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Chapter 2

Advances in Treatment of Hepatitis C

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Abstract

Hepatitis C infection (HCV) is a major cause of chronic hepatitis and cirrhosis worldwide. Interferon-based regimen has been the sole therapy to eradicate HCV infection for decades. However, this interferon and ribavirin combination is associated with several serious adverse events and the sustained virologic response rate was suboptimal. The recent discovery of oral direct-acting antiviral agents (DAAs) heralded a revolution in the treatment of chronic HCV. This breakthrough in HCV resulted in high rates of HCV eradication with sustained virologic response rates ranging between 90 and 100% across different genotypes. New therapies were administered orally for 12 or 24 months and this resulted in better compliance and few adverse events. DAAs are categorized into four major groups namely: NS5B nucleotide inhibitors, NS5B nonnucleoside inhibitors, NS5A replication complex inhibitors, and NS3/4A protease inhibitors (PI). Several interferon-free regimens have been approved and adequately assessed and several new regimens with high potencies, less cross-resistance, and better safety profile are in the process of approval. Thus, the era of HCV eradication and cure has begun.

Keywords: hepatitis C, direct-acting antivirals, interferon-free regimen

1. Introduction

Hepatitis C virus (HCV) is a major cause of liver cirrhosis, end-stage liver disease, and liver transplantation throughout the world [1]. Approximately 170–200 million people equating to 3% of the world's population are infected with HCV [2]. The prevalence of HCV varies in different geographic regions. The prevalence of HCV infection is greater in Africa and Asia, with infection rates exceeding 5% [3–5]. Egypt has the highest prevalence of hepatitis C in the world, with 15% of the population affected [6–8]. In the USA, nearly 2% of the population is infected [9, 10]. In Europe, the prevalence ranges from 0.1% in northern European countries and 1% in

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countries on the Mediterranean [10, 11]. The immigration crisis may increase HCV prevalence in Europe given that immigrants originate from countries with high rates of HCV [12].

2. Natural history and outcome of HCV infection

Acute HCV infection is mostly asymptomatic and rarely recognized clinically. Spontaneous viral clearance (SVC) occurs in approximately 25% of patients [13, 14]. The striking feature of HCV infection is its tendency to persist and evolve to chronic hepatitis. In some patients, chronic HCV progresses to liver cirrhosis and hepatocellular carcinoma (HCC) [14, 15].

The outcome of HCV infection depends largely on several host, viral and environmental factors. During an early stage, HCV infection triggers viral-associated molecular pattern (PAMP) receptors resulting in induction of an antiviral state through several pathways such as limiting cellular, modifying and degrading viral RNA, altering cellular vesicle trafficking and probably other not yet discovered antiviral mechanisms [15–17]. Clearance of HCV is associated with the development of robust and multispecific $CD4^+$ and $CD8^+$T-cell responses in blood and liver that can be maintained for years after recovery from acute disease [18–20]. In contrast, individuals who progress to chronic infection fail to mount such a response or may have inadequate production of the cytokines essential to control viral replication. Incomplete control of viral replication by $CD8^+$ T cells in the absence of sufficient memory $CD4^+$T cells leads to viral persistence and emergence of CTL escape mutants [21–24].

Acute resolving hepatitis has been shown to be associated with HCV homogeneity, whereas progressing hepatitis correlated with genetic diversity, presumably reflecting greater immune pressure during acute spontaneous clearance [25]. Polymorphisms of genes involved in innate immunity as well as those in genes encoding cytokines and other immunologic mediators may explain spontaneous recovery from acute HCV and influence the strength and nature of immune defense. Genes encoding the inhibitory NK cell receptor *KIR2DL3* and its human leukocyte antigen C group 1 (*HLA-C1*) ligand influenced spontaneous resolution of HCV infection suggesting that inhibitory NK cell interactions are critical for antiviral immunity [26, 27].

To date, there are no reliable methods to predict who will resolve acute HCV spontaneously and who will develop chronic HCV. Similarly, no reliable indicators exist for distinguishing chronic hepatitis C patients who may develop cirrhosis or HCC. Thus, early effective treatment of patients with HCV is necessary for prevention of progression of liver disease to cirrhosis, hepatocellular carcinoma. In the absence of a vaccine against HCV, efficient treatment is important for prevention of transmission along with adoption of infection control measures.

3. Evolution of HCV therapy

The ultimate goal of hepatitis C treatment is to reduce the occurrence of end-stage liver disease and its complications including decompensated cirrhosis, liver transplantation, and

HCC. Treatment success is assessed by sustained virologic response (SVR), defined undetectable HCV RNA in blood several months after completing a course of treatment [28].

For two decades, the standard of care (SOC) for hepatitis C infection was interferon based. IFNα has potent antiviral activity due to its ability to induce IFN-stimulated genes (ISGs) that encode proteins which inhibit various stages of viral replication [29]. Type I IFNs bind a unique ubiquitous heterodimeric receptor consisting of interferon-alpha receptor 1/2 (IFNAR1/IFNAR2), resulting in the activation of signaling pathways and induction of a large number of IFN-stimulated genes (ISGs). ISG-encoded proteins mediate the antiviral and other effects of interferons [29]. IFNAR1 and IFNAR2 are associated with the Janus-activated kinases (JAKs) tyrosine kinase 2 (TYK2) and JAK1, respectively. Binding of type I IFNs to their heterodimeric receptors leads to activation of JAKs, which results in tyrosine phosphorylation of signal transducer and activator of transcription 2 (STAT2) and STAT1; STAT1/STAT2 migrates into the nucleus and associates with the IFN regulatory factor 9 (IRF9) to form the STAT1-STAT2-IRF9 complex. This complex then binds IFN-stimulated response elements (ISREs) inside DNA to initiate the transcription of hundreds of different ISGs [30, 31]. IFN regulatory genes (IRGs) facilitate both clearance of virus from infected cells and protection of neighboring uninfected cells from incoming viral progeny. The antiviral-associated protein kinase R (PKR) plays an important role in restricting HCV 1a replication through regulating the NF-κB pathway [32, 33].

Initially, chronic hepatitis C was treated by conventional interferon (IFN) monotherapy which yielded very poor response rates. Addition of the guano sine analog, ribavirin, to conventional interferon was associated with slight improvement in sustained virologic response (SVR) although the improvement was far from satisfactory particularly in HCV genotypes 1 and 4. Pegylation of the interferon molecule resulted in modification of the pharmacokinetic profile of IFN-α-2. Both PEG-IFN-α-2a and PEG-IFN-α-2b have slower absorption, more reduced distribution and lower elimination rate than the nonpegylated IFN-α. The maintained concentrations of PEG-IFNα allowed longer periods of viral inhibition with once a week dosing. Pegylated interferon and ribavirin therapy resulted in improved sustained virologic response (SVR), defined as undetectable HCV RNA 24 weeks after completion of treatment. With pegylated interferon alpha-2 and ribavirin (RBV) combination, response rates in genotypes 2 and 3 range between 70 and 80%. However, SVR rates in chronic HCV genotypes 1 and 4 infection are suboptimal. Adverse events are common with interferon-based regimen and include fatigue, flu-like symptoms, anxiety, skin rash, and gastrointestinal symptoms such as nausea and diarrhea. Hemolytic anemia is frequent due to the use of ribavirin. Some patients treated with PEG-IFN and RBV may develop cardiac arrhythmias or severe neuropsychiatric adverse events depression and suicidal tendency. The various adverse effects, the long duration of therapy and the need to inject interferon reduce compliance and treatment adherence. These factors have driven the urgent need to develop new treatments that are safer and more effective (**Figure 1**). The discovery of direct-acting antiviral agents (DAAs) heralded the dawn of a new era of HCV cure which was a dream.

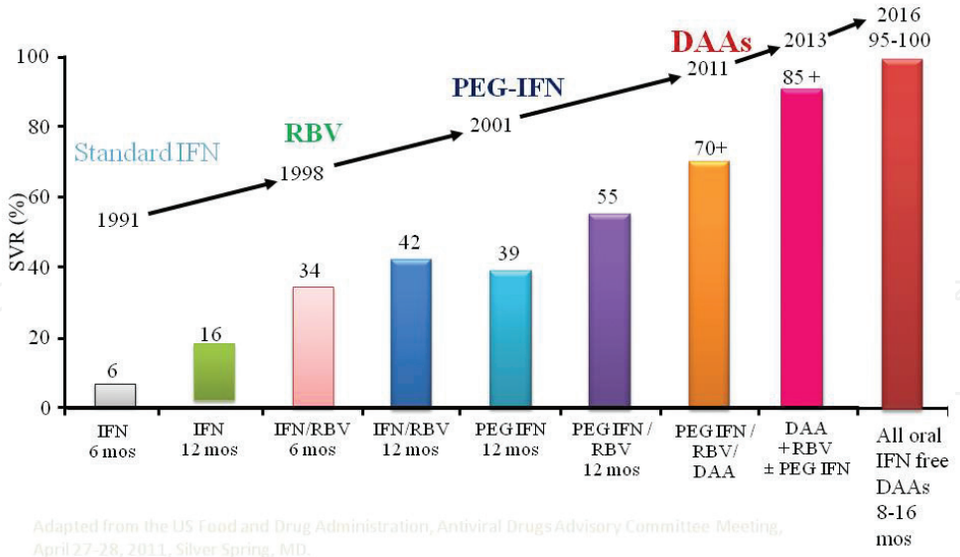


Figure 1. Evolution of HCV therapy.

4. Direct-acting antiviral agents (DAAs)

Direct-acting antiviral agents (DAAs) represent a revolution in HCV drug discovery. DAAs were developed to improve the SVR rates, reduce adverse events, and improve adherence to therapy among HCV patients. DAAs were initially introduced as add-ons to the previous standard of care (SOC) consisting of pegylated interferon alpha plus ribavirin (PR). Recently, a breakthrough in HCV therapy has been achieved with the introduction of interferon-free all-oral DAAs, with SVR rates now in excess of 90% after 12 weeks of therapy for genotype 1 patients.

DAAs target specific steps within the HCV life cycle and disrupt viral replication in an attempt to terminate that cycle before its completion (**Figure 2**) [34]. The first step in the life cycle of the virus is cell attachment and entry of HCV RNA through hepatocyte surface receptors. The HCV RNA is then translated to one polyprotein of 3010 amino acids that is subsequently cleaved by protease. It is then processed into four structural proteins (namely Core, E1, E2, and P7) as well as the nonstructural proteins (NS2-3 and NS3-4A proteases, NS3 helicase, and NS5B RdRp). All of these enzymes are essential for the replication of the virus and are potential drug discovery targets [35–37].

4.1. Goals of HCV and endpoints of treatment with DAAs

The goal of therapy is to eradicate HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, and severe extrahepatic manifestations. The endpoint of therapy is undetectable HCV RNA in blood by a sensitive assay (with the lower limit of detection <15 IU/ml) 12 weeks (SVR-12) and/or 24 weeks (SVR-24) after the completion of treatment. Undetectable HCV core antigen (HCV c Ag) 12 or 24 weeks after the completion of therapy can be an alternative to HCVRNA testing to assess the SVR12 or the SVR24, respectively [38]. In patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of

decompensation and will reduce, albeit not abolish the risk of HCC. In these patients surveillance for HCC should be continued.

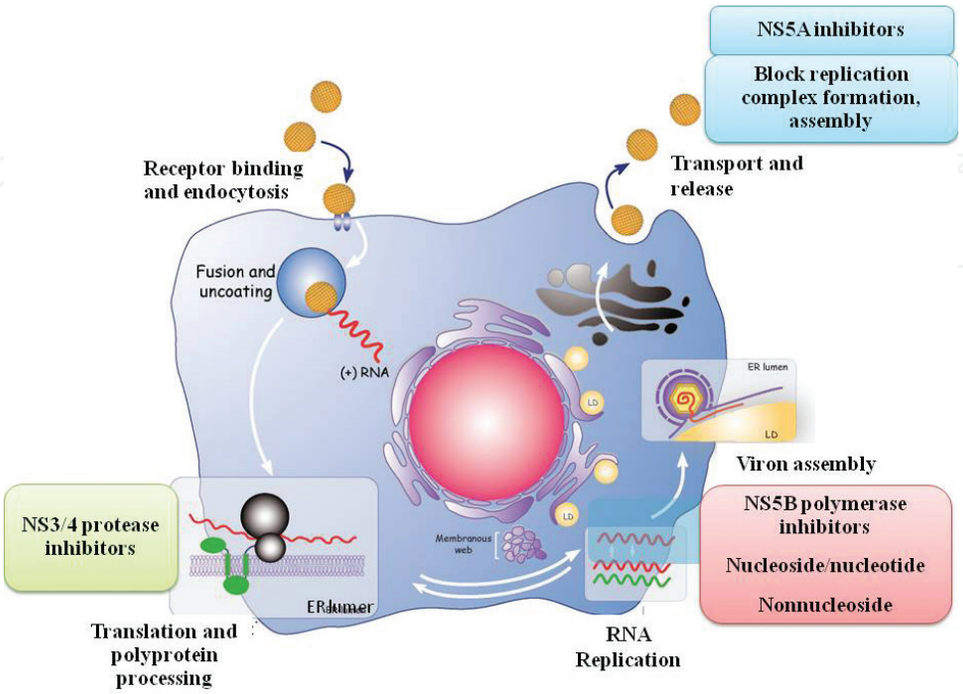


Figure 2. Hepatitis C life cycle and the targets of direct-acting antiviral agents.

4.2. Classes of DAAs

There are four classes of DAAs, which are defined by their mechanism of action and therapeutic target. DAAs include NS5B nucleotide inhibitors, NS5B nonnucleoside inhibitors, NS5A replication complex inhibitors, and NS3/4A protease inhibitors (PI) (**Figure 3**).

Characteristic	Protease Inhibitor*	Protease Inhibitor**	NS5A Inhibitor	Nuc Polymerase Inhibitor	Non-Nuc Polymerase Inhibitor
Resistance profile	🔴	🟡	🟡	🔵	🔴
Pangenotypic efficacy	🔴	🟡	🟡	🔵	🟡
Antiviral potency	🟡	🔵	🔵	🔵	🟡
Adverse events	🔴	🔵	🔵	🟡	🟡

🔵 Good profile 🟡 Average profile 🔴 Least favorable profile

*First generation. **Second generation.

Figure 3. Resistance patterns in different direct-acting antiviral agents (DAAs).

4.2.1. NS3/4A protease inhibitors (PIs)

PIs block the activity NS3/4A serine protease, an enzyme which inhibits TRIF-mediated Toll-like receptor signaling and Cardif-mediated retinoic acid–inducible gene 1 (RIG-1) signaling resulting in impaired induction of interferons and blocking viral elimination [39, 40]. PIs have been grouped according to their resistance profile into first- and second-generation agents and into separate waves according to dosing, safety, and tolerability characteristics.

4.2.1.1. First-generation PIs

Telaprevir and boceprevir were the first direct-acting antivirals for treatment of HCV and represented the first generation of PIs. Telaprevir or boceprevir was used in combination with peginterferon and ribavirin for the treatment of genotype 1 [40, 41]. Although telaprevir or boceprevir regimen enhanced SVR rates; the clinical efficacy of the triple regimen was limited by narrow genotype specificity, low barrier to resistance, and drug-drug interactions. This regimen also increased adverse events such as rash and moderate to severe anemia to an extent that might require the reduction of the RBV dose. Patient adherence and tolerability to triple therapy with BOC or TPV is a challenging issue as the two DAAs should be given three times daily with food. Triple therapy was not very effective in previous PEG-IFN/RBV dual therapy, no responders. From an economic perspective, the triple therapy dramatically increased the costs of HCV treatment which are originally prohibitive. Thus, the clinical importance of these agents diminished substantially with the discovery of subsequent-generation protease inhibitors.

4.2.1.2. Second-wave, first-generation protease inhibitors

The second wave of PIs for HCV includes agents such as simeprevir, asunaprevir, danoprevir, faldaprevir, and vaniprevir [42, 43]. Simeprevir (*Olysio*) is a NS3/4A HCV PI. Simeprevir is a macrocyclic compound that noncovalently binds to and inhibits the NS3/4A HCV protease, a protein that is responsible for cleaving and processing the HCV-encoded polyprotein, a critical step in HCV viral life cycle [42, 43]. Simeprevir shows enhanced binding affinity and specificity to NS3/4A when compared with the first-generation PIs, TPV, and BOC.

The safety and efficacy of SIM/PEG-IFN/RBV combination was investigated in treatment-naïve patients with HCV genotype 1 infection (PILLAR trial) [44]. Enrolled patients received different SIM doses administered once-daily (QD) with pegylated interferon (Peg-IFN)-α-2a and ribavirin (RBV). According to response-guided therapy (RGT) criteria, 79.2–86.1% of SMV-treated patients completed treatment by week 24; 85.2–95.6% of these subsequently achieved SVR. The safety profile of triple therapy with SIM was found to be comparable to that of PEG-IFN/RBV combination therapy [44]. In the QUEST 1 and QUEST 2 studies [45, 46], conducted on treatment-naïve genotype 1, patients were randomized to receive either triple therapy with simeprevir plus PEG-IFN and RBV using a response-guided therapy (RGT) approach or standard of care (48 weeks of PEG-IFN and RBV with placebo control). SVR12 rates were 81% in the simeprevir arm versus 50% in the control arm. The majority of

simeprevir-treated patients met the RGT and received 24 weeks of treatment and 86% of these patients achieved an SVR12.

Simeprevir also enhanced SVR in treatment-experienced patients. In the ASPIRE trial [47] treatment-experienced patients (with prior failure to PEG/RBV) were randomized to receive placebo plus PEG/RBV, or one of six regimens consisting of SMV plus PEG-IFN-α-2a plus ribavirin. In the SMV-treated patients, the SVR 24 rates ranged from 61 to 80% (according to the regimen used), which was significantly higher than the 23% SVR in patients treated with PEG-IFN/RBV. The safety profile observed among patients in the simeprevir arm was similar to the safety profile for patients in the placebo arm. These results were supported by those of another clinical trial conducted on treatment-experienced HCV genotype 1 patients with a history of viral relapse. The overall SVR12 in patients treated with SIM/PEG-IFN/RBV was of 79% compared to 36% for the peginterferon plus ribavirin arm. Patients with advanced fibrosis (F3-F4 by METAVIR) also had superior SVR12 rates with the addition of simeprevir (73% SVR12 compared with 24% in control arm) [48].

The efficacy of SIM/PEG-IFN/RBV in treatment-naïve and treatment-experienced patients with chronic HCV genotype 4 was evaluated in the RESTORE trial. Overall, 65.4% of the patients achieved an SRV12. The SVR12 rates varied with treatment group being 83% in treatment-naïve, 86% in treatment-experienced with prior relapse, 60% in prior partial responders, and 40% in prior null responders [49].

These trials showed that simeprevir-based/PEG-IFN/RBV triple therapy was effective, well-tolerated, and safe. However, the fast-paced HCV drug discovery paved the way to new interferon-free combinations which combine efficacy, safety, and convenience. Thus, SMV was included with other DAAs such as sofosbuvir to form one of the earliest interferon-free combinations (discussed later).

Danoprevir (DNV) is a highly selective and potent second-wave inhibitor of HCV NS3/4A protease. Coadministration of 100 mg of ritonavir with DNV has been shown to optimize the pharmacokinetics of DNV, allowing for lower dosing and better antiviral activity The DAUPHINE trial [50] evaluated three different dosages of DNV/r: 50, 100, and 200 mg danoprevir, boosted with 100 mg ritonavir, consumed twice a day for 24 weeks. A study arm also explored danoprevir/r 100/100 mg, in a response-guided therapy (RGT) algorithm, in which patients reaching an RVR received a total of 12 weeks of treatment. Overall, the better SVR rates were achieved in higher dosage arms compared to lower dosage arms. SVR rates decreased with decreasing dosage of danoprevir/r as follows: 89.1, 78.5, and 69.1% [50]. Faldaprevir was evaluated in IFN-free regimen in combination with deleobuvir, an NS5B no nucleoside polymerase inhibitor and ribavirin, in HCV-1b patients. The combination was highly efficacious, with 95% achieving SVR12 including patients with compensated cirrhosis [51].

Taken together, the second-wave, first-generation protease inhibitors offer several benefits over the first-generation PIs, TVR, and BOC in terms of less side effect profile and more convenient dosing. However, these preparations still have low genetic barrier to resistance particularly for HCV-1a.

4.2.1.3. Second-generation protease inhibitors

Recent second-generation PIs such as the macrocyclic compound grazoprevir offer several benefits over earlier protease inhibitors, including fewer drug-drug interactions, improved dosing schedules, and less frequent and less severe side effects. Grazoprevir is distinct from earlier-generation protease inhibitors in potency against a broader array of HCV genotypes, as well as its activity against some of the major resistance-associated variants (R155K and D168Y) resulting from failure with first-generation protease inhibitors. Grazoprevir is available in combination with the NS5A inhibitor elbasvir. Elbasvir/grazoprevir (Zepatier) [52] is available as fixed dose tablets (50/100 mg) are prescribed as one tablet orally once daily, with or without food. The treatment duration and whether to take with or without ribavirin are dependent on genotypes and other patient variables [53].

The C-EDGE treatment-naïve trial assessed the safety and efficacy of the fixed-dose combination of elbasvir-grazoprevir (50/100 mg) in patients with genotype 1, 4, or 6 hepatitis C infection, with or without compensated cirrhosis. The overall SVR12 rate was 95%, with rates of 92% for genotype 1a, 99% for genotype 1b, 100% for genotype 4, and 80% for genotype 6. No statistically significant difference in SVR12 was found between cirrhotic and noncirrhotic patients [54]. The C-EDGE CO-STAR trial enrolled treatment-naïve patients who inject drugs and were infected with chronic HCV genotype 1, 4, or 6. In this difficult to treat cohort, the SVR12 were 95% [55].

Treatment-naïve patients with compensated cirrhosis and treatment-experienced patients with a prior null response to PEG plus RBV were randomized to receive elbasvir plus grazoprevir, with or without ribavirin, for 12 or 18 weeks. The SVR12 rates ranged between 90 and 97% in cirrhotics and 94% in null responder cirrhotic patients. The SVR12 was 100% for genotype 1b. No additional benefit was achieved by adding ribavirin to elbasvir plus grazoprevir in a subset of patients [56]. Treatment-experienced patients with genotype 1 HCV with previous failure of peg interferon/ribavirin (PR) and an earlier-generation protease inhibitor (BOC, TPV, or SIM) achieved SVR 24 of 96% when treated with elbasvir plus grazoprevir and RBV [57].

In the C-EDGE coinfection trial, patients with chronic hepatitis C genotype 1, 4, or 6 and HIV coinfection received elbasvir-grazoprevir once daily for 12 weeks. Patients were on antiretroviral therapy with HIV viral suppression and the median CD4 cell count was 568 cells/mm^3. The overall SVR12 rate was 96, with the breakdown by genotype SVR12 rates were 96.5, 95.5, and 96.4% for genotypes 1a, 1b, and 4, respectively. All cirrhotic patients achieved an SVR12 [58].

Thus, zepatier is active against a broad array of HCV genotypes including genotypes 1, 4, 6, as well as some of the major resistance-associated variants (R155K and D168Y) resulting from failure with first-generation protease inhibitors. Elbasvir/grazoprevir is generally well tolerated; however, the adverse effects reported include headache, nausea, fatigue, decreased appetite, anemia, pyrexia, and elevations of ALT.

4.2.2. NS5B nucleoside polymerase inhibitors (NPIs)

NS5B is an RNA-dependent RNA polymerase (RdRp) involved in posttranslational processing which is vital for HCV replication. NPIs are analogs of natural substrates that bind the

active site of NS5B and terminate viral RNA chain generation. Given that the structure of NS5B is highly conserved across all HCV genotypes, NPIs are effective against all genotypes. NPIs show high antiviral activities in all genotypes and provide a high genetic barrier to resistance. Thus, NPIs are included in several efficacious all-oral combination therapies. Polymerase inhibitors are categorized according to their mode of action and specificity into NPIs and NNPIs. These two classes generally differ in specificity. Nucleoside inhibitors (NIs) bind to the catalytic site of the RNA polymerase causing chain termination. Nonnucleoside inhibitors bind to a less conserved site resulting in a conformational change that distorts the positioning of residues binding RNA resulting in inhibition of polymerization [59, 60].

4.2.2.1. Sofosbuvir (sovaldi)

Sofosbuvir is a nucleoside analog inhibitor of hepatitis C virus NS5B polymerase. The triphosphate form of sofosbuvir mimics the natural cellular uridine nucleotide and is incorporated by the HCV RNA polymerase into the elongating RNA primer strand, resulting in viral chain termination. Sofosbuvir is a prodrug which is rapidly converted after oral intake to GS-331007 which is taken up by hepatocytes. The cellular kinases convert GS-331007 to its pharmacologically active uridine analog 5′-triphosphate form (GS-461203) that is incorporated by the HCV RNA polymerase into the elongating RNA primer strand, resulting in chain termination. Sofosbuvir is a potent pangenotypic NS5B polymerase inhibitor with a high barrier to resistance. It is available as 400 mg tablets administered once a day with or without food. The discovery of sofosbuvir has been a breakthrough in HCV treatment. Currently, SOF represents the backbone of several interferon-free regimens for the treatment of chronic hepatitis caused by various HCV genotypes. Excretion of sofosbuvir is through the kidney (80%) [58, 59, 61].

4.2.3. Efficacy of sofosbuvir plus peginterferon and ribavirin

The ATOMIC and ELECTRON (Arms 1-8 studies) [62, 63] established the effectiveness of a 12-week course of sofosbuvir plus peginterferon and ribavirin in treatment-naïve patients with HCVgenotype-1 with SVR rates ranging between 87 and 100%. In genotypes 3, the SVR 12 rates were 71% with the 16-week SOF plus RBV regimen, 84% with 24 weeks of SOV plus RBV, and 93% with 12 weeks of SOF plus RBV plus PEG-IFN. For the patients with genotype 2 infections, the SVR 12 rates were 87% with the 16-week SOF plus RBV regimen, 100% with 24 weeks of SOF plus RBV, and 94% with 12 weeks of SOF plus RBV plus PEG-IFN [64].

4.2.4. Efficacy of interferon-free sofosbuvir regimen

4.2.4.1. Sofosbuvir (SOF) and simeprevir (SIM) combination (Olysio)

This combination is the earliest interferon-free regimen that reached optimal results in terms of SVR. Trials showed efficacy and safety of this drug combination in treatment-naïve and treatment-experienced patients across several genotypes. The OPTIMIST-1 trial evaluated the efficacy of sofosbuvir plus simeprevir for 8 or 12 weeks in treatment naive or experienced patients with chronic HCV genotype 1 infection without cirrhosis. The sustained response rates were 97% in patients treated for 12 weeks and the SVR was 83% in patients treated for 8

weeks. These findings were further confirmed in the OPTIMIST-2 trial which demonstrated that 12-week regimen of SOF plus SIM is effective in treatment-naïve and treatment-experienced patients with cirrhosis and HCV genotype 1 infection, with the exception that patients with genotype 1a and the baseline Q80K mutation have SVR rates of only 74% [66].

A large cohort prospective study in genotype 1 patients treated with SOF plus SIM for 12–16 weeks showed that the overall SVR rate was 84%. Model-adjusted estimates demonstrated that patients with cirrhosis, prior decompensation, and previous protease inhibitor treatments were less likely to achieve an SVR. Addition of ribavirin enhances SVR rates in such patients [67].

Taken together, several clinical trials demonstrate that all-oral 12-week regimen of simeprevir plus sofosbuvir is effective and well tolerated in treatment-naïve and treatment-experienced HCV genotype 1 patients without and with cirrhosis. Ribavirin may be needed in patients with decompensation, and previous protease inhibitor treatment failure. The frequent adverse events include fatigue, headache, nausea, rashes, and insomnia. Serious adverse events and treatment discontinuation occur in only 3% of patients.

4.2.4.2. Sofosbuvir with the NS5A inhibitor ledipasvir (Harvoni)

- Treatment-naïve and treatment-experienced genotype 1 patients

Gane et al. [68] evaluated an all-oral regimen comprising sofosbuvir with ledipasvir or the NS5B nonnucleoside inhibitor GS-9669 in patients with genotype 1 HCV infection. Sofosbuvir (400 mg once daily) and ledipasvir (90 mg once daily) plus ribavirin were given for 12 weeks to treatment-naïve patients and prior null responders. Sofosbuvir and GS-9669 (500 mg once daily) plus ribavirin were given for 12 weeks to treatment-naïve patients and prior null responders. Additionally, prior null responders with cirrhosis were randomly assigned to groups given a fixed-dose combination of sofosbuvir and ledipasvir, with ribavirin or without ribavirin and a group of treatment-naïve patients received sofosbuvir, ledipasvir, and ribavirin for 6 weeks. SVR12 was 100, 92, and 68% in treatment-naïve patients receiving sofosbuvir, those receiving SOV, ledipasvir, ribavirin, GS-9669, and ribavirin and patients receiving 6 weeks of sofosbuvir, ledipasvir, and ribavirin, respectively. All noncirrhotic prior null responders receiving 12 weeks of sofosbuvir along with another DAA plus RBV achieved SVR12 of 100%.

In the NIAID SYNERGY (genotype 1 study) [69], treatment-naïve patients with genotype 1 chronic HCV were randomized to receive either ledipasvir-sofosbuvir for 12 weeks; or ledipasvir-sofosbuvir (90-400 mg) plus the nonnucleoside NS5B inhibitor GS-9669 (500 mg once daily) for 6 weeks, or ledipasvir-sofosbuvir (90-400 mg) plus the NS3/4A protease inhibitor GS-9451 (80 mg once daily) for 6 weeks. Patients in the 12-week ledipasvir-sofosbuvir arm with any stage of fibrosis could be enrolled in the study. The SVR12 rates were 100, 95, and 95% in the ledipasvir-sofosbuvir arm, the ledipasvir-sofosbuvir plus GS-9669 group, and the ledipasvir-sofosbuvir plus GS-9451 group, respectively.

A trial [70] evaluated 8- and 12-week courses of the fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg), with or without ribavirin in treatment-naïve and treatment-experienced patients with chronic HCV genotype 1 infection. In all of the five study arms,

SVR12 was achieved in 95–100% of patients. The regimen of ledipasvir-sofosbuvir was well tolerated; only one patient had a serious adverse event of anemia, thought to be related to ribavirin. A recent large study that enrolled 4365 genotype 1, treatment-naïve, HCV-infected patients treated with LDV/SOF±RBV demonstrated SVR rates of 91.3 and 92.0% (3191/3495) for LDV/SOF and LDV/SOF+RBV, respectively [71].

Thus, the combination of ledipasvir-sofosbuvir with or without ribavirin is highly effective in treatment-naïve and treatment-experienced patients with chronic HCV genotype 1.

- Sofosbuvir- ledipasvir in HCV nongenotype 1 patients

Patients with genotype 3 and 6 achieved good SVR rates when treated with ledipasvir-sofosbuvir. The SVR 12 responses in treatment-naïve patients with genotype 3 were superior in the regimen with ribavirin (100%) than without ribavirin (64%). Among the treatment-experienced patients, 82% of treated ledipasvir-sofosbuvir plus ribavirin achieved an SVR 12 and the SVR 12 rate was 96% in the patients with genotype 6 [72].

The NIAID SYNERGY (Genotype 4) trial enrolled treatment-naïve and treatment-experienced patients with genotype 4 chronic HCV to receive ledipasvir-sofosbuvir for 12 weeks. Patients with compensated cirrhosis were allowed to enroll in the study. Overall, in the intent-to-treat SVR was 95% [73]. A recent study that enrolled treatment-naïve and -experienced patients with chronic HCV genotype 4 revealed SVR12 of 78% in patients treated with ledipasvir-sofosbuvir for 12 weeks and SVR 12 in patients treated with 24 weeks [74]. These findings suggest that further studies are still needed to optimize ledipasvir-sofosbuvir therapy in patients with different stages of chronic HCV genotype 4. To date, the efficacy and duration of DAAs in HCV genotype 4 have not been adequately studied and further trials are required to optimize therapy in this genotype.

A clinical trial assessed response to ledipasvir-sofosbuvir in 41 patients with chronic HCV genotype 5 (21 treatment-naïve and 20 treatment-experienced). The overall SVR12 was 95% in treatment-naïve and treatment-experienced patients, while the SVR12 was 97% in patients without cirrhosis and 89% in patients with cirrhosis [75].

- HCV and HIV coinfected patients

The ERADICATE trial investigated the safety and efficacy of a 12-week regimen of ledipasvir-sofosbuvir in HCV treatment-naïve patients with genotype 1 chronic hepatitis C who are coinfected with HIV. Patients on antiretroviral therapy were allowed to receive tenofovir-emtricitabine plus either efavirenz, raltegravir, rilpivirine, rilpivirine plus raltegravir, or efavirenz plus raltegravir. In patients taking antiretroviral therapy, SVR12 was 97% [76]. The SVR12 was 96.4% in German HIV-HCV coinfected patients [77]. A study investigated the efficacy and safety of ledipasvir/sofosbuvir plus ribavirin for 24 weeks in HCV/HIV-coinfected patients who relapsed after receiving 12 weeks of ledipasvir/sofosbuvir therapy. The SVR12 was 89% suggesting that ledipasvir/sofosbuvir can be an effective salvage therapy for patients for whom direct-acting antiviral treatment has failed [78].

Thus, ledipasvir-sofosbuvir is well tolerated and effective in patients with genotype 1 HCV and HIV coinfection. However, more studies are required to investigate the efficacy and safety of ledipasvir/sofosbuvir in treatment of HIV patients infected with various HCV genotypes.

Importantly the drug-drug interactions between ledipasvir/sofosbuvir and antiretroviral therapy need extensive investigations on large cohorts.

-Retreatment of sofosbuvir failures

In the NIAID retreatment of sofosbuvir failures trial [79], patients with genotype 1 HCV who previously had failed a 24-week course of sofosbuvir plus ribavirin achieved SVR12 ranged between 98 and 100% when retreated with fixed-dose combination of ledipasvir-sofosbuvir for 12 weeks. Despite the small sample size in this study, the trial showed that 12-week regimen of ledipasvir-sofosbuvir without or with ribavirin was well tolerated and shows promise as a treatment option for patients with prior sofosbuvir failure.

4.2.4.3. Sofosbuvir/velpatasvir (Epclusa)

Sofosbuvir-velpatasvir (sofosbuvir 400 mg plus velpatasvir 100 mg) is an oral fixed-dose combination of sofosbuvir, and the novel NS5A replication complex inhibitor, velapatasvir. Velpatasvir (formerly GS-5816) has potent *in vitro* anti-HCV activity across all genotypes at the picomolar level. The combination of sofosbuvir-velpatasvir is the first once-daily single-tablet regimen with pangenotypic activity. Sofosbuvir-velpatasvir is indicated for patients with chronic HCV genotype 1 through 6 [80]. A clinical trial [81] assessed the efficacy and safety of the combination of the nucleotide polymerase inhibitor sofosbuvir, the NS5A inhibitor velpatasvir, and the NS3/4A protease inhibitor GS-9857 in patients with hepatitis C virus (HCV) genotype 1 infection. Among treatment-naïve patients without cirrhosis, the SVR rates were 71 and 100% after 6 and 8 weeks of treatment, respectively. Among treatment-naïve patients with cirrhosis, 94% achieved SVR12 after 8 weeks therapy and 81% after 8 weeks of treatment with ribavirin. The SVR12 rates were 100% in DAA-experienced patients without cirrhosis and with cirrhosis, respectively.

Sofosbuvir-velpatasvir showed high efficacy in non-1 genotypes. ASTRAL-2 study demonstrated that the SVR12 was 99% treatment-naïve and treatment-experienced patients infected with HCV genotype 2 [82]. Among HCV with chronic HCV genotype 3 treated with sofosbuvir-velpatasvir, the ASTRAL-3 trial showed that the SVR12 rate were 93% for treatment-naïve and 89% for treatment-experienced patients [83]. SVR12 was 100% in patients with chronic HCV genotype 4 [84]. The ASTRAL-4 studies [82] demonstrated that sofosbuvir/velpatasvir plus ribavirin were effective in achieving a high SVR12 rate in patients with decompensated cirrhosis [85].

The ASTRAL-5 study investigated the safety and efficacy of 12 weeks sofosbuvir-velpatasvir in patients with HIV and HCV coinfection. Enrolled patients were infected with genotype 1, 2, 3, 4, or 6 HCV infection; 18% had compensated cirrhosis and 29% were treatment-experienced. The mean CD4 count was 583 cells/mm^3 and all patients had HIV viral suppression. The antiretroviral regimens included tenofovir disoproxil fumarate (DF). The overall SVR12 rate was 95%. The presence of cirrhosis or treatment experience did not negatively influence treatment response [86].

4.2.5. Nonstructural protein 5A (NS5A) inhibitors

The NS5A protein is essential for replication and assembly of HCV. Inhibitors of NS5A block viral production at an early stage of assembly, so that no viral RNA or nucleocapsid protein is released [87]. Therefore, agents that block NS5B activity (polymerase inhibitors) inhibit the

virus's RdRp [87]. Nucleoside inhibitors (NIs) bind to RdRp's active site, whereas the non-nucleoside inhibitors (NNIs) bind to the enzyme outside the active site, inducing conformational changes that downregulated RdRp's activity. As a result of mechanistic and potency differences, the NIs tend to have broad potency against multiple HCV genotypes and are less likely to select for resistant strains than are the NNIs [88]. Cyclophilin is a host protein that interacts with NS5B and appears to promote the HCV protein's ability to bind.

4.2.5.1. Daclatasvir (Daklinza)

Daclatasvir HCV is first-in-class inhibitor of the nonstructural viral protein 5A (NS5A), a phosphoprotein that plays an important role in hepatitis C replication. The exact mechanism by which daclatasvir inhibits the NS5A replication complex is unclear, but it is believed that daclatasvir inhibits viral RNA replication and virion assembly. It may also inhibit phosphorylation of the NS4A, and therefore the formation and activation of the HCV replication complex. Based on *in vitro* data, daclatasvir has shown activity against HCV genotypes 1 through 6, with EC50 values ranging from picomolar to low nanomolar against wild-type HCV [89].

When used in combination with sofosbuvir, with or without ribavirin, daclatasvir showed high efficacy in pangenotypic all-oral regimen. According to the results of the AI444040 and ALLY-3 trials [90, 91], a 12-week regimen of daclatasvir plus sofosbuvir in patients with chronic HCV genotype 1 or 3 infection without cirrhosis resulted in high SVR12 rates, regardless of prior treatment experience. The ALLY-3 [91] trial demonstrated high SVR12 rates with a 12- or 16-week regimen of daclatasvir plus sofosbuvir and ribavirin in patients with chronic HCV genotype 3 infections and advanced fibrosis or compensated cirrhosis. A daclatasvir plus sofosbuvir-based regimen demonstrated efficacy in patients with chronic HCV genotype 1, 3, or 4 infection and advanced cirrhosis or posttransplant recurrence in the ALLY-1 trial [92], and in patients coinfected with HCV genotype 1, 3, or 4 and HIV-1 in the ALLY-2 trial [93].

Daclatasvir plus sofosbuvir with or without ribavirin was generally well tolerated. Fatigue, headache, nausea, and diarrhea were the adverse events reported in some patients treated with daclatasvir [91–93]. Daclatasvir and sofosbuvir combination can potentially cause serious bradycardia when coadministered with amiodarone. Given that daclatasvir is a substrate of CYP3A, it is contraindicated for use with drugs that are strong inducers of CYP3A, including phenytoin, carbamazepine, and rifampin [94].

Data from clinical trials showed resistance-associated substitutions in the *NS5A* gene [95]. Thus, the AASLD/IDSA HCV Guidance Panel recommends testing for these substitutions when NS5A inhibitors fail [96]. Baseline NS5A polymorphisms may also impact the emergence of NS5A resistance [96].

Taken together, daclatasvir plus sofosbuvir with or without ribavirin is an important option for use in treatment-naïve or treatment-experienced patients with chronic HCV genotype 1, 3, or 4 infections, including patients with advanced liver disease, posttransplant recurrence, and HIV-1 coinfection. Daclatasvir with sofosbuvir is a particularly useful ribavirin-free oral option for genotype 3 patients. Testing for the presence of NS5A polymorphisms is recommended at baseline for patients with HCV genotype 1a prior to initiation of treatment with in patients with genotype 1a and cirrhosis prior to sofosbuvir plus daclatasvir treatment.

4.2.5.2. Liedipasvir

Ledipasvir is a potent inhibitor of HCV NS5A, a viral phosphoprotein that plays a critical role in viral replication, assembly, and secretion [97]. The results of clinical trials assessing ledipasvir combinations with SOF have been discussed previously.

Coadministration of amiodarone and ledipasvir-sofosbuvir is not recommended given that severe cases of symptomatic bradycardia have been reported. Ledipasvir-sofosbuvir has significant drug-drug interactions with P-gp inducers such as rifampin that may cause a significant reduction in levels of ledipasvir and sofosbuvir and reduced efficacy of ledipasvir-sofosbuvir [97].

4.2.6. Ombitasvir-paitaprevir-ritonavir-dasabuvir (Viekira Pak)

The four medications: ombitasvir, paritaprevir, ritonavir, and dasabuvir are combined as a fixed-dose tablet and the dasabuvir is a separate tablet. Ombitasvir is an NS5A inhibitor with potent pangenotypic picomolar antiviral activity, paritaprevir is an inhibitor of the NS3/4A serine protease, and dasabuvir is a nonnucleoside NS5B polymerase inhibitor. Ritonavir is a potent inhibitor of CYP3A4 enzymes and is used as a pharmacologic booster for paritaprevir—it significantly increases peak and trough paritaprevir plasma concentrations, as well as the area under the curve of paritaprevir [98].

PEARL III trial demonstrated the SVR12 rate of 99.5% in treatment-naïve patients with chronic HCV genotype 1b treated with ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin group and 99% in patients who received ombitasvir-paritaprevir-ritonavir and dasabuvir without ribavirin [99]. The TURQUOISE trial assessed the efficacy and safety of ombitasvir, paritaprevir, ritonavir, and dasabuvir plus RBV in HCV/HIV-1 coinfected patients for 12 or 24 weeks. The study enrolled HCV treatment-naïve or PEG-IFN/RBV-experienced patients, with or without Child-Pugh A cirrhosis. Patients with CD4+ count ≥200 cells/mm3 or CD4+ % ≥14%, and plasma HIV-1 RNA suppressed on a stable atazanavir- or raltegravir-inclusive antiretroviral (ART) regimen were included. Among patients treated with 3D+RBV for 12 weeks, 93.5% achieved SVR12. Among patients receiving 24 weeks of treatment, 96.9% achieved EOTR; the most common AEs were fatigue, insomnia, and nausea. Elevation in total bilirubin was the most common laboratory abnormality, occurring predominantly in patients receiving atazanavir.

This combination was effective liver transplant recipients who have recurrent hepatitis C genotype 1 infection [101]. In patients with stage 4 or 5 renal disease and patients on dialysis treated with ombitasvir-paritaprevir-ritonavir and dasabuvir., EOT response was 100% and SVR12 response was achieved in 85% of patients with genotype 1b [102].

5. Treatment of different HCV genotypes

According to the 2016 HCV treatment guidelines of the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) [96] and European Association of Study of Liver Diseases (EASL) [99], chronic HCV due to any genotype can be efficiently treated using all-oral DAA interferon-free regimens.

5.1. HCV genotype 1 (Figure 4)

Optimizing the regimen of therapy for chronic HCV genotype 1 depends on several factors such as whether the patient is treatment naïve or experienced and the previous therapies provided and the status of resistance in some cases. Given the high cost of IFN-free regimen and difficulties in access to this therapy in various countries, it is necessary to tailor therapy according to the patient population treated and the available therapies.

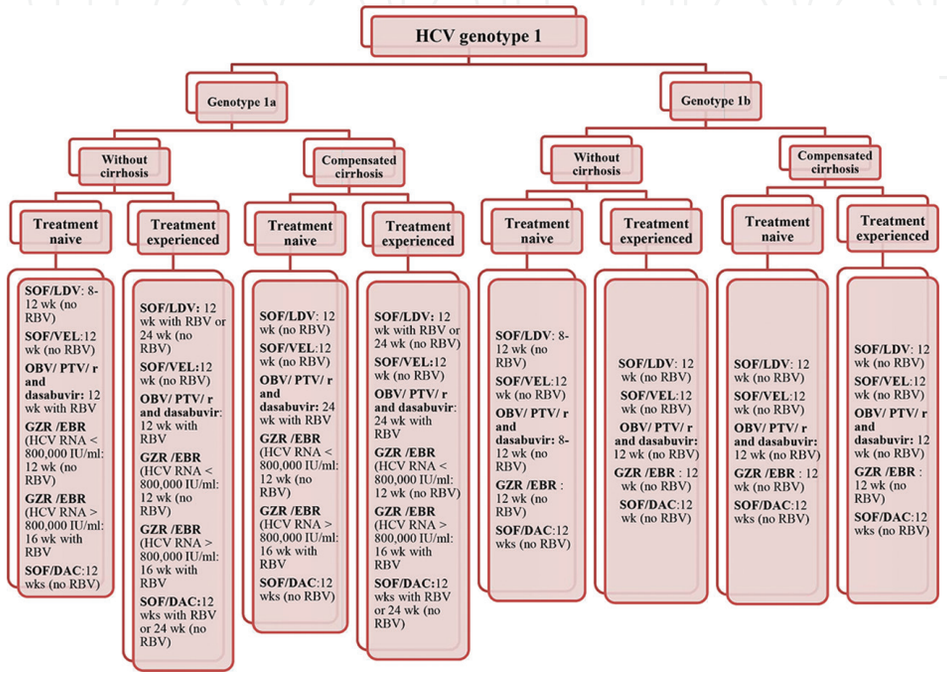


Figure 4. Treatment of HCV genotype 1.

5.2. Ledipasvir-sofosbuvir combination

- Treatment-naïve patients with or without compensated cirrhosis patients are treated with a fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks.
- Therapy may be shortened to 8 weeks in patients with a viral load <6 million IU/ml.
- Treatment-experienced, DAA-naïve patients infected with genotype 1b with or without compensated cirrhosis are treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin.
- Treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis are treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or =75 kg, respectively).
- If there is a contraindication to ribavirin, the treatment-experienced, DAA-naïve patients are treated with Harvoni for 24 weeks.

- Treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis who have NS5A RASs and resistance to ledipasvir (M28A/G/T, Q30E/G/H/K/R, L31M/V, P32L/S, H58D, and/or Y93C/H/N/S) are treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks with ribavirin.

5.3. Sofosbuvir-velpatasvir

- Genotype 1a, regardless of the presence of cirrhosis: sofosbuvir-velpatasvir is prescribed for 12 weeks without ribavirin in treatment naïve or treatment experienced.
- Genotype 1b, regardless of the presence of cirrhosis: sofosbuvir-velpatasvir is prescribed for 12 weeks without ribavirin in treatment naïve or treatment experienced.

5.4. Elbasvir-grazoprevir

Elbasvir-grazoprevir (50 mg/100 mg) therapy in chronic hepatitis C genotypes 1 is tailored according prior treatment experience and the presence of baseline polymorphisms at amino acid positions 28, 30, 31, or 93.

- Genotype 1a, treatment-naïve or peginterferon/ribavirin-experienced with no baseline NS5A polymorphisms: elbasvir-grazoprevir is given for 12 weeks.
- Genotype 1a, treatment-naïve or peginterferon/ribavirin-experienced with baseline NS5A polymorphisms: elbasvir-grazoprevir plus ribavirin is prescribed for 16 weeks.
- Genotype 1b, treatment-naïve or peginterferon/ribavirin-experienced: elbasvir-grazoprevir is given for 12 weeks.
- Genotype 1a or 1b, peginterferon/ribavirin/protease inhibitor-experienced: elbasvir-grazoprevir plus ribavirin is given for 12 weeks.

5.4.1. Sofosbuvir and daclatasvir

In genotype 1 infections, sofosbuvir and daclatasvir are used with or without ribavirin depending on the patient population

- Genotype 1, without cirrhosis: daclatasvir plus sofosbuvir are prescribed for 12 weeks.
- Genotype 1 with compensated cirrhosis: daclatasvir plus sofosbuvir are given for 12 weeks.
- Genotype 1 with decompensated (Child-Pugh B or C) cirrhosis: daclatasvir plus sofosbuvir plus ribavirin are given for 12 weeks.

5.4.2. Ombitasvir-paritaprevir-ritonavir-dasabuvir

In regions where this combination is available, the therapeutic strategy is recommended as follows:

- Genotype 1a, without cirrhosis: ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin are prescribed for 12 weeks.

- Genotype 1a, with cirrhosis: ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin are prescribed for 24 weeks.
- Genotype 1b, without cirrhosis: ombitasvir-paritaprevir-ritonavir and dasabuvir are prescribed for 12 weeks.
- Genotype 1b, with cirrhosis: ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin are prescribed for 12 weeks

Thus, Viekira Pak prescribed with ribavirin except in patients without cirrhosis

*Genotype 2 (***Figure 5***)*

Chronic HCV genotype 2 treatment-naïve or treatment-experienced patients are treated with either with aofosbuvir/velpatasvir for 12 weeks without ribavirin or sofosbuvir and daclatasvir without ribavirin.

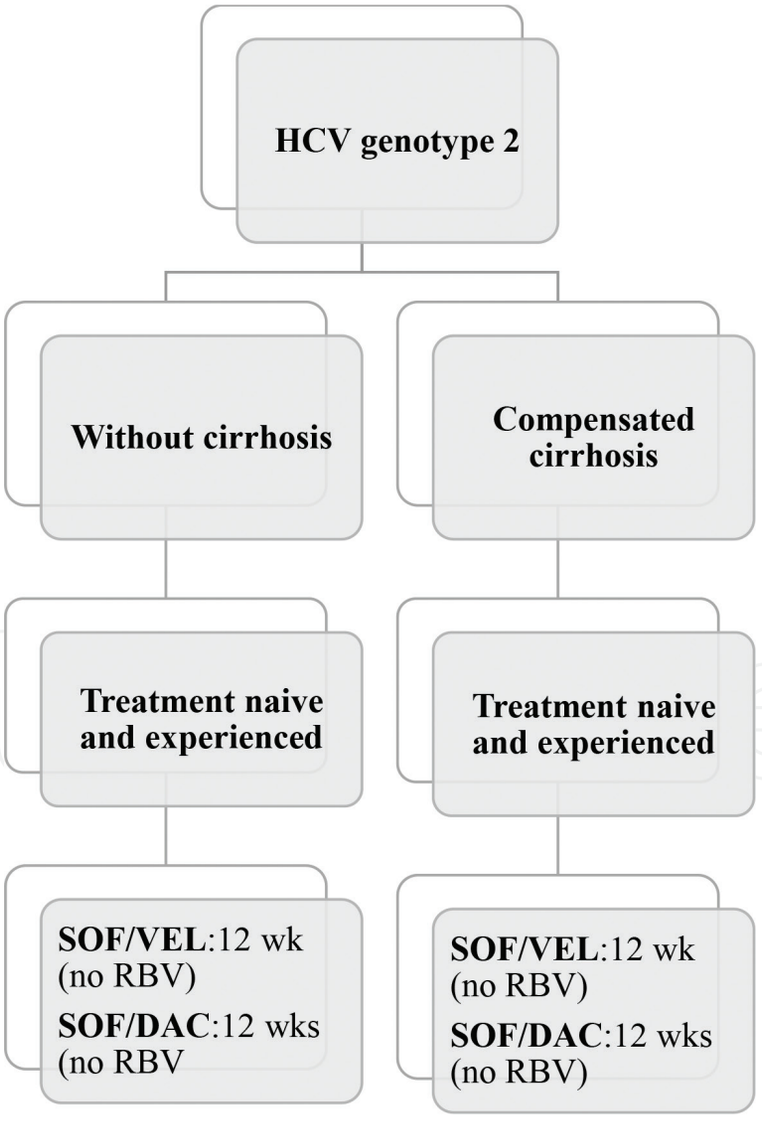


Figure 5. Treatment of HCV genotype 2.

HCV genotype 3 (**Figure 6**)

Chronic HCV genotype 2 treatment-naïve patients are treated with either sofosbuvir/velpatasvir for 12 weeks without ribavirin or sofosbuvir and daclatasvir without ribavirin. Ribavirin is added for the therapy of treatment-experienced patients.

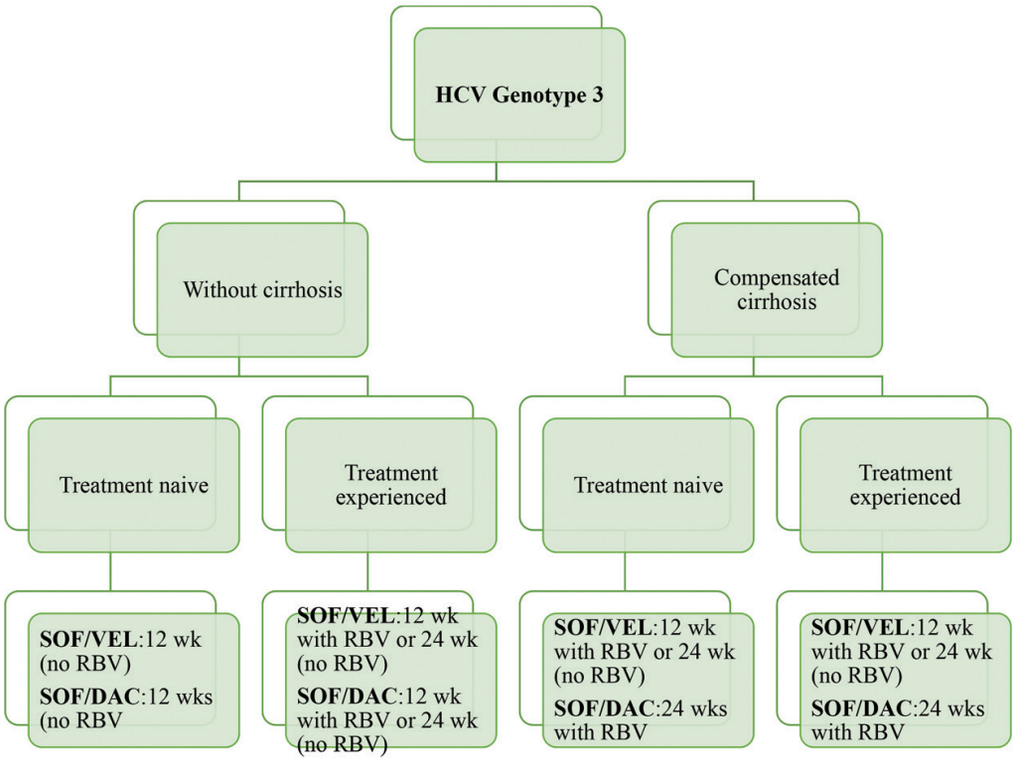


Figure 6. Treatment of HCV genotype 3.

HCV genotype 4 (**Figure 7**)

Treatment-naïve patients with chronic hepatitis C genotype 4 can be treated by one of the following regimen according to availability:

- Sofosbuvir (400 mg)/ledipasvir (90 mg) for 12 weeks without ribavirin is prescribed for treatment-naïve patients with or without compensated cirrhosis. In treatment-experienced patients, ribavirin is added as a daily weight-based dose (1000 or 1200 mg in patients <75 kg or =75 kg, respectively). Sofosbuvir and ledipasvir for 24 weeks is recommended for treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin.

- Sofosbuvir/velpatasvir combination for 12 weeks without ribavirin is given to treatment-naïve and treatment-experienced chronic HCV genotype 4 patients with or without compensated cirrhosis.

- Ombitasvir (12.5 mg), paritaprevir (75 mg), and ritonavir (50 mg) is given as two tablets once daily without dasabuvir to patients infected with HCV genotype 4 with and without compensated cirrhosis.

- Grazoprevir (100 mg) and elbasvir (50 mg) without ribavirin is prescribed as one tablet daily to treatment-naïve patients infected with genotype 4 with or without compensated cirrhosis. In treatment-experienced patients infected with genotype 4 with or without compensated cirrhosis with an HCV RNA level at baseline >800,000 IU/ml are treated with grazoprevir and elbasvir for 16 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or =75 kg, respectively).
- Sofosbuvir (400 mg) and daclatasvir (60 mg) is given to treatment-naïve patients with or without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin. Ribavirin (1000 or 1200 mg in patients <75 kg or =75 kg) is added for treatment-experienced patients with or without compensated cirrhosis.

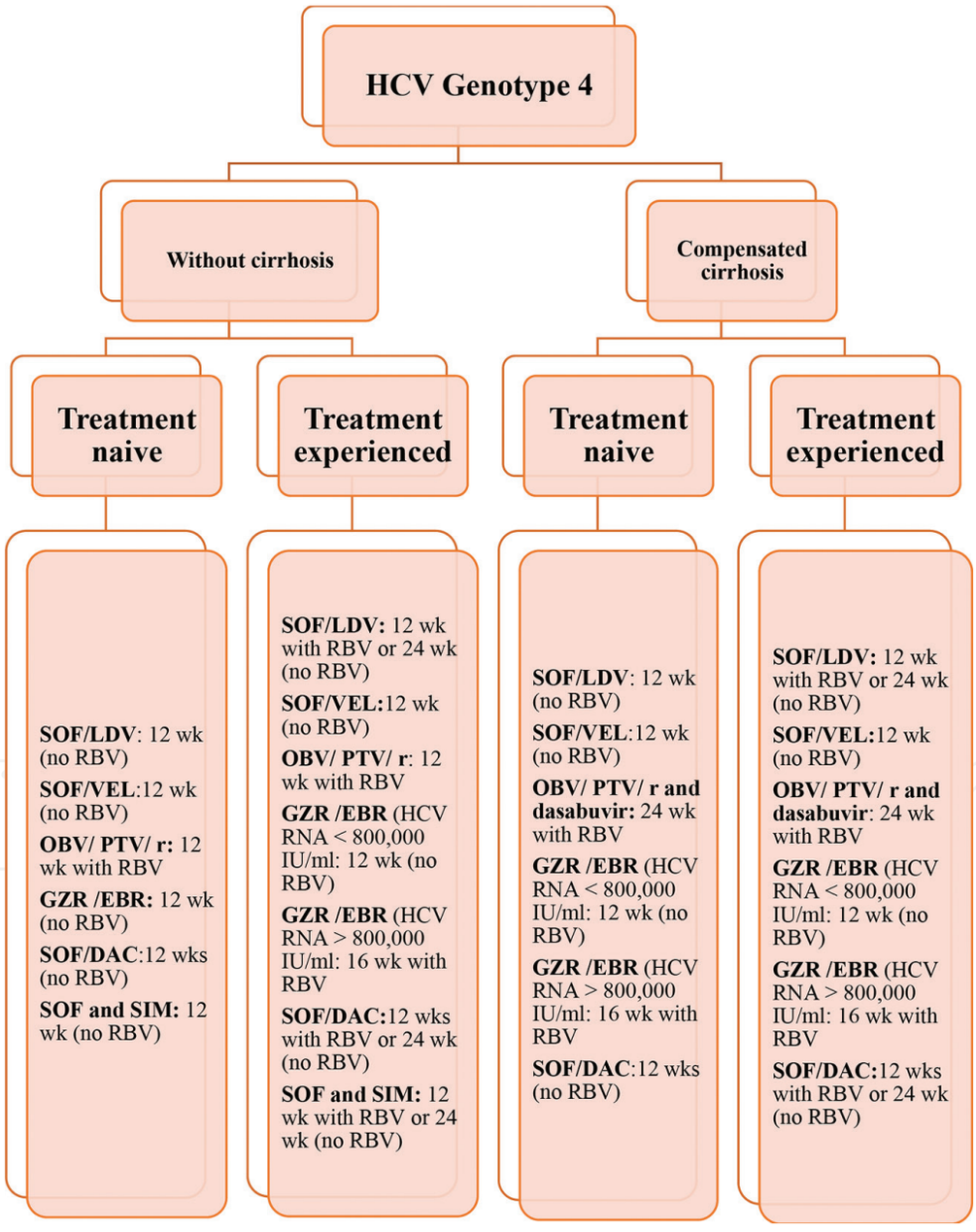


Figure 7. Treatment of HCV genotype 4.

HCV genotype 5 or 6 (**Figure 8**)

Treatment-naïve patients with or without compensated cirrhosis patients with chronic HCV genotype 5 or 6 are treated with sofosbuvir and ledipasvir for 12 weeks without ribavirin. Treatment-experienced patients with or without compensated cirrhosis are treated with the combination of sofosbuvir and ledipasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or =75 kg, respectively. Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis are treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, and ribavirin is added in patients with treatment-experienced patients.

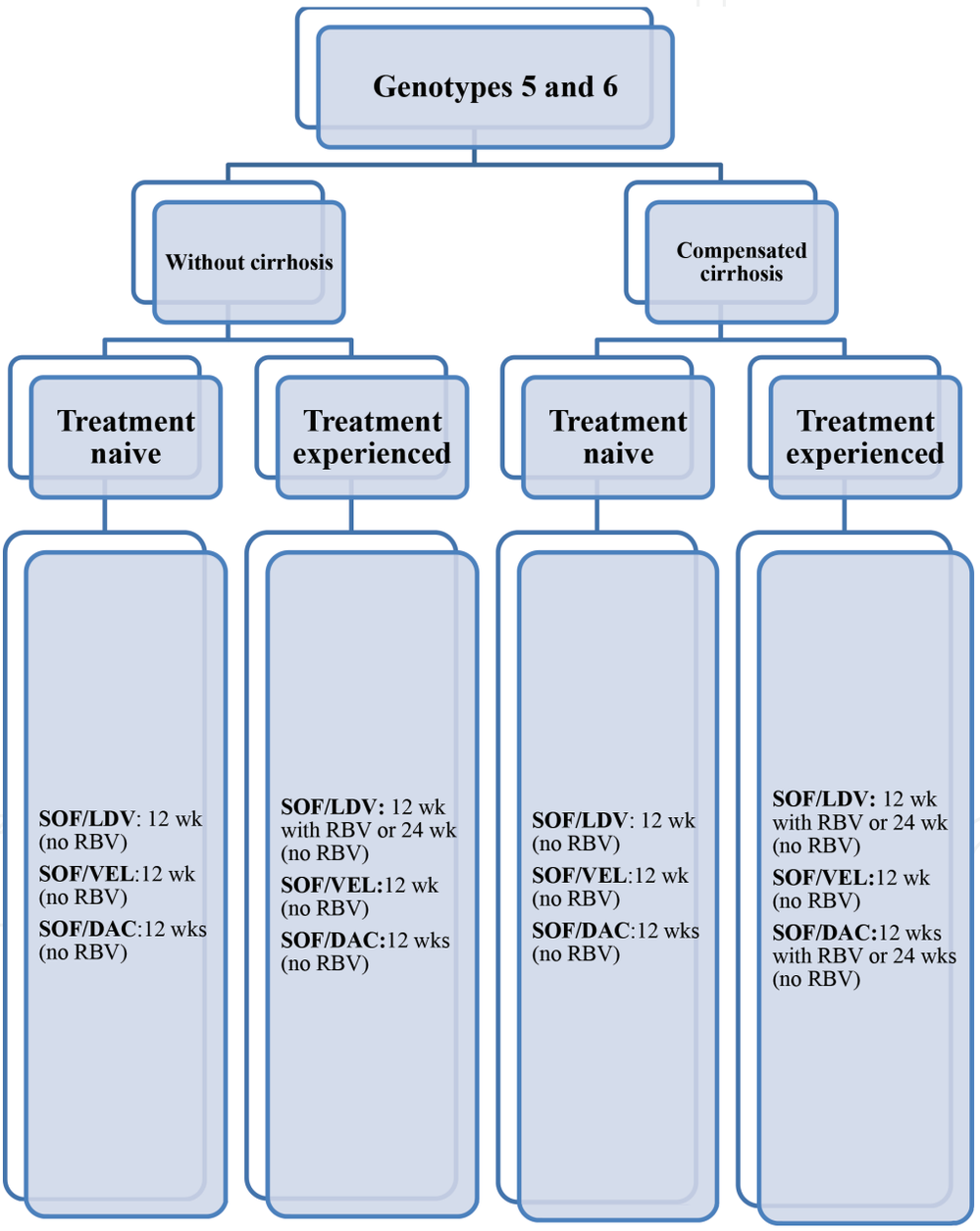


Figure 8. Treatment of HCV genotype 5, 6. *Note*: Ledipasvir: LDV; Sofosbuvir: SOF; Ribavirin: RBV; Simeprevir: SIM, Velpatasvir: VEL; Elbasvir: EBR; Grazoprevir: GZR; Daclatasvir: DAC; Ombitasvir: OBV; Paritaprevir: PTV; Rintonavir: r.

6. Patients with HCV and HIV coinfection

Patients with HCV and HIV coinfection are treated according to genotype and prior treatment status as follows [96, 99, 100, 101]:

(1) Genotype 1a, treatment-naïve patients may be treated with any of the following regimen:
   a. Sofosbuvir/ledipasvir for 12 weeks without ribavirin
   b. Sofosbuvir/velpatasvir for 12 weeks without ribavirin
   c. Ombitasvir/paritaprevir/ritonavir and dasabuvir for 12 weeks with ribavirin
   d. Grazoprevir/elbasvir for 12 weeks without ribavirin if HCV RNA=800,000 IU/ml or 16 weeks with ribavirin if HCV RNA >800,000 IU/ml
   e. Sofosbuvir/daclatasvir for 12 weeks without ribavirin

   Genotype 1a, treatment-experienced patients may be treated with any of the following regimen:
   a. Sofosbuvir/ledipasvir for 12 weeks with ribavirin or 24 weeks without ribavirin
   b. Sofosbuvir/velpatasvir for 12 weeks without ribavirin
   c. Ombitasvir/paritaprevir/ritonavir and dasabuvir for 12 weeks with ribavirin
   d. Grazoprevir/elbasvir for 12 weeks without ribavirin if HCV RNA=800,000 IU/ml or 16 weeks with ribavirin if HCV RNA >800,000 IU/ml
   e. Sofosbuvir/daclatasvir for 12 weeks with ribavirin or 24 weeks without ribavirin

(2) Genotype 1b, treatment-naïve and treatment-experienced patients may be treated with any of the following regimen:
   a. Sofosbuvir/ledipasvir for 12 weeks without ribavirin
   b. Sofosbuvir/velpatasvir for 12 weeks without ribavirin
   c. Ombitasvir/paritaprevir/ritonavir and dasabuvir for 12 weeks with ribavirin
   d. Grazoprevir/elbasvir for 12 weeks without ribavirin
   e. Sofosbuvir/daclatasvir for 12 weeks without ribavirin

(3) Genotype 2, treatment-naïve and treatment-experienced patients may be treated with any of the following regimen:
   a. Sofosbuvir/velpatasvir for 12 weeks without ribavirin
   b. Sofosbuvir/daclatasvir for 12 weeks without ribavirin

(4) Genotype 3, treatment-naïve and treatment-experienced patients may be treated with any of the following regimen:

a. Sofosbuvir/velpatasvir for 12 weeks with ribavirin or 24 weeks without ribavirin

b. Sofosbuvir/daclatasvir for 12 weeks with ribavirin

(5) Genotype 4 treatment-naïve patients may be treated with any of the following regimen:

a. Sofosbuvir/ledipasvir for 12 weeks without ribavirin

b. Sofosbuvir/velpatasvir for 12 weeks without ribavirin

c. Ombitasvir/paritaprevir/ritonavir with ribavirin for 12 weeks

d. Grazoprevir/elbasvir for 12 weeks without ribavirin

e. Sofosbuvir/daclatasvir for 12 weeks without ribavirin

f. Sofosbuvir and simeprevir for 12 weeks without ribavirin

Genotype 4 treatment-experienced patients may be treated with any of the following regimen:

g. Sofosbuvir/ledipasvir for 12 weeks with ribavirin and 24 weeks with ribavirin

h. Sofosbuvir/velpatasvir for 12 weeks without ribavirin

i. Ombitasvir/paritaprevir/ritonavir with ribavirin for 12 weeks

j. Grazoprevir/elbasvir for 12 weeks without ribavirin if HCV RNA =800,000 or 16 weeks with ribavirin if HCV RNA >800,000 IU/ml

k. Sofosbuvir/daclatasvir for 12 weeks with ribavirin or 24 weeks without ribavirin

l. Sofosbuvir and simeprevir for 12 weeks with ribavirin or 24 weeks without ribavirin

Daclatasvir, dose requirement is needed with ritonavir-boosted atazanavir and efavirenz or etravirine. Simeprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions. In addition, it is recommended daily fixed doses of combined sofosbuvir (400 mg)/velpatasvir (100 mg) and of ledipasvir (90 mg)/sofosbuvir (400 mg). For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended. Regarding HCV/HIV individuals, they should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications [100, 101].

6.1. Treatment of patients with decompensated cirrhosis

Patients with decompensated cirrhosis and those awaiting liver transplantation are managed according to the HCV genotype. Patients with genotypes 1 and 4 are treated with daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks. Another regimen is a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks. Finally, daily doses of daclatasvir (60 mg) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) are given for 12 weeks. For patients who are ribavirin ineligible, the

recommended regime is a daily fixed dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 24 weeks. Another regime is a combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks. Patients who previously failed sofosbuvir-based treatment are given a combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 24 weeks [96, 99, 102]. Patients with HCV genotype 2 or 3 infection and decompensated cirrhosis are treated with daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks [96, 99, 102].

6.2. Patients with HCV recurrence after liver transplantation

Patients who develop HCV after transplantation and with compensated cirrhosis are treated with daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks. Treatment-naïve patients with HCV genotype 1 or 4 infection in the allograft and with compensated liver disease and who are ribavirin ineligible can be treated by a daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks [96, 99, 103]. Patients with HCV genotype 1 infection in the allograft, including those with compensated cirrhosis can receive daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 12 weeks. For those with early stage fibrosis, the recommended regimen is daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin for 24 weeks. Treatment-naïve and -experienced patients with HCV genotype 2 infection in the allograft, including those with compensated cirrhosis, are treated with daclatasvir (60 mg) plus sofosbuvir (400 mg), with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks [92, 96, 99].

7. Patients with HCV and renal impairment

In patients with mild to moderate renal impairment, no dosage adjustment is required when using daclatasvir (60mg), fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), fixed-dose combination of sofosbuvir (400mg)/velpatasvir (100mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with (or without for HCV genotype 4 infection) twice-daily dosed dasabuvir (250 mg), simeprevir (150 mg), or sofosbuvir (400 mg) to treat or retreat HCV infection in patients with appropriate genotypes [96, 99, 104].

For patients with severe renal impairment or end stage renal disease and patients with genotype 1a, or 1b, or 4 infection and CrCl below 30 ml/min, for whom treatment has been elected before kidney transplantation, the recommended daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100mg) for 12 weeks. Genotype 1b infection patients and CrCl below 30 ml/min for whom the urgency to treat is high and treatment has been elected before kidney transplantation, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks. For patients with HCV genotype 2, 3, 5, or 6 infection and CrCl below 30 ml/min for whom the urgency to treat is high and treatment has been elected before kidney transplantation, PEG-IFN and dose-adjusted ribavirin (200 mg daily) [104–107].

8. Retreatment of patients who failed prior therapy [57, 96, 99, 108, 109]

Patients who failed PEG-IFN-α, ribavirin, and DAA or all DAA regimens are retreated according to the previous therapies and genotype as follows:

- Patients infected with HCV genotype 1 who failed after a triple combination regimen of PEG-IFN-α, ribavirin and telaprevir, boceprevir or simeprevir are treated with combination of sofosbuvir and ledipasvir or sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, with ribavirin for 12 weeks.
- Patients who failed on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus pegylated IFN- α and ribavirin can be retreated with any of the following:
    - Genotypes 1, 4, 5, or 6 can be treated with sofosbuvir and ledipasvir
    - All genotypes can be treated with sofosbuvir and velpatasvir
    - Genotype 1 may be treated with ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir
    - Genotype 4 is treated with ritonavir boosted, paritaprevir and ombitasvir or sofosbuvir plus simeprevir
    - Genotypes 1 or 4 are treated with grazoprevir and elbasvir for 24 weeks in F0-F2 patients with HCV RNA >800,000 IU/ml)
    - All genotypes may be treated with sofosbuvir plus daclatasvir

9. Treatment of HCV and HBV coinfection

The goal of therapy in HBV and HCV coinfection is to eradicate HCV infection and inhibit HBV replication. Evaluation of liver disease progression, predominance of one virus over another, and comorbidities are essential for optimal antiviral regimens. For patients with active hepatitis C, the same regimens following the same rules as for monoinfected patients should be applied based on AASLD and EASL recommendations [96, 99]. For patients with active hepatitis B before, during or after HCV clearance or with established cirrhosis, nucleoside or nucleotide analog (NA), tenofovir or entecavir is indicated [110, 111]. Concurrent HBV nucleoside/nucleotide analog therapy is indicated either if there is a potential risk of HBV reactivation during or after HCV clearance or if HBV replication is detectable at a significant level before initiation of HCV treatment [112].

Patients should be carefully investigated for the replicative status of both HBV and HCV, and hepatitis delta virus infection prior selecting the treatment strategy. When HCV is replicating and causes liver disease, it should be treated following the same rules as applied to HCV monoinfected patients. There is a potential risk of HBV reactivation during or after HCV clearance. Prior initiating DAA-based treatment for hepatitis C, patients should be tested

for HBs antigen, anti-HBc antibodies and anti-HBs antibodies. If HBs antigen is present or if HBV DNA is detectable in HBs antigen-negative, anti-HBc antibody-positive patients ("occult" hepatitis B), concurrent HBV nucleoside/nucleotide analog therapy is indicated [96, 99].

9.1. DAA resistance

Despite the great efficacy of the interferon-free DAA regimen, real-life experience revealed that approximately 5–10% of patients end up with virologic failure. Treatment failure raised the issue of resistance and occurrence of mutations. To date, the impact of such mutations on the treatment outcome is not clarified. It is not clear if the presence of mutations at baseline may independently lead to relapse [113]. HCV resistance-associated variants (RAVS) remain a challenging issue in HCV therapy. The prevalence of NS5A RAVs at baseline was shown to vary considerably across genotypes 1a, 1b, 3 and 4. Some studies showed that virologic failure tended to be more frequent when an NS5A Y93H substitution was present at baseline. Resistance-associated substitutions (RASs) have been reported both in treatment-naïve patients and following treatment with protease (NS3), phosphoprotein (NS5A) and polymerase (NS5B) inhibitors [113].

The different next-generation sequencing (NGS) technologies for (HCV) are critical for identification of both viral genotype and resistance genetic motifs in the era of DAA therapies. A study [114] compared the ability of high-throughput NGS methods to generate full-length, deep, HCV sequence data sets and evaluated their utility for diagnostics and clinical assessment. The study showed that the consensus sequences generated by different NGS methods were generally concordant, and majority RAVs were consistently detected. However, methods differed in their ability to detect minor populations of RAVs. NGS provided a rapid, inexpensive method for generating whole HCV genomes to define infecting genotypes, RAVs, comprehensive viral strain analysis and quasispecies diversity. Enrichment methods are particularly suited for high-throughput analysis while providing the genotype and information on potential DAA resistance [114].

In conclusion, discovery of short duration, safe and highly effective regimens has opened up new horizons for HCV cure. However, real-life experience demonstrated some challenges such as emergence of mutations and management of special patient populations. Despite the optimism for the near future and the excellent efficacy, the prohibitive cost of such regimen is a great obstacle that interferes with accessibility of patients in countries with high HCV prevalence to the new IFN-free regimens. Thus, more efforts should be made to make IFN-free cost-effective in all clinical scenarios and accessible to all patients.

Abbreviations

HCV	hepatitis C
HCC	hepatocellular carcinoma

PEG IFN	peginterferon
RBV	ribavirin
DAA	direct-acting antiviral
GT	genotype
NNI	nonnucleotide polymerase inhibitor
NS5A	nonstructural protein 5A
Nuc	nucleotide polymerase inhibitor
PI	protease inhibitor
RAV	resistance-associated variant
TPV	telaprevir
BOC	boceprevir
RGT	response-guided therapy
RdRp	RNA-dependent RNA polymerase
SIM	simeprevir
DNV	danoprevir
EBR-GZR	elbasvir-grazoprevir
SOF	sofosbuvir
VEL	velpatasvir
EOTR	ombitasvir/paritaprevir/ritonavir + dasabuvir
GT	genotype
HCV	hepatitis C virus
OMV, RTV	ritonavir
ART	antiretroviral

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