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REVIEW

An update on direct antiviral agents for the treatment of hepatitis C

Carol Stanciu, Cristina Maria Muzica, Irina Girleanu, Camelia Cojocariu, Catalin Sfarti, Ana-Maria Singeap, Laura Huiban, Stefan Chiriac, Tudor Cuciureanu and Anca Trifan

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ABSTRACT

Introduction: The development of direct-acting antiviral (DAA) agents for the treatment of hepatitis C virus (HCV) infection has completely transformed the management of this disease. The advantages of using DAA therapies include high efficacy (sustained virological response (SVR) rate >95%) with minimal side effects, good tolerability, easy drug administration (once daily oral dosing), and short duration of treatment (8–12 weeks). This transformative nature of DAA therapy underpins the goal of the World Health Organization to eliminate HCV infection as a public health threat by 2030.

Areas covered: This review seeks to address the current status of DAA therapies, including recent developments, current limitations, and future challenges.

Expert opinion: The current DAA regimens, with their high effectiveness and safety profiles, have changed patient perception of HCV infection from a disease that requires complex evaluation and long-term monitoring to a disease that can be cured after one visit to the general practitioner. Despite the remarkably high success rate of DAAs, few patients (4–5%) fail to obtain SVR even after treatment. Five years ahead, the landscape of HCV treatment will undoubtedly continue to evolve, and more pan-genotypic treatment options will be available to all patients.

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Direct-acting antiviral agents; hepatitis C virus; recent developments; remaining challenges

1. Introduction

The goal of antiviral therapy against hepatitis C virus (HCV) infection is to completely eradicate the virus, which is considered as the equivalent to sustained virological response (SVR) by all guidelines, that is, undetectable HCV-RNA 3–6 months after the end of treatment (EOT) [1,2]. Growing evidence shows that obtaining SVR after direct-acting antiviral (DAA) agent treatment is associated with diminished HCV-induced morbidity and enhanced health-related quality of life. One of the greatest advances in clinical medicine in the past decade is the development of DAA therapies for chronic HCV infection, which possess several benefits, such as high efficacy (SVR rates >95%) with minimal side effects, good tolerability, short duration of treatment (8–12 weeks), and easy drug administration (once daily oral dosing). This transformative nature of DAA therapy underpins the goal of the World Health Organization to eliminate HCV infection as a public health threat by 2030 [1].

The ffirst-generationDAAs were introduced in 2011 and 2013. Different combinations of DAAs without interferons (IFN) were developed that were extremely efficient (SVR rates: 95–100%), safe, and showed good tolerability [3]. Since then, several articles on DAA therapies for chronic HCV infection have been published [4].

In 2013, sofosbuvir (SOF), a highly potent inhibitor of the HCV non-structural protein 5B (NS5B) polymerase, was approved by the Food and Drug Administration (FDA) and was considered a genuine breakthrough in the course of developing efficient strategies for HCV therapy [5].

5 October 2020 marked a milestone in the field of hepatology, when the Nobel Prize in Medicine, an award that recognizes a quantum leap in virology, was awarded for the discovery of HCV. This discovery revolutionized the clinical care of millions of patients by aiding in the development of effective treatment strategies to cure this infection.

2. The life cycle of HCV and the targets of DAA therapy

HCV shows genetic variability, having seven genotypes along with different subtypes worldwide, with each showing specific geographical distribution and different rresponsesto treatment [6].

HCV has a positive RNA genome. The core proteins and genome are enveloped by a lipid membrane containing apolipoproteins. Two main glycoproteins, E1 and E2, are fixed in the lipid membrane and they participate in the first phase of cell attachment along with the protein receptor, scavenger receptor class B type I (SR-BI) [7]. After cell attachment, HCV particles enter the hepatocytes via endocytosis. The viral genome is then directed to the perinuclear endoplasmic reticulum (ER) and serves as a template for HCV protein synthesis. The N-terminal end produces the core structural proteins, E1 and E2, and the C-terminal end expresses seven non-structural (NS) proteins (Figure 1).

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Article highlights

- DAAs have completely changed the treatment paradigm for HCV infection
- The complex life cycle of HCV provides several types of treatment targets that are involved in viral suppression.
- The pan-genotypic DAA combinations are highly effective across all genotypes, even in patients that were previously considered to be 'hard to treat', with good safety profiles and short treatment durations.
- Generic DAAs may represent valuable alternatives in limited-resource countries.
- DAA failures (~5%) are mainly related to virological failure caused by resistance-associated variants, which have been reported for all DAAs. SOF/velpatasvir±voxilaprevir (SOF/VEL±VOX) or glecaprevir/pibrentasvir (GLE/PIB) are the only options currently available for re-treatment.

The development of DAA therapy opened the door to a very ambitious goal—the elimination of HCV by 2030.

This box summarizes key points contained in the article.

NS5B polymerase is the key enzyme involved in the synthesis of HCV-RNA. Non-structural protein 3/4A (NS3/4A), non-structural protein 4B (NS4B), and non-structural protein 5A (NS5A) are also needed for translation and replication of the system. All these proteins form the cornerstones of the process used for anti-HCV drug development. Translation starts at the internal ribosome entry site (IRES) and the polyprotein is cleaved by viral proteases.

After replication, viral assembly occurs in lipid droplets where the core proteins are present. NS5A is the main protein involved in this phase, along with the non-structural protein 2 (NS2) and p7. Structural proteins interact with the genome and assemble into virions. The assembly process requires interaction with lipid droplets and lipoproteins, which is why the structure of viral particles resembles that of very-low-density lipoproteins (VLDL). The virions are then secreted via an exocytic pathway involving the Golgi apparatus and fully assembled HCVs are released.

Along with these virus-related factors, several host factors are involved in HCV replication [8]. Cyclophilins and phosphatidylinositol-4-phosphate-kinase-III alpha are important guest-related co-factors involved in the HCV replication process [9–11].

Some proteins and proteases are particularly relevant to the therapeutic development of HCV antiviral agents. NS2 is a viral protease involved in the assembly and maturation of viral particles, while NS3 has a double role of being a protease involved in proteolysis and a helicase that mediates the cleavage between NS2 and NS3. NS4A is a co-factor for NS3 protease, while P7 is a viroporin that plays complex roles in virion assembly and secretion. NS4B is implicated in the formation of the replication complex, which closely interacts with NS5A during the viral replication cycle. NS5B is an RNA-dependent RNA polymerase that mediates viral replication.

The mechanisms of action and pharmacokinetic characteristics of the main DAA agents are presented in Table 1.

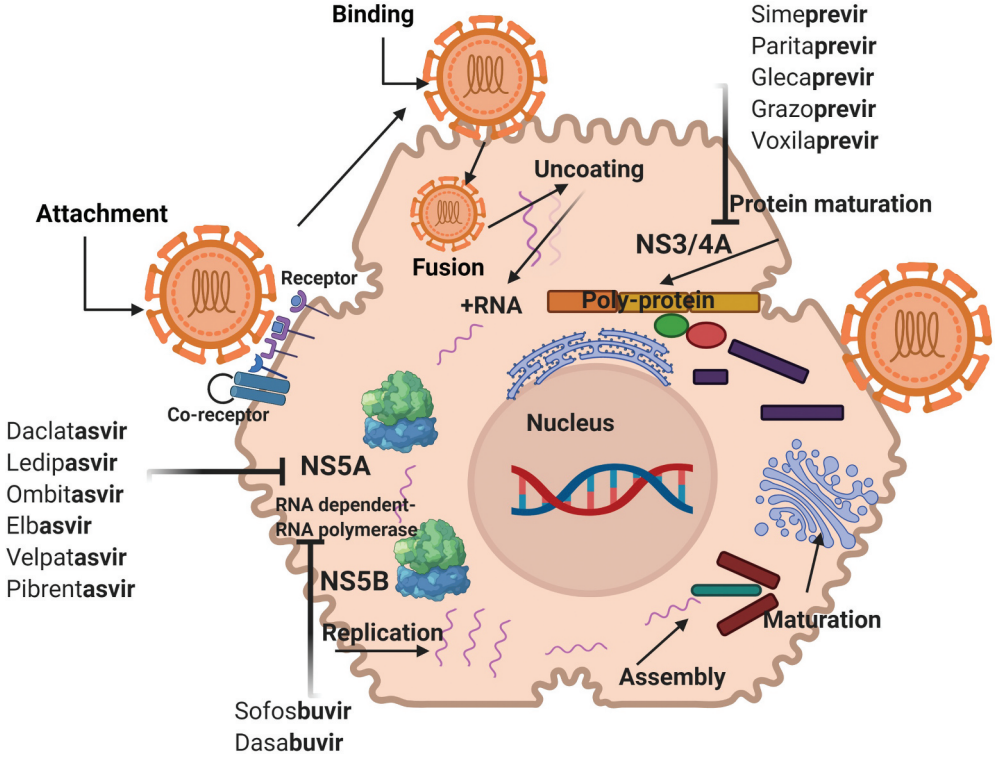

Figure 1. HCV life cycle and DAAs treatment targets.

The infection of HCV is initiated by the attachment, binding and entry of virus particles through a number of cell-surface receptors. After fusion with the hepatocyte, HCV RNA is uncoated, binds to ribosome and translates a single large poly-protein, which is processed into structural and nonstructural proteins. Genomic HCV RNA packages into complete infectious virus particles that are released through exocytosis. The nonstructural proteins – NS3/4A, NS5A, and NNS5B – arethe targets of the DAAs. Created with BioRender.com

Table 1. Mechanisms of action and pharmacokinetic characteristics of DAAs (3,5, 12–14,16,21,22,43).

Molecule	Targets	Mechanism	Molecular formula	Absorbtion	Distribution	Cmax	Half life	Metabolism	Elimination	Adverse events
Simeprevir	**NS3/4A protease**	Preventing viral maturation through inhibition of protein synthesis Inhibition of proteolytic activity of NS3/4A enzymes	$C_{38}H_{46}N_5NaO_7S_2$	Increased by food	99% PPB	4–6 h	41 h	Liver, CYP3A	<1% renal 91% billiary-fecal	Rash, pruritus, photosensitivity, bradycardia
Paritaprevir			$C_{40}H_{43}N_7O_7S_1$	Increased by food	97–98% PPB	4 h	6 h	Liver, CYP3A4/5	88% fecal 8.8% renal	Headache, fatigue, diarrhea, nausea
Glecaprevir			$C_{38}H_{46}F_4N_6$					O_9S (anhydrate)	Increased by food	97.5% PPB
5 h			6 h	Liver, CYTP3A	92.1% billiary-fecal 0.7% renal			Fatigue, headache, nausea		
Grazoprevir			$C_{38}H_{50}N_6O_7$	Increased by fatty food	98.8% PPB	1–3 h	31 h	Liver, CYP3A	>90% fecal, <1% renal	Fatigue, headache, nausea,
Voxilaprevir	$C_{40}H_{52}F_4N_6O_9S$	Increased by food	>99% PPB	4 h	33 h		CYP1A2,	CYP2C8, CYP3A4	94% billiary-fecal	Headache, fatigue, diarrhea, nausea
Sofosbuvir	**NS5B RNA-dependent RNA polymerase**	Nucleoside inhibitors inhibitor of viral RNA synthesis	$C_{22}H_{29}FN_3O_9P$	Not influenced by food intake	61–65% PPB	0.5–2 h	27 h	Liver, pro-drug is phosphorilated to activ-form	80% renal 12% billiary-fecal	Fatigue, headache, nausea, insomnia, pruritus, asthenia, diarrhea, irritability
Dasabuvir		Non-nucleoside inhibitors Blocking RNA polymerization and stopping the replication of the HCV genome	$C_{26}H_{26}N_3NaO_5S$	Increased by food	99% PPB	4 h	6 h	Liver, CYP2C8 CYP3A CYP2D6	94.4 fecal, 2% renal	nausea, insomnia, pruritus, asthenia, headache, diarrhea
Daclatasvir	**NS5A**	**phosphoprotein**	Inhibits viral RNA replication and virion assembly	$C_{40}H_{52}Cl_2N_8O_6$	Decreased by food	99% PPB	2 h	13 h	Liver, CYP3A	53% billiary- fecal 7% renal
Headache, fatigue, nausea, diarrhea										
Ledipasvir		Inhibits viral replication, assembly, and secretion	$C_{52}H_{60}F_2N_8O_7$	Decreased by increasing gastric pH	99% PPB	4 h	47 h	Liver, minimally metabolized	86% billiary-fecal <1% renal	Diarrhea Nausea,fatigue, headache, insomnia, bilirubin and lipase elevation
Ombitasvir	inhibitor of the HCV non-structural protein 5A, inhibits viral replication and virion assembly	$C_{50}H_{67}N_7O_7$	Increased by food	99% PPB	5 h		21–25 h	Amide hydrolysis	90.2% fecal	asthenia, fatigue, nausea, insomnia, pruritus
Velpatasvir		endoplasmic reticulum to the surface of lipid droplets, modification of the HCV replication complex	$C_{49}H_{54}N_8O_8$	Increased by food	99.5% PPB	2 h	15 h	CYP2B6 CYP2C8 CYP3A4	77% fecal, 0.4% renal	Fatigue, headache, nausea,
Pibrentasvir		Inhibition of	$C_{57}H_{65}F_5N_{10}O_8$	Increased by	99.9% PPB	5 h	13 h	Liver, CYP3A	>96% billiary-	Fatigue, headache,
HCV NS5A, inhibition viral replication and virion assembly		food					fecal	nausea,		

PPB = plasma protein binding

2.1. NS3/4A inhibitors

The first DAA agents targeted the protease domain of NS3. NS3 protease is involved in viral polyprotein maturation and together with the co-factor, NS4A, it cleaves peptide junctions into non-structural proteins. These molecules are suffixed with – previr and are considered to be protease inhibitors (PIs). The first antivirals that marked the beginning of the DAA era were boceprevir and telaprevir, followed by simeprevir. However, their low genetic barrier, severe side effects, and restriction to genotype 1 resulted in the discontinuation of their use in treatment [12]. Further research has resulted in the development of new PIs with higher antiviral potency and improved genetic resistance barriers, such as glecaprevir (GLE), paritaprevir (PTV), grazoprevir (GZR), and voxilaprevir (VOX).

2.2. NS5B inhibitors

There are two types of NS5B inhibitors that target the catalytic or noncatalytic sites of the NS5B protein. The first class includes the nucleo(s)tide inhibitors (NIs), which were the first molecules developed against NS5B targets and bind to the catalytic site of the enzyme. These molecules are suffixed with – buvir. In 2003, the FDA approved the first NI, SOF, followed by dasabuvir (DSV) [13]. SOF has a pan-genotypic effect because it involves the catalytic site of HCV RNA polymerase, which is highly conserved between viral genotypes. SOF is the most commonly used antiviral agent in most HCV therapies.

The next class of NS5B inhibitors consists of non-nucleoside inhibitors (NNIs). They inhibit conformational changes that are necessary for polymerase activity. DSV is the only NNI approved by the FDA and is recommended only for patients with the HCV genotype 1 [14]. Compared to NIs, NNIs have a lower genetic resistance barrier and show poorer pan-genotypic activity; when combined with other potent antiviral drugs, they can reduce the duration of treatment.

2.3. NS5A inhibitors

NS5A is a phosphoprotein that plays an essential role in viral RNA replication, viral assembly, and genome transfer to assembly sites. These molecules are suffixed with -asvir. The first-generation drugs included daclatasvir, ledipasvir (LED), and ombitasvir (OBV). The ssecond-generationdrugs, such as elbasvir (EBR), velpatasvir (VEL), and Pibrentasvir (PIB), were optimized to be pan-genotypic and have lower toxicity than the first-generation drugs.

3. Currently available DAA combinations

3.1. Genotype/subtype-based treatment of HCV-infected patients

Identifying certain genotypes before treatment can be useful if access to pan-genotypic treatment is difficult or if the patients face cost-related issues. It can also be useful for patients belonging to some regions in Africa or Asia (or in migrants from these regions), where certain rare subtypes that are resistant to NS5A inhibitors were identified.

3.1.1. HCV genotypes 1a, 1b, 2, 4, 5, and 6

Patients without cirrhosis or with compensated cirrhosis with no evidence of having undergone previous antiviral therapy as well as patients without cirrhosis who were non-responders to previous antiviral treatment, were treated with combinations of SOF (400 mg)/VEL (100 mg) for 12 weeks, GLE (300 mg)/PIB (120 mg) for 8 weeks, or LED (90 mg)/SOF (400 mg) for 12 weeks (Table 2) [14]. For patients with compensated

Table 2. Currently available DAA combinations.

DAAs regimen	Dosage	Brand name	FDA approval	EMA approval	Viral target	Genotype	Pivotal trials	Efficacy*
PAN-GENOTYPIC								
Sofosbuvir 400 mg/ velpatasvir 100 mg[16,17]	once daily	Epclusa	2016	2016	NS5B inhibitor (Sofosbuvir) NS5A inhibitor (velpatasvir)	1a, 1b,2,3,4,5,6	Phase 3 ASTRAL-1, ASTRAL-2, ASTRAL-3, ASTRAL-4	97%-100%
Glecaprevir 100 mg/ pibrentasvir 40 mg[21–31] 99.7%	3 doses once daily	Mavyret (US)/ Maviret (EU)	2017	2017	NS3/4A protease inhibitor (glecaprevir) and NS5A inhibitor (pibrentasvir)	1a, 1b,2,3,4,5,6	ENDURANCE1, –2,-3,-4, SURVEYOR-1, –2 EXPEDITION-1, –4 MAGELLAN-1	86.6%-
GENOTYPE SPECIFIC								
Elbasvir 50 mg/ grazoprevir 100mg[15]	once daily	Zepatier	2016	2017	NS5A inhibitor (elbasvir) and NS3/4A protease inhibitor (grazoprevir)	1b, 4	C-EDGE TN C-EDGE TE	86%-100%
Ledipasvir 90 mg/ sofosbuvir 400 mg[15]	once daily	Harvoni	2015	2014	NS5A inhibitor (ledipasvir) NS5B inhibitor (Sofosbuvir)	1	ION-1, –2, –3, –4	94%-99%
Sofosbuvir400mg+ Daclatasvir 60mg[14,15]	once daily once daily	Solvadi+ Daklinza	2015	2014	NS5B inhibitor (Sofosbuvir) NS5A inhibitor (daclatasvir)	2,3	ALLY-1, –2, –3, –3+	94%-100%

DAAs = direct-acting antivirals, FDA = Food and Drug Administration, EMA = European Medicines Agency
*sustained virologic response 12

cirrhosis and who previously underwent treatment, a 12-week treatment plan with the same regimens listed above is recommended. Only in patients with HCV genotype 1b or 4, without cirrhosis or with compensated cirrhosis, including both treatment-naïve and treatment-experienced patients, the combination of EBR (50 mg)/GZR (100 mg) can be used for a 12-week treatment plan. Due to increased evidence of patients showing an inferior response to treatment in the presence of NS5A resistance-associated substitutions (RASs), the current guidelines recommend conducting NS5A resistance tests for patients with genotype 1a who are eligible for EBR/GZR treatment.

3.1.2. HCV genotype 3 infection

HCV genotype 3 infection was considered to be difficult-to-treat in patients during both the IFN era and the beginning of the DAA era [15]. Although the genetic profile exhibited by HCV has created major challenges and barriers for developing effective pan-genotypic therapies, the launch of novel and highly efficient regimens has overcome the previous treatment challenges, including the management of genotype 3 infection. The current recommendations for the treatment of HCV genotype 3-infected patients are listed in Table 2.

3.2. Pan-genotypic DAA combinations for chronic HCV infection

The recent advent of pan-genotypic DAA agents represents a revolutionary breakthrough in the development of DAA therapies, which has simplified the treatment strategies and has the advantage of bypassing genotype testing before treatment (Table 2).

Data from ASTRAL 1–4 phase III clinical trials led to the emergence of the first-line pan-genotypic regimen represented by the SOF/VEL combination, which was approved by the FDA in 2016 [16,17]. The current standards of care for patients with HCV-related decompensated cirrhosis include the administration of SOF/VEL (Epclusa) and ribavirin (RBV) drugs. Furthermore, SOF/VEL is recommended without RBV in patients without cirrhosis or with compensated cirrhosis and is highly effective in both naïve and treatment-experienced patients [16,18].

Another pan-genotypic DAA combination of SOF/VEL and the NS3/4A protease inhibitor, VOX, sold under the brand name Vosevi, was approved in 2017 based on the results from several phase III clinical trials. SOF/VEL/VOX is currently recommended for the treatment of patients with HCV genotype 1a and HCV genotype 3, whose previous treatment involving a DAA regimen that included either an NS5A inhibitor or SOF without an NS5A inhibitor failed [19,20].

In 2017, the FDA and European Medicines Agency (EMA) authorized another pan-genotypic DAA combination containing GLE (an NS3/4A protease inhibitor) and PIB (an NS5A inhibitor), which was sold under the brand name Mavyret (US) and Maviret (EU) [21,22]. According to evidence from several phase II and phase III trials, GLE/PIB is safe in patients with chronic kidney disease (CKD) and has a high efficacy in patients who had viral treatment failure with a previous DAA regimen [23–29]. The ongoing MAGELLAN-3 trial is currently assessing the efficacy and safety of the combination of GLE/PIB and SOF/RBV drugs in patients who failed to achieve SVR under a previous regimen with GLE/PIB (ClinicalTrials.gov Identifier: NCT02939989). Another important trial is EXPEDITION-5, which seeks to evaluate the efficacy and safety of GLE/PIB drugs in patients with HCV genotypes 1–6 and CKD [30,31].

3.3. Generics

Access to treatment could be a barrier in the management of chronic HCV infection due to the high costs of the original drug regimens. In the early era of DAA treatment, restrictions regarding the fibrosis stage were imposed in many countries, thereby limiting the access to reimbursed medicines. For all countries, especially the low- and middle-income countries which hold the majority of infected people, managing the drug costs is an important financial issue. Recently, important steps have been taken in this direction. According to the March 2018 WHO Progress Report on Access to Hepatitis C Treatment, two originator companies signed voluntary license agreements for manufacturing generic DAA agents [32]. In 2017, three products (SOF, SOF/LED, and SOF/VEL) were licensed by Gilead to several Indian generic manufacturers. Similarly, Bristol-Myers Squibb voluntarily licensed 10 companies to manufacture generic daclatasvir. Since then, their generic formulations are sold and marketed in more than 100 low- and middle-income countries, thereby aiding in providing treatment to patients at a significantly lower cost [33]. Pharmacokinetic studies have confirmed the bioequivalence of generic SOF and daclatasvir to their original drugs and evidence from real-world studies have showed that patients treated with these generic drugs exhibit similar efficacy rates as those treated with the originator agents. The current European Association for the Study of the Liver (EASL) guidelines stipulate that generic drugs may be included in the management of chronic HCV infection as long as quality requirements are fulfilled and warranted by the manufacturer. Furthermore, in areas where the pan-genotypic DAA combinations are unaffordable, the combination of generic SOF and daclatasvir can be administered as it has an excellent safety profile and is highly efficacious at a very low price [15]. Once the quality requirements are met, generic DAA agents may prove to be valuable alternatives to high-cost drugs, especially in limited-resource and low-income countries.

3.4. Shortening the duration of DAA therapy

A 12-week treatment prescribed to most patients has shown high efficacy for different viral and host characteristics [15]. Patients who underwent treatment for a shorter duration of 8 weeks were shown to have similar SVR rates as those who underwent a 12-week therapy; thus, there was a reduction in the overall treatment costs and associated-adverse effects along with an improvement in the adherence of patients to treatment [34]. However, there is no such evidence regarding the benefits of shortening the treatment duration to less than 8 weeks, and thus, it should not be recommended.

4. Combination of pan-genotypic DAA agents for the treatment of HCV in 'special populations'

Despite the improvements and simplification of DAA regimens, several population groups present particular needs that require careful consideration for effective management of the infection [1]. What does the syntagm 'special populations' mean? The term is somewhat evasive, covering those patients that are difficult-to-treat, or those with associated comorbidities and concomitant treatments, prior DAA failure, post-treatment reinfection, CKD, HCV/HIV or HCV/HBV co-infection, decompensated cirrhosis, active HCC, persons who inject drugs (PWID), men who have sex with men (MSM), persons deprived of their liberty, and pediatric populations [35,36]. However, owing to the very high efficacy (SVR >95%) and safety of DAA therapies, the notion of 'special population' will no longer be pertinent, remaining only in a few groups of patients, such as those with decompensated cirrhosis as well as pregnant women (which need 'special' consideration).

4.1. Chronic kidney disease

Current DAA regimens in patients with chronic HCV infection and CKD/end-stage renal disease (ESRD) are associated with high SVR rates (SVR >90%), similar to patients without CKD/ESRD [36]. According to the results of various clinical trials, there is no need for DAA dose adjustments in patients with chronic HCV infection, having an estimated glomerular filtration rate (GFR) <30 mL/min or those on dialysis, when using EBR/GRZ, GLE/PIB, SOF/LDV, and SOF/VEL [37].

However, special considerations are needed in patients with CKD regarding dose adjustments for RBV. In the DAA era, eligible patients for RBV are those with decompensated cirrhosis who receive SOF/VEL as well as those with HCV genotype 1a infection who receive EBR/GRZ and associate baseline NS5A RASs for EBR.

4.2. HCV/HIV co-infection

Treatment of patients with HCV/HIV co-infection remains a high priority because 80–90% of liver-related deaths in persons with HIV are due to co-infection with HCV infection and non-HIV-related complications [38]. Moreover, liver cirrhosis occurs earlier and more frequently in HCV/HIV co-infected patients than in only HCV-infected patients and the co-infected patients even face limited access to liver transplantation for a long time [35,38].

Treating hepatitis in HCV/HIV co-infected patients is extremely important for both patients and the society, as SVR achievement reduces hepatic and extrahepatic morbidity rates and related deaths in co-infected patients. Considering that the highest rate of HCV re-infection is reported in persons at risk of HIV infection (PWID, MSM, persons deprived of their liberty), HCV treatment of co-infected patients will also reduce the rate of HCV infection in these population groups [32,35,36,39].

Current antiviral regimens in HCV/HIV co-infection are associated with patients having similar SVR rates as those observed in the 'general population' (SVR >90%). Two of the initial trials on HCV/HIV co-infected patients treated with SOF/LDV showed SVR rates of 96–98% in genotype 1 and 100% in genotype 4 [40,41].

According to the current guidelines, all patients with HCV/HIV co-infection should be treated in the same way (concerning treatment regimens and treatment duration) as those with HCV mono-infection [15,37].

4.3. HCV/HBV co-infection

According to all guidelines, the status of patients with chronic hepatitis B (CHB) infection should be closely monitored. It is mandatory that all HCV-infected patients undergo screening for hepatitis B virus (HBV) surface antigen (HBsAg) and anti-HBV core antigen (anti-HBc) antibodies before starting DAA therapy, and treatment/monitoring should be carried out according to the HVB profile [15,37].

Patients with HCV/HBV co-infection are treated using the same DAA regimens as in HCV mono-infected patients and those meeting the criteria for HBV therapy should be treated with nucleos(t)ide analogs (NUC). Patients who are HBsAg negative/anti-HBc positive and HBsAg-positive patients with undetectable baseline HBV DNA have to be monitored using alanine aminotransferase (ALT) alone until 12 weeks after the conclusion of treatment (SVR12), and should undergo HBV DNA testing only if ALT increases under DAA therapy. HBsAg-positive patients with baseline HBV DNA levels meeting the HBV treatment criteria and those with detectable HBV DNA but not meeting the HVB treatment criteria should undergo NUC therapy [35,42].

Despite the fact that the optimal treatment duration of NUCs is currently unknown, it seems reasonable to continue the therapy at least to SVR12. Regardless of the strategy, it is important to continue monitoring patients after DAA cessation and/or NUC withdrawal, because withdrawal flares remain a challenge in the treatment of HCV/HBV co-infected patients.

4.4. HCV in prisons

The prevalence of HCV infection is much higher in incarcerated individuals than in the general community and many of the undiagnosed HCV-infected people are among this population group.

The treatment of HCV infection for inmates is the same as that for any HCV patient, but unfortunately, there are certain hurdles that need to be taken into account when planning HCV-treatment strategies for incarcerated individuals. Most of them are ignorant of their diagnosis and lack awareness, while the medical staff needed to treat hepatitis C is also deficient along with the funds to cover the costs of therapy. Given that these people show an increased risk of infection transmission, curing HCV infection in these patients provides a double benefit, both for the patient (who receives treatment like any other person) and the society.

4.5. HCV in intravenous drug users (PWID)

The American Association for the Study of Liver Diseases (AASLD) considers that, at present, intravenous drug use is not a contraindication for antiviral therapy [37]. Recent evidence clearly shows that the use of DAA agents in PWID populations results in SVR rates comparable to those seen in the general population. According to the guideline recommendations, PWID patients should be treated the same as the general population. The Achilles heel in PWIDs is the high risk of reinfection after SVR, especially in those users who continue to inject drugs or have unprotected sexual contact, particularly among the MSM groups. Thus, a multidisciplinary approach (with social workers, psychotherapists, etc.) to address common psychiatric disorders is suggested. Treatment of HCV in PWIDs has an impact on the whole society by diminishing the transmission of HCV through these patients.

4.6. DAA therapy in children and adolescents

Recently, the landscape of HCV infection in children has changed due to positive results from clinical trials showing excellent safety profiles and efficacy of DAA agents in the pediatric population. This has led to the approval of several DAA combinations: expansion to pediatric indications for (1) LDV/SOF (Harvoni) in patients aged 3 years or older with HCV genotypes 1, 4, 5, and 6, with a treatment duration of 12/24 weeks; (2) SOF/RBV (Sovaldi) in patients aged 3 years or older with HCV genotypes 2 and 3, with a treatment duration of 12/24 weeks; and (3) GLE/PIB (Mavyret) in patients aged 12 years or older with a weight of ≥45 kg, with HCV genotypes 1–6, taking into account previous antiviral treatment failure, presence of cirrhosis, and other genotypes [43–45].

Although DAA agents show good tolerability and do not exhibit significant adverse effects, their use in the management of chronic HCV infection in the pediatric population is still debatable, with different recommendations from the EMA and FDA (Table 3) [46]. Differences between the indications stipulated by the EMA and FDA ttarget-specificsubgroups (cirrhotic pediatric population and IFN-based therapy experienced groups, and groups based on children's weight) and lead to difficulties in the implementation of DAA agents in health protocols. These minor differences between recommendations are probably due to different healthcare policies and insufficient data.

To accomplish the established eradication targets for chronic HCV infection by 2030, children and adolescents should be included in a campaign that involves raising awareness of HCV transmission routes, easing access to screening and treatment, and accelerating the approval of pediatric regimens.

4.7. DAA treatment in patients with decompensated liver cirrhosis

Patients with decompensated liver cirrhosis represent a difficult-to-treat population for various reasons and DAA-

Table 3. FDA and EMA approved DAAs for HCV infection in children (3–11 years) and adolescents (12–18 years).

Regimen	Duration	Doses	EMA	FDA
SOF/LED[43]	GT 1, 4, 5, 6: 12 wks GT 1, treatment experienced (IFN-based therapy) or cirrhosis: 24 wks	12–17 y: 400/90 mg/day 6–11 y: 200/45 mg/day 3–5 y: 200/45 mg/day if ≥17 kg; 150/33.75 mg/day if <17 kg	>12 y without any specific weight indication GT 3: 24 wks with RBV GT 1, treatment-naive and HCV RNA < 6 X 10^6: 8 wks Not yet approved for children <12 y	The dose indicated for use in adolescents 12–17 y of age can be used independently of the age of the patient for children weighing ≥35 kg
SOF	+RBV[44]	GT 2: 12 wksGT 3: 24 wks	SOF 12–17 years: 400 mg/day 6–11 y: 200 mg/day 3–5 y: 200 if ≥17 kg; 150 mg/day if <17 kg RBV 15 mg/kg/day in 2 divided doses	>12 y without any specific weight indication Not yet approved for children <12 y of age
The SOF dose	indicated for use in adolescents 12–17 y of age can be used independently of the age of the patient for children weighing ≥35 kg			
GLE/PIB[45]	All GTs: 8 wks All GTs with cirrhosis: 12 wks GT 3, treatment experienced: 16 wks	12 to 17 y: 300/120 mg/day	Approved for use in adolescents > 12 y without any specific weight indication	The dose indicated for use in adolescents 12–17 y of age can be used independently of the age of the patient for children weighing ≥45 kg

GLE = glecaprevir, LED = ledipasvir, PIB = pibrentasvir, SOF = sofosbuvir, RBV = ribavirin, GT = genotype, IFN = interferon, wks = weeks, y = years;

based pangenotypic combinations seem to be the most reasonable choices. Portal-systemic shunts decrease the bioavailability of DAAs, resulting in a suboptimal response, and PIs are contraindicated because of substantially increased drug exposure and the cumulative risk of drug-induced toxicity.

Several pivotal studies, such as SOLAR-1 and SOLAR-2, reported SVR rates as high as 87% and 85–86% in patients with Child-Pugh class B and C, respectively, after a 12-week course of SOF/LDV regimen [47,48]. Moreover, the ASTRAL-4 study included all patients with decompensated cirrhosis. They received SOF and VEL at a fixed dose for 12 weeks, with or without RBV. Adding RBV improved the SVR 12 rate up to 94%; however, in genotype 3 patients, the SVR12 rate was only 85% [49]. Another study including Child-Pugh class C patients who received SOF/VEL and RBV reported an SVR12 rate of only 70% in an intention-to-treat analysis [50].

A retrospective data analysis from four trials evaluating the efficacy of DAA therapy including SOF in patients with decompensated cirrhosis demonstrated that the presence of ascites, hepatic encephalopathy, increased weight, high ALT, and low albumin levels are the main factors associated with failure to decrease the Child-Pugh score after treatment [51]. It was also reported that patients had a reduction in liver cirrhosis severity and were delisted from the liver transplant (LT) list, although more than 40% of the patients showed an increase in the model for end-stage liver disease (MELD) after viral eradication [52].

Considering the frailty of decompensated cirrhotic patients, these patients should receive treatment in experienced centers to ensure that they can be closely monitored and rapidly referred to LT units in case of further decompensation. The recent European Consensus of HCV treatment recommends that patients with decompensated liver cirrhosis and those with compensated liver cirrhosis and previous episodes of decompensation should receive a 12-week treatment with a fixed-dose of SOF and VEL with RBV according to the patients' weight (1,000 mg in patients <75 kg or 1,200 mg in patients >75 kg, respectively). Patients with contraindications or intolerance to RBV should receive treatment for 24 weeks without RBV [15].

4.8. DAAs treatment and liver transplant patients

The treatment of HCV infection before LT has two main goals: to prevent liver graft infection after LT and to stabilize liver function until LT. Previous studies have demonstrated a decreasing mortality rate for patients with HCV infection after DAA treatment [53,54]. Therefore, in patients with HCV infection, the outcomes after LT could be improved if they received DAA treatment before LT. These data were confirmed by an observational study including 1,483 patients with HCV infection, which reported that the 3-year post-LT survival rate increased from 76% to 91% in the pre-2014 cohort, compared to the post-2014 cohort [55]. Similarly, in a study including subjects from the European Liver Transplant Registry database, on a cohort of more than 60,000 transplanted patients, investigators reported an improved 3-year post LT survival rate from 65.1% to 76.9% in the IFN era compared to the DAAs era in patients transplanted for HCV liver cirrhosis without hepatocellular carcinoma (HCC). In this cohort, there was also a statistically significant decrease in HCV recurrence as the main cause of death or graft loss in patients receiving DAA treatment (1.27%), compared to those treated with interferon (6.37%) [56].

Patients with a MELD score >18–20 should receive DAA treatment after LT if the donor is available within 6 months; this is because side effects associated with this treatment could impair the patient's outcome [15,57]. Moreover, DA treatment before LT was demonstrated to be more cost-effective and safer for patients without HCC and an MELD score <20 [58].

DAA treatment after LT should be started as soon as possible after LT, generally following the first 3 months post-transplant, because HCV graft infection tends to accelerate fibrosis evolution, with a high risk of developing fibrosing cholestatic hepatitis and graft loss within 1 year [57].

The fixed-dose combination of SOF and VEL for 12 weeks, without RBV, was demonstrated to have an SVR12 rate of up to 96% in LT patients, with only one relapse in 15 patients with genotype 1a [59]. There are no drug–drug interactions (DDIs) between this fixed-combination and immunosuppressive agents in LT transplant patients (tacrolimus, sirolimus, everolimus, cyclosporine, mycophenolate mofetil, or corticosteroids). In patients with decompensated liver cirrhosis, the association of RBV with the SOF/VEL regimen is recommended.

The fixed combination of SOF/VEL or GLE/PIB for 12 weeks should be recommended in patients with HCV recurrence after LT, as the GLE/PIB regimen requires close monitoring of serum drug levels of immunosuppressive treatment.

In decompensated liver cirrhosis and failure of previous DAA therapy, it is recommended to initiate treatment after LT with pangenotypic regimens, such as GLE/PIB or SOF/VEL/VOX.

4.9. DAAs therapy in patients with HCC

The use of DAAs in patients with active HCC involves particular considerations if we consider the possibility that the presence of HCC could affect the antiviral efficacy and that these patients are more prone to have severe liver-related complications; thus, close surveillance is needed [60].

Several studies have highlighted that patients with active HCC have a lower SVR rate than those without HCC [61,62]. Although the mechanisms of treatment failure in patients with active HCC are not fully understood, there are several hypotheses that could explain the phenomena: (1) the impaired immunity system, which is constantly found in these patients, could represent an obstacle in the clearance of HCV; (2) the existence of several different viral populations in patients with HCC could lead to DAA resistance; (3) a poor blood flow within HCC could be an obstacle for the delivery of DAAs to affected hepatocytes; and (4) a virological failure could also be induced by local fibrosis subsequent to radioembolization [62–64].

Current guidelines recommend active treatment with DAA regimens of all HCV infected patients, except those with a low life expectancy that 'cannot be remediated by HCV therapy, liver transplantation, or another directed therapy' [65]. This

indication of treatment emerges from robust data that demonstrated early improvement in disease severity after DAA-SVR and long-term preservation of liver function, which could prevent treatment discontinuation because of decompensation in patients with HCC and non-curative therapy.

5. Treatment failure and options for retreatment

Despite the SVR rates exceeding 90% with the current DAA-based therapies, treatment failure still occurs in 2%–5% of patients and is related either to poor adherence or virological failure [66]. Depending on their viral target and mechanism of action, there are four types of DAAs: NS3/4A protease inhibitors, NS5A inhibitors, nucleotide analog inhibitors of NS5B RdRp, and non-nucleoside inhibitors of RdRp. Due to the high specificity of DAAs for their viral targets, any minor change in the HCV viral sequence could lead to the emergence of viral resistance, which is the cornerstone for DAA failure. It is well known that HCV has high genetic variability, making it possible to select several mutations in NS3 protease, NS5B polymerase, and NS5A. These selected mutations alter the viral susceptibility to DAAs, subsequently changing the treatment outcome. All DAAs have a certain resistance profile with an impact on the genetic barrier to resistance [67].

The resistance-associated substitutions (RAS) emerging after DAA failure are as follows: (i) R155, A156, and D168-RAS in NS3, (ii) S282T in NS5B, (iii) L31 and Y93-RAS in NS5A, and (iv) P32del or the A92K RAS in NS5A [68–75]. All these RASs could attenuate the retreatment efficacy; of great importance is the presence of the A92K RAS, which determines a high resistance profile to NS5A inhibitor-containing pangenotypic combinations. A strong resistance to DAAs could be secondary to the coexistence of several RASs.

Data from the ION study, which assessed the impact of baseline resistance to HCV therapy in patients treated with SOF/LED, without any prior antiviral therapy, showed a 98% SVR rate in patients without baseline NS5A RAS and 96% in patients with baseline NS5A RAS. These results reveal a modest influence on treatment outcomes in patients without previous antiviral treatment [76]. Furthermore, this finding was confirmed by numerous phase I, II, and III clinical trials; therefore, resistance testing is not indicated in naïve patient candidates for DAAs mainly because of the low prevalence of RAS at baseline, but also because of the high efficacy of the first DAA regimens in obtaining SVR, despite the infinite number of potential resistance profiles. In the current practice, RAS testing is of high interest only if the results could impact the therapeutic approach (i.e. therapy duration, association of RBV, or selection of another regimen). In addition, the usefulness of RAS testing depends on patient characteristics and DAA-based treatment [77].

Besides RAS, there are other baseline predictors of treatment failure, such as decompensated cirrhosis, genotypes 1a and 3, a high HCV-RNA load, and previous DAA failure [78].

The clinical significance of viral failure relies on the presence of previous failure of NS3 or NS5A inhibitors to the combination of GLE/PIB [79]. Current guidelines recommend that patients with treatment failure after DAA-based regimens should be retreated after HCV resistance testing to guide the retreatment strategy.

The available retreatment options are based on the results from phase 3 POLARIS trials and the MAGELLAN-3 trial [19,25]:

(1) Patients without cirrhosis or with compensated cirrhosis, with treatment failure with a protease inhibitor and/or NS5A inhibitor, were eligible for the SOF/VEL/VOX combination for a 12-week period. If these patients also associate baseline predictors of treatment failure (advanced liver disease, multiple treatment failures with DAAs, and the identification of NS5A RAS), the most appropriate option is SOF plus the fixed-dose combination of GLE and PIB for 12 weeks.

(2) Patients with NS5A RASs with treatment failure more than once with a protease inhibitor and/or NS5A inhibitor, are eligible to be retreated with either the combination of SOF/VEL/VOX, or with a combination of SOF/GLE/PIB for a 12-week course in association with weight-based RBV (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively), and/or treatment duration can be extended up to 16/24 weeks.

(3) Patients with treatment failure following retreatment with SOF/VEL/VOX should receive a combination of SOF/GLE/PIB for 24 weeks in association with weight-based RBV.

(4) Patients with decompensated cirrhosis with treatment failure after a regimen containing a protease inhibitor and/or NS5A inhibitor should be treated with SOF and VEL with weight-based RBV for 24 weeks.

6. The potential drug–drug interactions of DAAs

Most of the DDIs of DAAs involve the cytochrome P450–3 A4 (CYP3A4) metabolic pathway or hepatic and/or intestinal organic anion-transporting polypeptides. DAA concentrations may be modified by CYP3A4 and P-glycoprotein inducers or inhibitors. This process results in increased concentrations of the administered drugs [80]. The selection of common drugs frequently used with DAAs is shown in Table 4.

The DDI risk profile is considered moderate for the majority of DAAs, and patients should consequently be screened for chronic concomitant medication use before initiating DAA therapy. The DDIs can be checked by consulting the University of Liverpool's HEP Drug Interactions Resource [81] and the Lexicomp database [82], or information from the summary of product characteristics approved by the EMA and the prescribing information approved by the US FDA [81,83].

Despite improvements in the pharmacokinetics of the new generation of DAAs, the frequency of DDIs remains stable. Consequently, patient medications should be carefully assessed to prevent adverse events or treatment failure [84].

7. Remaining challenges and future directions

7.1. Remaining challenges

Even if real-world observational studies indicate that more than 95% of patients with HCV achieve SVR with DAA

Table 4. Selection of common drugs frequently used with DAAs.

Drug class	SOF	LDV	OBV/PTV/r OBV	PTV	DSV	EBR/GZR EBR	GZR	VEL	VOX	GLE/PIB GLE	PIB
Immunosuppressants[59]											
Cyclosporine	↑	–	↔	↑	↑	↑	↑	↑	↑	↑	↑
Mycophenolate mofetil	–	–	•	–	–	↔	↓	–	–	•	–
Sirolimus	–	–	↔	↑	–	•	–	–	–	•	–
Tacrolimus	↑	–	•	↓	–	↔	↔	–	–	•	–
Cardiovascular[82]											
Amiodarone	↔	–	↑	↑	↑	↑	↑	–	–	•	–
Amlodipine	↔	–	↔	↓	–	↔	↔	–	–	•	–
Digoxin	↔	–	↔	–	–	•	–	–	–	•	–
Statins[81]											
Atorvastatin	↔	–	•	–	–	↑	–	–	–	•	–
Rosuvastatin	↔	–	↔	↑	–	↔	↔	–	–	•	–
Simvastatin	↔	–	↑	↑	↑	↑	↑	–	–	•	–
Acid-reducing agents[80]											
Famotidine	↔	↔	–	–	–	↔	↔	↔	–	•	–
Omeprazole	↔	↓	↔	↔	↔	•	–	↓	↔	↓	–
Pantoprazole	–	–	•	–	–	↔	↔	–	–	•	–
Antiretroviral agents[80]											
NRTIs											
ABC	–	↔	↔	↔	↔	•	–	–	–	↔	↔
FTC	↔	↔	•	–	–	↔	↔	↔	↔	–	–
TAF	–	↔	–	–	–	•	–	↔	↔	↔	↔
TDF	–	↔	–	–	–	↔	↔	↔	↑	•	–
3TC	–		–	–	–	–	–	–	–	•	–
Non-NRTIs											
EFV	↔	↔	–	–	–	↔	↔	–	–		
RPV	↔	↔	↑	↑	↑	↔	↔	↔	↔	↑	↑
Protease inhibitor											
ATV	–	↔	↔	↔	↔	↔	↑	–	–	•	–
DRV	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
LPV	–	–	↔	↔	↔	↔	↔	–	–	•	–
Integrase inhibitor											
DTG	–	↔	↑	↑	↑	↑	↔	–	–	•	–
EVG	–	↔	–	–	–	↔	↔	↔	↔	↔	↔
RAL	↔	↔	–	–	–	↔	↑	–	–	↑	↑
HBV[80]											
Tenofovir	↔	↓	↔	↔	↔	↔	↔	↑	↑	↔	↔

ABC- abacavir; **ATV**- atazanavir; **DRV**- darunavir; **DTG**- dolutegravir; **EBR**- elbasvir; **EFV**- efavirenz; **EVG**- elvitegravir; **FTC**- emtricitabine; **GLE**- glecaprevir; **GZR**- grazoprevir; **LDV**- ledipasvir; **LPV**- lopinavir; **NRTIS**- nucleoside or nucleotide reverse transcriptase inhibitors; **OBV**- ombitasvir; **PIB**- pibrentasvir; **PTV**- paritaprevir; **r**- ritonavir; **RAL**- raltegravir; **RPV**- rilpivirine; **SOF**- sofosbuvir; **TAF**- tenofovir alafenamide; **TDF**- tenofovir disoproxil fumarate; **3TC**- lamivudine; **VEL**- velpatasvir; **VOX**- voxilaprevir; ↑: increase in exposure; ↓: decrease in exposure; ↔: no change; – : data not available.

regimens, several challenges remain: to prevent viral resistance, to treat all genotypes, and to increase treatment access in low-resource countries and in special populations. Another emerging challenge is the limited screening programs for HCV, particularly in special populations such as PWID, MSM, or inmates. Significant efforts must be made worldwide to prevent and treat multidrug-resistant strains. Patients with decompensated liver cirrhosis and failure to DAAs still have no treatment option at this moment, as all PIs are contraindicated in these patients.

7.2. Potential future targets

All proteins that are indispensable for viral replication could represent new potential targets and the key to a fundamental strategy to prevent viral resistance. Combining inhibitors of different viral targets and host-related co-factors could block the development of multi-drug resistant strains. The most attractive future target is the small protein p7, which is implicated in different stages of the virus life cycle. This molecule was classified as viroporin because it has the ability to form ion channel structures. P7 inhibitors, such as N-carbamimidoyl-5-(1-methyl-1 H-pyrazol-4-yl)-2-naphthamide (BIT225), glycogen synthetase kinase 2 (GSK-2), and hexamethylamiloride (HMA) have been described [85–87]. BIT225 could represent a common treatment for HCV/HIV co-infected patients, because this molecule blocks p7 as well as some molecules involved in HIV replication. Host-targeting antivirals could also represent a potential target for HCV treatment. Furthermore, cyclophilin and miR-122 inhibitors have been identified as potential therapeutic targets.

Regardless of the potency of the currently developed antiviral drugs, they do not offer protection against re-infection. Preventing the virus from entering hepatocytes is an important goal that could concur with virus eradication. Neutralizing antibodies against host or viral proteins proved effective in animal models of chronic HCV infection [88]. A major challenge is the development of a vaccine that stimulates the T-cell response and produces neutralizing antibodies against viral lipoparticles. This vaccine will potentially decrease the re-infection rate in special populations, such as PWID or MSM.

DAA therapy decreases the progression of liver disease, although an increased risk of HCC remains after HCV eradication in patients with advanced liver fibrosis and comorbidities. Further studies are needed to complete the therapeutic arsenal of DAAs by combining different targets, such as viral structure, host characteristics, and comorbidities. Diabetes mellitus, metabolic syndrome, steatohepatitis, and CKD represent comorbidities that could negatively influence patients' evolution after achieving SVR. Future challenges include developing a personalized treatment regimen for such patients, targeting viral elements and host-related pathways involved in liver metabolism and fibrosis development.

Recognizing the mechanism linking liver fibrosis, carcinogenesis, and HCV infection will help us develop drugs with pleiotropic effects.

8. Expert opinion

The novel DAA regimens showing high effectiveness, safety, ease of administration, and less DDIs are appropriate for almost all types of HCV-infected patients, irrespective of age, comorbidities, co-infections, and stage of the disease. This has drastically changed the patient perspective on hepatitis C, from a disease that required careful evaluation and long-term observation to a disease that can be healed, in the

majority of cases, after one visit to the general practitioner. Expert hepatologists are now required only in complex cases to coordinate the battle with hepatitis C at other levels. Today, the great success of DAA regimens has moved the battle from the office and individual patient care to a global level. The WHO established a strategy for eliminating viral hepatitis as a health threat by 2030, setting specific goals and a timeline for eradication. Every physician involved in HCV care is invited to help in reaching this goal – a world without hepatitis C. Thus, DAA therapy has drastically transformed the way hepatitis C is understood and treated, thereby opening the door to a very ambitious medical goal – the worldwide elimination of HCV.

With the current DAA regimens, it is possible to obtain SVR in almost all patients with HCV. However, we still cannot find an appropriate regimen for a very small proportion of patients, who have previously failed under different DAA regimens and need new therapies, which are currently under research.

The difficult task of the HCV elimination program is to identify not only the infected patients but also the asymptomatic ones and treat 'those missing millions' population. Despite the attractive goal of completely eliminating a viral disease for the first time, we believe that we should appeal to the traditional way of eliminating an infectious disease, that is, through vaccination. The greatest unmet medical need in the field of HCV infection is the use of prophylactic vaccines. Unfortunately, research to discover a vaccine against this infection has received little attention in the past decade. We believe that medical research should focus on developing an effective HCV vaccine that could aid in the battle to eliminate HCV infection, especially in countries with high prevalence of HCV (e.g. Egypt) and in populations with a high rate of reinfection (PWID). Further research might also help to provide a solution to prevent the spread of super-virulent HCV strains from patients who faced multiple failures with DAA-based treatments. The recent success in discovering several severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) vaccines in less than a year, using different technologies, either new or traditional, has provided new hope that another disease caused by an RNA virus could soon be prevented by vaccination. The battle against HCV is not over!

8.1. Five years from now

Five years ahead, the landscape of HCV treatment will undoubtedly continue to evolve, and more pan-genotypic treatment options will be available to all patients. The current unmet therapeutic needs of patients, including those with decompensated liver cirrhosis, ESRD, and previous failures to DAA treatment will hopefully be addressed by further HCV-targeted research. However, the worldwide elimination of HCV infection within the time frame suggested by WHO is unlikely in the absence of vaccination, as it has now become clear that DAA treatment alone may not be sufficient to eradicate HCV.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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