additional 19 patients with HCV genotype 4 were also enrolled in the SOF/VEL/VOX group. Overall, 46% of the patients had compensated cirrhosis and most of them had failed previous treatment with SOF. The rates of response were 98% and 90% in SOF/VEL/VOX and SOF/VEL treatment arms, respectively. Baseline RASs to NS3/4A and/or NS5A were present in 46% of SOF/VEL/VOX-treated study participants, all of whom achieved SVR. Furthermore, RASs did not emerge in patients who relapsed following SOF/VEL/VOX therapy. In contrast, only 90% of patients in the SOF/VEL arm with baseline RASs achieved SVR.

POLARIS-2 was an open-label, randomised trial comparing SOF/VEL/VOX for 8 weeks to SOF/VEL for 12 weeks in DAA-naïve patients infected with all HCV genotypes with and without compensated cirrhosis, except patients with genotype 3 and cirrhosis. Overall, 95% of patients had an SVR after 8 weeks of SOF/VEL/VOX compared to 98% with an SVR following 12 weeks of SOF/VEL.

Finally, POLARIS-3 was a randomised comparison trial comparing 8 weeks of SOF/VEL/VOX (n = 105) vs. 12 weeks of SOF/VEL (n = 106) in DAA-naïve patients with genotype 3 and compensated cirrhosis. SVR rates were 96% in both treatment groups, with only two patients experiencing virologic failure in each group.

In all POLARIS trials, there were no serious adverse events leading to treatment discontinuation. The most commonly reported side effects were headache, fatigue, diarrhoea, and nausea. Nausea and diarrhoea were more common in SOF/VEL/VOX-treated patients. However, 95% of the events were mild in severity.

How the new DAA regimens will fit into modern treatment algorithms

Pangenotypic therapies

From a global perspective, HCV elimination can only be achieved with DAA regimens that are highly active in all known HCV genotypes, while having excellent tolerability profiles and few drug-drug interactions. The two direct-acting antiviral drug combinations GLE/PIB and SOF/VEL, with SOF/VEL/VOX as a backup, have the ability to address most, if not all, existing therapeutic challenges and limitations associated with HCV therapy. This is particularly true for the treatment of HCV genotypes 4, 5, and 6, which were under-represented in most clinical trials but are highly prevalent in many middle- and low-income countries across the globe.

GLE/PIB is a once-daily regimen for the treatment of all HCV genotypes, with an 8-week treatment duration in most non-cirrhotic patients. However, the most distinctive feature of this regimen is the high antiviral activity in HCV genotype 1a, even in patients with prior PEG-IFN failure and those with cirrhosis. In a pooled analysis of phase II/III clinical studies, there were only two genotype 1a virologic failures, one with cirrhosis and another patient with the NSSA RAS Y93N at baseline, while no genotype 1b failures were reported. This represents a major advantage over current practice of resistance testing prior to grazoprevir/elbasvir and extensive use of ribavirin with either paritaprevir/ombitasvir/dasabuvir or LDV/SOF in treatment-experienced patients with and without cirrhosis.

Because 8 weeks of SOF/VEL failed to show noninferior efficacy compared to 12 weeks in a phase II clinical trial, this DAA regimen is only approved for 12 weeks. Against this background, one aim of the POLARIS-2 and -3 trials was to evaluate the efficacy of 8 weeks of SOF/VEL/VOX across all HCV genotypes in patients with and without cirrhosis and with or without prior PEG-IFN experience. Surprisingly, POLARIS-2 failed to prove that 8 weeks of SOF/VEL/VOX was noninferior to SOF/VEL for 12 weeks, mainly because of an unexpectedly high number of treatment failures among HCV genotype 1a infected patients. Although the NS3/4A RAS Q80K was shown to confer no change to voxilaprevir susceptibility in vitro, Q80K was detectable at baseline in the majority of genotype 1a patients with post-treatment virologic relapse, indicating that there may be some link after all. However, it remains unclear whether it was the Q80K substitution per se that led to the increased rate of treatment failure, or if it served as a surrogate marker for an unidentified feature of the genotype 1a clade that is particularly prevalent in the United States. Consequently, in the United States and Canada the SOF/VEL/VOX regimen was not submitted for approval in patients without prior DAA experience, whereas in Europe SOF/VEL/VOX was also approved for DAA-naïve patients. A possible explanation may be found in the European summary of product characteristics which states that SVR rates were 89% in genotype 1a infected patients enrolled at sites in the United States and 97% in genotype 1a infected patients enrolled at sites outside the United States, thereby raising the possibility, discussed above, that there may be a difference between HCV genotype 1a
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HCV genotype 3

HCV genotype 3 infection in patients with cirrhosis and/or prior treatment failure has been the Achilles heel of many interferon-free regimens. The story is no different with GLE/PIB. While 8 weeks are recommended in treatment-naïve, non-cirrhotic patients with HCV genotype 3,83 treatment extension to 16 weeks is recommended in those with prior peg-IFN failure, regardless of the presence of cirrhosis. However, it remains unclear whether prior treatment failure, presence of NS5A RASs at baseline, or both were responsible for GLE/PIB treatment failure.25 Certainly, more data need to be collected in this patient population. Moreover, because other 12-week regimens are available, a 16-week GLE/PIB regimen will rarely be necessary.

While SOF/VEL has excellent activity in treatment-naïve patients with HCV genotype 3, with and without cirrhosis, SVR rates were lower in treatment-experienced patients, particularly in those who also had cirrhosis or baseline NS5A RASs (SVR 89–91%).41 Therefore, the combination of SOF/VEL with ribavirin has been recommended in this particular patient population, although recent real-world data suggest that ribavirin may not be required in those with compensated cirrhosis.76,77 In POLARIS-3, only two genotype 3 infected patients treated with SOF/VEL/VOX experienced virologic failure, both of whom had no NS5A RASs at baseline. Moreover, all patients with baseline RASs (either in NS3 and/or in NS5A) achieved SVR. Thus, 8 weeks of SOF/VEL/VOX may be a feasible option in treatment-experienced patients with compensated cirrhosis, as this combination achieved 97% SVR.70

Chronic kidney disease

Both GLE and PIB are primarily metabolised and excreted in the biliary system, with negligible renal excretion, making GLE/PIB an attractive DAA combination in patients with advanced CKD. Of note, the GLE/PIB package insert recommends 8 weeks of treatment in patients with CKD who do not have other indications for treatment extension (e.g., cirrhosis), whereas patients in the EXPEDITION-4 trial were treated for a total of 12 weeks.84 However, despite the lack of a trial to support this recommendation, we believe that truncation of treatment to 8 weeks is justified. While the already approved regimen of grazoprevir/elbasvir has been shown to be effective in patients with CKD and genotypes 1 and 4, GLE/PIB holds promise as an effective and safe treatment option for patients with other HCV genotypes.

Patients with prior DAA failure

Based on the Magellan-1 study, GLE/PIB has been approved for salvage therapy of DAA-experienced patients in the United States and Canada but not in Europe.67,68 However, Canadian and United States approval is restricted to patients infected with genotype 1, as only few patients with genotype 4 were enrolled in this study. Salvage therapy with GLE/PIB is not recommended in patients with prior failure to both NS3/4A and NS5A inhibitors, primarily because clinically meaningful RASs which were associated with lower SVR rates in the Magellan-1 study are likely to occur in both targets. We believe that resistance testing may be useful to select the optimal combination and treatment duration, if considering GLE/PIB for treatment of patients with prior DAA failure.

SOF/VEL/VOX currently holds a unique position for the treatment of patients with prior DAA failure. Data from both POLARIS-1 and POLARIS-4 studies showed that there was no association between baseline RASs and treatment outcome.95 Thus, resistance testing is not recommended prior to SOF/VEL/VOX salvage therapy. However, if SOF/VEL/VOX fails, resistance testing may be required prior to selecting an individual retreatment strategy. Moreover, given the fact that four out of six SOF/VEL/VOX failures in POLARIS-1 had HCV genotype 3, ribavirin may still be considered in patients with HCV genotype 3 and prior NS5A failure, particularly in the presence of cirrhosis and/or other negative predictors of response.

SOF/VEL/VOX may also be the optimal choice for patients with prior GLE/PIB failure despite the current lack of available data.

Remaining challenges

As with all other regimens containing HCV NS3/4A protease inhibitors, GLE/PIB and SOF/VEL/VOX, which both contain an NS3/4A protease inhibitor, are not recommended in patients with decompen-sated cirrhosis (Child-Turcotte-Pugh stage B or C). Thus, patients with decompen-sated cirrhosis and prior DAA failure have no explicit treatment options at this time. For these patients, alternative treatment options, including off label DAA combinations without an NS3/4A inhibitor such as SOF/VEL ± ribavirin should be considered in a controlled setting. Another alternative approach is to treat HCV after liver transplantation in transplant-qualified patients with pangenotypic GLE/PIB or SOF/VEL/VOX.

Moreover, there are currently no treatment options for patients in whom SOF/VEL/VOX fails. In these patients, addition of ribavirin and treatment extension to 24 weeks, or GLE/PIB given in combination with SOF and ribavirin for 16 weeks,
may be a feasible treatment approach. The rationale for SOF/VEL/VOX given for a longer duration is theoretically attractive because of the absence of treatment-emergent RASs in patients who failed 12 weeks of SOF/VEL/VOX in the POLARIS trials, while 16 weeks of GLE/PIB plus SOF and ribavirin has been shown to be active in patients with prior GLE/PIB failure.78

One of the remaining challenges is treatment of children with HCV, given the lack of availability of most DAAs for this age group. Currently, only SOF/LDV and SOF plus ribavirin are approved for adolescent children aged 12 and over, whereas treatment in younger patients should be deferred until DAAs become available.2,3 Pangenotypic DAA regimens are currently not approved in patients aged 17 or younger. However, for both GLE/PIB and SOF/VEL, approval studies are already underway.

The WHO and major healthcare stakeholders have put HCV elimination high on the world health agenda. Taken together, the use of pangenotypic DAA regimens has the potential to support the worldwide goal of HCV elimination, both in a micro environment (e.g. in local drug user networks, prisons, and migrant communities) and as part of national HCV elimination plans, particularly once generic DAAs become more widely available.

Conflict of interest
J.V. reports personal fees from AbbVie, Gilead, Merck, outside the submitted work. I.J. reports personal fees from AbbVie, Bristol-Myers Squibb, Intercept; grants and personal fees from Gilead, Merck, Janssen, outside the submitted work. J.S.P. reports personal fees from AbbVie, Gilead, Merck, Janssen, Falk, Intercept, outside the submitted work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data
Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.07.002.

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Review


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