



# Direct-acting antivirals: the endgame for hepatitis C?

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Directly-acting antivirals (DAA) have finally allowed all patients to be potentially cured from chronic hepatitis C (HCV) infection. All-oral, Interferon (IFN)-free regimens are based upon the combination of molecules targeting different sites of the HCV replication process. Three classes of DAA exist: protease inhibitors (anti-NS3/4A), RNA-dependent polymerase inhibitors (anti-NS5B) and anti-NS5A inhibitors, which are characterized by different antiviral potency and barrier to resistance and therefore are usually combined in different treatment schedules. Treatment regimens are still largely dependent on HCV genotype and stage of liver disease, with duration ranging between 12 weeks and 24 weeks, while overall treatment efficacy has climbed to nearly 95% in most patient groups, including historically difficult-to-treat categories (HCV genotype 1, advanced liver disease). The elimination of IFN has allowed safe and efficacious treatment of patients formerly contraindicated to antiviral therapy, such as decompensated cirrhosis and solid organ transplant recipients. Availability of potent and safe antiviral drugs combined with improvement of worldwide access to treatment could finally lead to HCV elimination in the next decades.

## Addresses

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Current Opinion in Virology 2017, 24:31–37

This review comes from a themed issue on **Antiviral strategies**

Edited by **Fabien and Lieve**

<http://dx.doi.org/10.1016/j.coviro.2017.03.017>

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## Introduction

Directly-acting antivirals (DAA) have radically changed the chronic hepatitis C (CHC) therapeutic scenario, as treatment options with excellent efficacy and safety profiles are now available for most patients. DAAs combinations in all-oral regimens have led to overall high

sustained virological response (SVR), independently on liver disease severity and viral genotype.

DAAs have definitively replaced Interferon (IFN)-based regimens; however, Ribavirin (RBV) still remains essential in selected cases identified by Hepatitis C virus (HCV) genotype, previous treatment failure and disease stage. Finally, these IFN-free regimens can be safely used among subjects who were previously contraindicated to IFN, such as decompensated patients as well as solid-organ transplanted (SOT) patients. Moreover, the availability of several drugs with different pharmacologic properties, as well as the absence of treatment-related adverse events (AE) reported during randomized clinical trials (RCT) and real-life studies, *de facto* allows for tailoring of antiviral treatment according to patient clinical features, without major restrictions [1•].

Nowadays, every HCV chronically infected patient may benefit from new all-oral antiviral treatments.

## Approved DAA combinations

Available oral regimens are based upon the combination of DAAs that target HCV non structural (NS) proteins that are key players in HCV replication. Three classes on anti-HCV DAAs exist: the protease (NS3/4A) inhibitors (*i.e.* Paritaprevir, Simeprevir, Grazoprevir), the RNA-dependent polymerase (NS5B) inhibitors [nucleoside analogues (*i.e.* Sofosbuvir) and non-nucleoside (*i.e.* Dasabuvir)] and NS5A inhibitors (*i.e.* Ledipasvir, Ombitasvir, Daclatasvir, Velpatasvir, Elbasvir) [2].

The aim of combining DAAs is to achieve potent inhibition of HCV replication and concomitant high barrier to resistance, which means the ability to avoid selecting resistant HCV viral strains. None of the above mentioned compounds has both features when given in monotherapy, indeed all DAAs are potent as they rapidly suppress HCV RNA replication but most have low to medium genetic barrier to resistance. This means that when given in monotherapy they will rapidly select for Resistant Associated Variants that are part of the patients HCV quasispecies, indeed given the lack of proof reading ability of the NS5B RNA-dependent polymerase substitutions in the viral sequence of the target proteins of DAAs are produced continuously. These substitutions in the viral sequence defined Resistant Associated Substitutions (RAS) may alter the HCV protein functionality but affect negatively the antiviral effect of DAAs targeting the protein that carries the RAS [3•]. The only DAA that

is characterized by a high genetic barrier to resistance is Sofosbuvir (SOF). Sofosbuvir can be given in monotherapy combined with RBV in HCV genotype 2, 3 and 4, although the achievable SVR rates are lower than those obtained by combining SOF with an NS3 or NS5A inhibitor. A regimen can also achieve high genetic barrier by combining 3 DAAs with low genetic barrier, such as Paritaprevir/Ombitasvir (PTV/OBT) plus Dasabuvir (DSV), or by combining 2 second or third generation DAAs that as individual compounds are characterized by higher genetic barrier to resistance [4].

### SOF-based regimens

Sofosbuvir has been the first IFN-free DAA to be developed. It is characterized by high barrier resistance and pangenotypic activity, and it can be safely combined with anti-NS5A molecules to achieve high SVR rates in almost all HCV genotypes.

#### Genotypes 1 and 4

According to international recommendations for the treatment of chronic HCV infection, SOF combined with NS5A inhibitors (with or without RBV) represents one of the endorsed treatment options for HCV-1 and HCV-4 patients, since this regimen is associated with extremely high SVR rates independently on liver disease severity. According to the recently published EASL recommendations, the combination SOF/Ledipasvir (LDV), SOF plus Daclatasvir (DCV) or SOF/Velpatasvir (VEL) are all considered optimal options for HCV-1 and 4 patients [1<sup>••</sup>]. In fact, in genotype 1 and 4 infections, SOF plus Simeprevir (SMV) and SOF plus PegIFN and RBV are no more considered as first-treatment options, due to slightly lower SVR rates with the former and increased risk of AE mainly related to the use of IFN in the latter regimen. According to recent data, treatment schedules largely differ according to disease severity (cirrhosis *vs.* non-cirrhosis) and patient treatment history [naïve *vs.* treatment experienced (TE)]. Twelve-weeks of SOF/LDV, SOF plus DCV or SOF/VEL is enough to treat HCV-1b infection, independently on the presence of cirrhosis or previous treatment failures [5–8]. In genotype 1a RBV may be still required, in case of TE without cirrhosis (12-week SOF/LDV plus RBV) or in TE cirrhotic patients not treated with SOF/VEL (12-week SOF/LDV plus RBV or 12-weeks SOF + DCV plus RBV). Whenever RBV is contraindicated, the 24-weeks RBV-free option can be safely used [1<sup>••</sup>]. Moreover, in small groups of selected patients, short-treatment duration can confidently used. Data coming from Phase 3 trials and real-life data support the efficacy of 8-week SOF/LDV for naïve, non-cirrhotic HCV-1 patients who have a pre-treatment viral-load less than 6,000,000 IU/mL [10<sup>•</sup>]. Similarly, 8-week OBT/PTV-R plus DSV can be safely used in naïve HCV-1b patients without cirrhosis, as demonstrated by the 98% SVR rates achieved in the Garnet trial [11].

Genotype 4 recommendations are identical to those for HCV-1a patients [12], without the possibility of further shortening treatment duration to less than 12-weeks (see below). In patients with HCV-4, the combination of SOF and SMV still has a role, with or without RBV. In fact, naïve patients may benefit from 12-week SOF plus SMV, independently on disease severity, whilst TE subjects should be treated with RBV-containing regimens (12-week SOF plus RBV), at any stage of fibrosis [13]. Also in these cases, 24-week SOF plus SMV without RBV may replace short-duration therapies, when RBV is contraindicated.

#### Genotypes 2 and 3

Similarly, in HCV-2 and HCV-3 patients, the combination of SOF with DCV or SOF/VEL have replaced the combination of SOF plus RBV (12 weeks in genotype 2, 24 weeks in genotype 3) and SOF plus PegIFN and RBV (12 weeks in genotype 3), which were previously recommended [1<sup>••</sup>]. Ledipasvir does not have strong antiviral effect on genotypes 2 and 3. According to more recent data, genotype 2 patients may benefit from short-duration (12 weeks) and RBV-free regimens, independently on liver disease severity and treatment history with either SOF plus DCV or SOF/VEL [14]. In genotype 3 patients, the need for longer (up to 24 weeks) treatment duration or RBV use are based on fibrosis stage and previous treatment history. In fact, 12-week SOF plus DCV or SOF/VEL (without RBV) represent equivalent treatment options for non-cirrhotic, naïve HCV-3 patients. On the contrary, RBV is required in HCV-3 non-cirrhotic patients who failed previous IFN-based therapies (12-week SOF + DCV + RBV or SOF/VEL + RBV) or in cirrhotics, independently on their treatment-status (24-week SOF + DCV + RBV or 12-week SOF/VEL + RBV) [14–16].

#### Ombitasvir/Paritaprevir ± Dasabuvir

Patients with genotype 1 infection may benefit from the association of the Ritonavir (R)-boosted protease inhibitor Paritaprevir (PTV) and the non-NUC NS5B inhibitor Ombitasvir (OBT) with the anti-NS5A Dasabuvir (DSV). This regimen is effective against both genotype 1a and 1b infections [17–22]. RBV is not needed in HCV-1b patients, independently on disease severity and treatment status. On the contrary, in genotype 1a patients, RBV is still required in all cases [23].

In patients with HCV-4 infection, DSV is not effective. Therefore, PTV-R/OBT represents the recommended treatment option in combination with RBV for 12 weeks [24,25].

Because of the presence of the anti-NS3/4A PTV, these regimens are contraindicated in HCV patients with decompensated liver disease (CPT B and C) [1<sup>••</sup>].

### Grazoprevir and Elbasvir

The combination Grazoprevir (GRZ)/Elbasvir (EBV) is effective against HCV-1 and HCV-4 infections. Whereas in genotype 1b patients GRZ/EBV can be safely administered for 12 weeks without RBV, independently on fibrosis stage and treatment status, treatment duration and RBV need depend on clinical features in patients with HCV-1a and HCV-4 infections. In fact, 12-week GRZ/EBV without RBV can be enough in all patients with low viral-load ( $\leq 800\,000$  IU/mL). In the remnants categories of HCV-1a and HCV-4 patients, 16-weeks of treatment with RBV are required [26,27].

Efficacy data from published trials concerning different IFN-free treatment options are summarized in Table 1.

### Special populations

#### Decompensated patients

Until recently, anti-HCV treatment in patients with end-stage liver disease (ESLD) was contraindicated. The availability of all-oral regimens has changed this dogma. Registration trials [7,28–30] and real-life [31,32\*,33] data have demonstrated acceptable SVR rates among CPT-B and C patients, with no significant safety signals. Protease inhibitors such as SMV are contraindicated in CPT-C patients, and should be used with caution in CPT-B patients. The combination regimens of OBT/PTV-R plus DSV and GZR/EBR are contraindicated in CPT-B and C patients as they have not been formally studied in clinical trials, and their off-label use has resulted in serious adverse events [34].

### Treatment of HCV in patients who have received solid organ transplant (SOT)

#### Liver Transplant (LT)

In the post-LT setting, DAAs have demonstrated high SVR rates and excellent safety and tolerability profiles. Hepatitis C virus eradication, even in the early post-LT period, has led to a reduction in the fibrosis progression rate, which is usually accelerated by the concomitant immunosuppression. All-oral DAA regimens are safe and effective, with AE profiles similar to those observed in non transplanted HCV population [35–38]. The main issue in all patients receiving immunosuppressants following organ transplant are drug–drug interactions (DDI) with DAAs.

#### Non liver SOT

Interferon-based regimens have been largely contraindicated in non liver SOT patients, because of the potential risk of chronic rejection [39], which has been demonstrated especially in KT patients. Until recently, HCV chronic infection has represented a contraindication to Lung (LT) and Heart-Transplant (HT) [40], although solid data on the role of chronic HCV infection in patients and graft survival are lacking. HCV eradication should be mandatory nowadays that improvement in both surgical techniques and immunosuppressant management had greatly improved SOT patient survival. In SOT patients, SOF-based regimens are safe and effective due to the absence of SOF-related significant AE and the limited risk of DDI, particularly DDI. Excellent SVR rates (98%) have been reported among 114 HCV patients with KT,

**Table 1**

**SVR rates in HCV patients by genotype and antiviral regimen according to published data**

Patients	SOF/LDV	SOF/DCV	SOF/VEL	SOF/SMV	OBT/PTV-R + DSV	OBT/PTV-R	GZR/EBR
HCV-1	97–99% ION-1 [5] 94–99% ION-2 [6] 94% ION-3 [10*] →97% 8 weeks (no cirrhosis)	95–100% Sulkowski [7] 91% ALLY-1 [8]	98% ASTRAL-1 [9*]	–	95% vs 98% (1a vs 1b) SAPPHIRE [17] 90% vs 97% (1a vs 1b) PEARL-4 [23] 96% vs 97% (1a vs 1b) SAPPHIRE-2 [19] 97–99% MALACHITE I-II [18] 92% vs 99% (1a vs 1b) TURQUOISE-II [21] 98% GARNET trial [11] (8 weeks, no cirrhosis)	–	92% vs 99% (1a vs 1b) C-EDGE-TN [26] 95% vs 99% (1a vs 1b) C-EDGE-TE [27]
HCV-2	–	93% Sulkowski [7]	99% ASTRAL-2 [14]	–	–	–	–
HCV-3	–	80% ALLY-3 [15] 93% ALLY-3+ [16]	93% ASTRAL-3 [14]	–	–	–	–
HCV-4	95% SYNERGY [12]	100% ALLY-1 [8]	100% ASTRAL-1 [9*]	100% PLUTO [13]	–	100% PEARL-1 [25] 97% AGATE-1 [24]	100% C-EDGE-TN [26] 60–100% C-EDGE-TE [27]

treated for either 12 or 24 weeks with SOF/LDV [41], as well as among smaller real-life cohorts [42–44]. Moreover, SOF-based regimens have been demonstrated to be safe and effective in a small series of LT patients [45] (Figure 1).

### Patients with kidney impairment

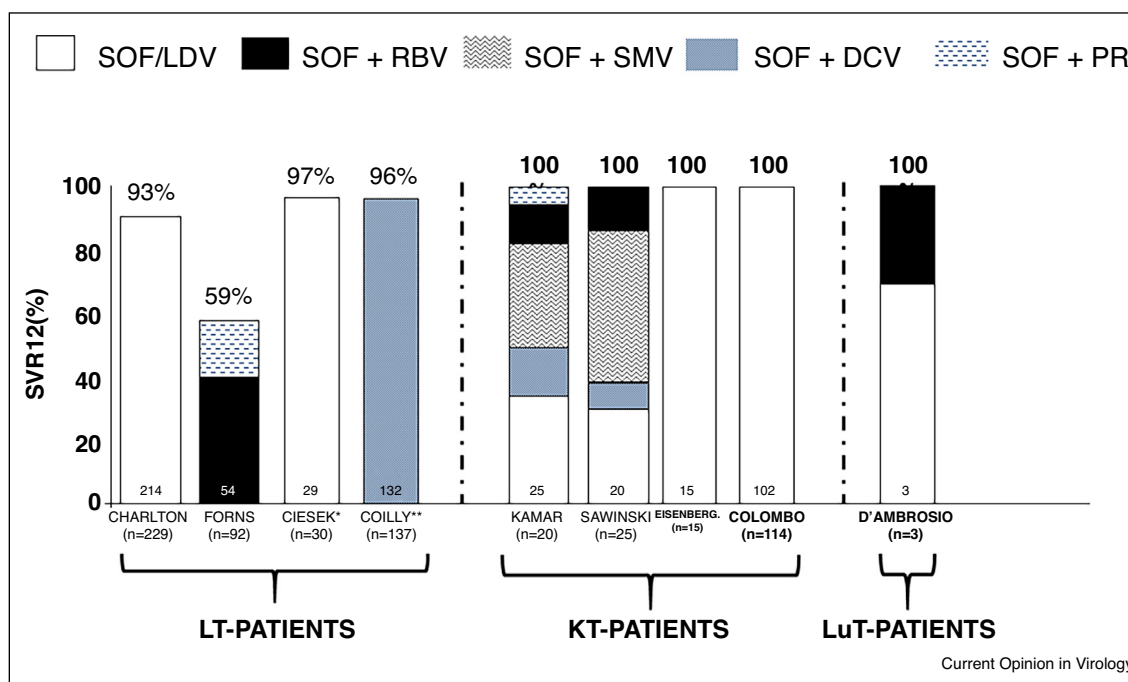
Treating HCV patients with concomitant chronic kidney disease with Interferon-based regimens was challenging, especially when the stage of CKD was 4–5 (eGFR <30 ml/min) due to increase RBV blood concentrations and related AE. Ribavirin-free DAAs schemes have changed this paradigm [46]. Most of the anti-HCV molecules do have a hepatic excretion, therefore, can be safely used in HCV patients with CKD. OBT/PVT-R ± DBV and GRZ/ELB regimens can be safely administered in CKD 4–5 patients. These 2 regimens have been studied in the RUBY-1 [47] and C-SURFER [48•] studies, two studies concentrating on CKD stage 4 and 5. Overall the SVR rates in these studies including only genotype 1 patients have been 90% and 99%, with no significant safety signals for either regimen. On the contrary, SOF-based regimens have not been formally studied in CKD stage 4–5 patients and currently should be used with caution in this group of HCV patients. Since SOF is renally excreted in CKD stage 4–5 the AUC of the GS331007 metabolite increases

significantly [49]. The toxicity of this metabolite is unknown, but given the preclinical toxicity of other nucleotide inhibitors, routine use of SOF in patients with eGFR <30 ml/min cannot be advocated. Real life SOF data in CKD stage 4–5 patients are consistent with no particular safety signal [50–52], however these cohorts are rather small, heterogeneous for liver and kidney disease stage and cannot ultimately provide definitive evidence.

### Real life data

Usually there is a gap between efficacy and effectiveness, that is the difference in efficacy of any drug in clinical trials compared to the real world setting. Clinical trials are designed to assess the safety and efficacy of a drug in an ideal setting, by limiting significant co-morbidities that might reduce efficacy or safety and also ensuring for optimal patients compliance. For this reason once drugs are commercialized, efficacy is generally lower and unexplored subcategories of patients cannot be reached by the drug due to lack of safety and efficacy data. This dogma has been challenged by the arrival of DAAs, as not only real life data have provided similar efficacy rates compared to randomized clinical trials, but also real life studies have provided solid data to support the safety and efficacy of DAAs in understudied patients populations such as those with decompensated cirrhosis or portal

Figure 1



SVR rates among SOT patients treated with DAA.

\*RBV in 25 (83%) patients.

\*\*RBV in 41 (30%) patients.

\*\*\*2 patients were lost at follow-up.



hypertension. The HCV Target study conducted in the USA, Europe, Canada and Israel has shown SVR rates to SOF/LDV to reach 99% [52], while other real life data from Italy and Spain have shown convincing efficacy of OBV/PTV-r plus DSV by reporting SVR of 93–97% and 96% in HCV-1a and 1b, respectively [54–56]. Large cohorts coming from France and Germany have analysed the safety and efficacy of SOF/DCV across all genotypes reporting SVR rates that ranged from 91 to 99% [57,58]. These large cohorts of patients cumulatively including more than 6500 patients, mostly with cirrhosis (58%), have also reported optimal safety of these regimens across all patients' subcategories, as the overall rate of serious adverse event or treatment discontinuation was 7.8% and 3.3%, respectively [53–58].

## Conclusions

The introduction of DAAs for the treatment of HCV, has finally allowed all HCV infected patients to be possibly cured of their disease. Indeed the availability of several DAA combinations with different pharmacokinetic properties and metabolism allows for safe and effective therapies even in groups of patients that have been historically considered difficult to cure. The development of guidelines by international scientific societies provides the basis for rational use of these compounds aimed at maximising SVR rates in the individual patient. Some recommendations have been criticized for leaning towards overtreatment (RBV, longer treatment duration), however this choice was made on purpose as re-treatment of DAA failures is still not simple and lacks codified treatment schemes and options. Following treatment failure with an NS5A containing regimen there is selection of RASs in the NS5A region, which have been shown to persist for up to 2 years. Their presence affects the efficacy of re-treatment options with the current available DAAs. In the future pan-genotypic DAA combinations with higher barrier to resistance such as Glecaprevir/Pibrentasvir or including 3 DAAs such as SOF/VEL/Voxilaprevir should allow for effective treatments also in these patients, but until they are EMA/FDA approved no approved regimens exist for NS5A failures.

The impressive improvements in safety and efficacy of drugs used in the treatment of HCV patients have de facto eliminated one of the biggest hurdles in the way of HCV elimination. Although several hurdles still remain that require concerted national plans between healthcare authorities to increase the number of diagnosed patients, improve the referral to treatment and increase treatment rate [59], modelling data has shown that HCV elimination can be achieved through DAA treatment of large volume of patients. Analyzing the Egyptian HCV pandemic where nearly 10 000 000 people are chronically infected with HCV, Ayoub and Abu-Raddad have shown that a reduction in HCV prevalence to 0.1% can be achieved with treatment scale up [60]. By Markov analysis the

authors found that by treating 350 000 patients per year until 2030 with DAAs, the 2030 WHO targets for HCV elimination (90% diagnostic rate, 80% treatment rate and 80% reduction in incidence) could be achieved. Similarly Australia, that has aggressively negotiated DAA pricings to ensure universal access treatment through the National Health system, has recently announced that it can reach the WHO targets in 2026 as a consequence of widespread HCV treatment among general practitioners [61]. These examples highlight that through political will and universal access to DAAs, HCV could be the first infectious disease to be eliminated worldwide in the absence of an effective vaccine.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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- of outstanding interest

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