

Eliminating hepatitis C within low-income countries – The need to cure genotypes 4, 5, 6

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Summary

Around 70 to 100 million people are chronically infected with HCV worldwide. HCV antiviral drug development has revolutionised the treatment of HCV, with several direct-acting antiviral agents offering patients the chance of cure after only 8–12 weeks of treatment. Drug development was initially focussed on HCV genotype 1 (GT1) infection, since this was the most prevalent worldwide, although clinical trials included all genotypes prevalent in the US and Europe. Because the earliest *in vitro* assays utilised the GT1b and 2 replicons, the initial classes of direct-acting antivirals (protease inhibitors, non-nucleotide polymerase inhibitors) were GT1-specific, albeit they had an effect on other less prevalent genotypes. Epidemiological data has shown the regional importance of other HCV genotypes. More than 50% of all HCV infections around the globe are not with GT1. The prevalence of HCV genotype 4 (GT4), 5 (GT5), and 6 (GT6) is increasing in North America and Europe due to migration from the Middle East, Africa and South-East Asia. With the successful development of the multi and pan-genotypic non-structural protein 5A inhibitors, second generation protease inhibitors and nucleotide non-structural protein 5B inhibitors comes a unique opportunity to achieve global HCV elimination. The goal of this review is to summarise the available information pertaining to GT4, GT5 and GT6, with a specific focus on direct-acting antiviral agents.

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Open research questions

There are still several open research questions which should be addressed by future studies:

- Although the numbers of patients infected with HCV genotype 4 (GT4), 5 (GT5) and 6 (GT6) recruited into phase II and III clinical trials has been small, the SVR rates achieved suggest that infections with these uncommon genotypes is easier to treat with DAAs than the more common HCV GT1 and GT3. Future studies should be designed to determine whether treatment can be shortened in HCV GT4, GT5 and GT6 non-cirrhotic treatment-naïve patients – *i.e.* reduce sofosbuvir-ledipasvir to eight weeks, glecaprevir-pibrentasvir to less than eight weeks.
- Studies of resistance-associated substitutions which pertain to HCV GT4, GT5 and GT6 and GT4 subtypes are needed.
- Further studies must elucidate the modes of transmission of HCV GT5 and identify measures to eliminate HCV GT5 in south west African countries.
- The impact of generic drugs on relapse rates, and their impact in poor countries should be monitored.
- Global trends in new HCV infections must be identified.

HCV genotype 4-5-6 epidemiology

HCV genotype 4

Among the 70 to 100 million HCV-infected subjects worldwide, HCV GT4 accounts for around

15% of those infected.^{1–3} HCV GT4 is most prevalent in the Middle East and sub-Saharan African regions, and accounts for most new infections in that region.^{2,3} In Egypt, where the prevalence of HCV is the highest in the world, the reuse of glass syringes during parenteral campaigns to control the endemic of schistosomiasis in the 1950–70s is widely held to be responsible for a large number of iatrogenic transmissions.⁴ Epidemiologic studies report an increase in the HCV GT4 infected population in Southern Europe and worldwide as a result of large-scale migration.⁵

HCV genotype 5

HCV GT5 accounts for about 1.4 million cases of HCV infection worldwide; with more than 80% of cases occurring in southern and eastern sub-Saharan Africa.² GT5 was first reported in South Africa.⁶ An analysis of blood donors and the general population in South Africa showed that overall GT5 was a prevalent genotype and accounted for 54% of HCV infections in Black South Africans.⁷ HCV GT5 has also been reported in some regions of Belgium, France, Spain, Greece, the Netherlands, Luxembourg and Syria.^{8–13} These unusual pockets of GT5 infection in Europe are among individuals who have not travelled. Modes of transmission among these patients are known in most cases.^{14,15}

HCV genotype 6

HCV GT6 represents about 1% of HCV infection worldwide and is found mainly in Southeast Asia

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Key point

Epidemiology: among the
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worldwide.

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Key point

Genotypes and natural history: the association between HCV genotype and disease progression is unclear and controversial. If there is a role for genotype, it appears to be minor.

Key point

Viral diversity: there is a high genetic diversity for GT4 and GT6, with at least 17 subtypes of GT4 reported, and 23 subtypes described for GT6. GT5 is highly conserved with only one subtype (GT5a).

and Southern China.¹⁶ GT6 accounts for 20–50% of HCV infections in Indochina (Laos), Cambodia, Thailand, Vietnam and Myanmar.¹⁷

A map representing HCV GT4, GT5, and GT6 distribution worldwide is provided (Fig. 1).

HCV genotype 4-5-6 diversity

There is high genetic diversity of GT4, with at least 17 subtypes of GT4 reported.¹⁸ The prevalence of these subtypes varies geographically. While GT4a predominates in Egypt, GT4d in the Middle East, non-4a and non-4d subtypes are the most commonly reported in Africa. Numerous subtypes of GT4 have been reported in several countries in Africa. There is a more heterogeneous distribution of GT4 subtypes in Europe, probably reflecting the diverse country of origin of the infected individuals.¹⁹ HCV GT5 is highly conserved, with only one subtype, 5a, identified until now,^{2,20} while GT6 is genetically diverse, with 23 subtypes described.¹⁷ Moreover, several HCV GT4 and GT6 subtypes have not been cloned, limiting *in vitro* testing for direct-antiviral agents (DAAs).

HCV genotype 4-5-6 natural history**HCV GT4**

We have to point out that data on GT4, GT5 and GT6 were not derived from typical studies of natural history, but rather from mainly cross-sectional or retrospective analyses. The association between HCV genotype and disease progression is unclear and controversial. If there is a role for genotype, it appears to be minor. In the era of interferon-based therapy, genotype was clinically relevant to predict treatment response and to select the duration of treatment.²¹ In the future, with pan-genotypic DAAs, the need for genotyping and subtyping might lose its importance.

A study to understand the natural history (and response to treatment) was performed in a large single centre cohort of 164 patients with HCV GT4 infection, from three different ethnic groups with 70 (43%) Egyptians, 53 (32%) Europeans, and 37 (23%) sub-Saharan Africans.²² More than 50% had significant fibrosis by liver biopsy. The genotype distributions for the single nucleotide polymorphism rs12979860 were significantly different between the three ethnic groups ($p < 0.0002$). Frequencies of the C allele were 61.4%, 54.7%, and 31.0% for patients of Egyptian, European and sub-Saharan African origin, respectively. Univariate analysis showed no relationship with fibrosis and either age at therapy, gender, obesity (body mass index), baseline viral load or viral genotype (4a vs. other subtypes). Moreover, no significant relationship between IL28B rs12979860 and fibrosis stage was observed. In contrast, a significant relationship was observed between fibrosis and alcohol consumption

(a higher consumption linked to fibrosis) and ethnicity (lower rate of fibrosis for sub-Saharan African patients).²² In a multivariate analysis, these two factors showed a significant effect providing additional, non-redundant information on fibrosis progression.

HCV genotype 5

Due to their relatively low prevalence, the natural history and results of treatment of GT5 and GT6 are less well known. In some regions, patients infected with GT5 are generally older, have higher viral loads, and have cirrhosis more frequently than patients infected with other genotypes.²³

HCV genotype 6

HCV GT6 long-term infection appears to be associated with the similar risk of cirrhosis and liver-related complications as HCV GT1 infection.²⁴ The effects of environmental factors known to be found in South East Asia, which are associated with hepatocarcinogenesis in patients with chronic HBV infection (aflatoxin, alcohol, smoking) are not well studied in chronic HCV.

Historical treatment: pegylated interferon plus ribavirin**HCV genotype 4**

HCV GT4 has been considered “difficult to treat” with pegylated interferon (PegIFN) and ribavirin (RBV) treatment, with sustained virological response (SVR) rates around 50%.¹⁹ The SVR rates reported in the real-life Prophesys study with PegIFN and RBV therapy for 48 weeks were poor for patients with GT4 infection (SVR at 24 weeks [SVR24] in 41% of 317 patients).²⁵ Among patients with HCV GT4 infections who achieved rapid virological response ($n = 30$), when treated with PegIFN-RBV for 24 weeks, 80% achieved SVR.²⁶

A major predictor of response to PegIFN-RBV therapy in patients with HCV GT4 was the IL28B genotype.²² SVR rates for IL28B rs12979860 CC patients ranged from more than 80% to around 30% for TT patients. Egyptian patients infected with HCV GT4, treated with PegIFN-RBV in Europe, responded better than French/European or African patients infected with the same genotype. A better overall response was observed in patients infected with the HCV GT4 subtype 4a, which was the predominant subtype among patients infected in Egypt compared to patients from sub-Saharan Africa who were infected with diverse subtypes. In France, the patient population infected with HCV GT4 is diverse (sub-Saharan Africans, Caucasians, Egyptians). The distribution of IL28B polymorphism in different ethnicities appears to be the explanation for this difference in terms of SVR. A simple scoring system has been proposed to identify patients infected with GT4 who have a high probability of achieving an SVR with dual PegIFN alfa-2a plus RBV therapy.²⁷

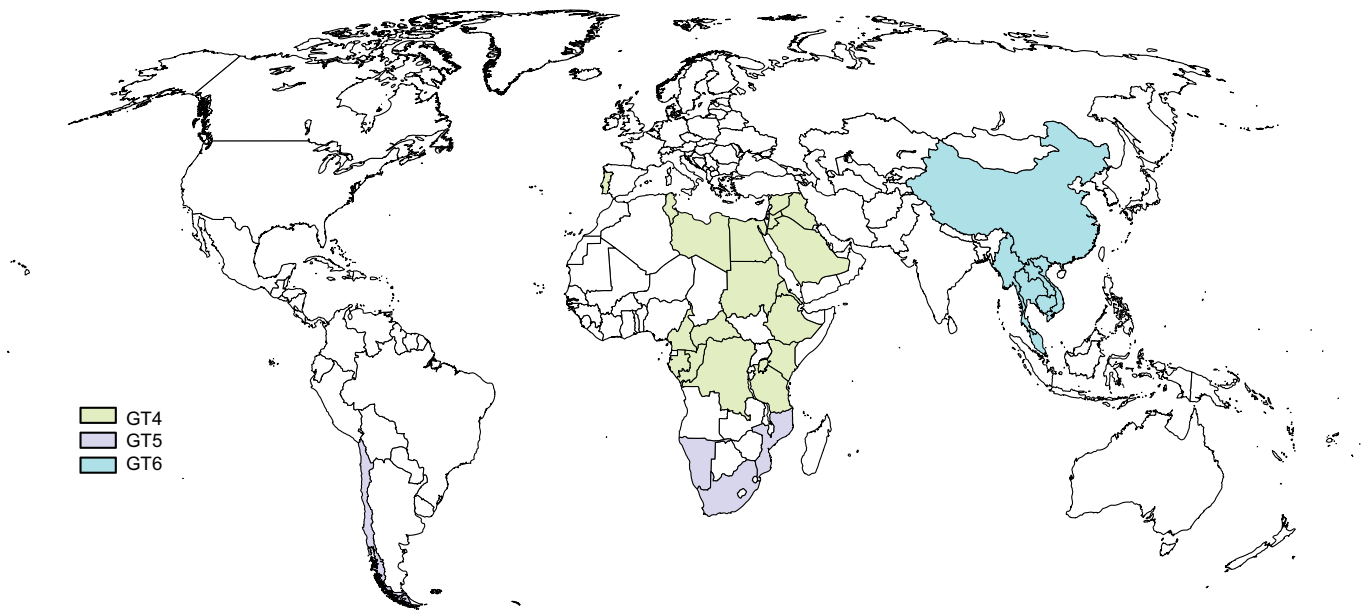


Fig. 1. HCV GT4, GT5, and GT6 distribution worldwide. HCV GT4, GT5, and GT6 infect an estimated 30 million people worldwide and account for approximately 20% of global HCV infections.

HCV genotype 5

In the real-life Prophesys study, SVR rates of 67% were reported for patients with HCV GT5 treated with PegIFN and RBV therapy for 48 weeks (however, the sample size was small: 10 of 15 [67%] patients with HCV GT5 reached SVR24).²⁵

A meta-analysis of ten studies including a total of 423 patients, confirmed similar SVR rates.²⁸

Genotype 6

In the real-life Prophesys study, SVR rates of 80% were reported for patients with HCV GT5 treated with PegIFN and RBV therapy for 48 weeks (however, the sample size was very small; 8 of 10 [80%] patients with HCV GT6 reached SVR24).²⁵

A meta-analysis of 13 studies with 641 patients, confirmed similar SVR rates.²⁹

Direct-acting antivirals: mechanisms of action

HCV, identified in 1989, is an enveloped virus with a 9.6 kb single-stranded RNA genome, belonging to the genus *Hepacivirus*, a member of the *Flaviviridae* family.³⁰ The development of a subgenomic HCV RNA replicon capable of replication in the human hepatoma cell line, HuH7, has been a major advance.^{31,32} Replicon-based systems improved our understanding of HCV replication, and enabled evaluation of potential DAAs for efficacy and resistance. The HCV replication cycle starts with virion attachment to its specific receptor. The HCV RNA genome serves as a template for viral replication and as viral messenger RNA for viral production. It is translated into a polyprotein that is cleaved by proteases. Subsequently, viral assembly occurs.

In 2002, the proof-of-concept for the first DAA (a protease inhibitor) was reported.^{33,34} All the HCV enzymes (non-structural protein 2/3 and non-structural protein 3/4A [NS3/4A] proteases, non-structural protein 3 [NS3] helicase and non-structural protein 5B [NS5B] RNA-dependent RNA polymerase) are essential for HCV replication, and are therefore potential drug discovery targets. In addition, DAAs targeting non-structural protein 5A (NS5A) have been developed³⁵ over the last fifteen years.

DAAs with different viral targets (NS3 protease inhibitors, nucleoside/nucleotide analogues and non-nucleoside inhibitors of the RNA-dependent RNA polymerase and NS5A inhibitors) have been developed³⁶ in combination and lead to higher efficacy, reduced risk of resistance and shorter treatment duration (Fig. 2A).

Protease inhibitors

The NS3 serine protease, located in the N-terminal region of NS3, associates with the non-structural protein 4A cofactor to cleave four specific sites on the HCV polyprotein. This enzyme has been characterised biochemically and its structure has been established.^{37,38} The serine protease activity of NS3 is an interesting target for drugs that could effectively block viral replication. The NS3/4A protease inhibitors can be divided into two classes: macrocyclic inhibitors and linear tetra-peptide a-ketoamide derivatives.

In 2003, a macrocyclic protease inhibitor (BILN 2061; faldaprevir) that blocks HCV replication in the replicon model demonstrated efficacy in humans.^{33,34} The main weaknesses of the first-generation PIs (boceprevir, teleprevir, and simeprevir) were their low genetic barrier to

Key point

Recent development of pan-genotypic DAA regimens, provide safe and effective treatment for patients infected with GT4, GT5 or GT6.

resistance and the fact that their effectiveness was limited to patients with GT1 infections³⁹

The genetic barrier to resistance is defined as the number of amino acid substitutions required to confer full resistance to a drug. Usually, DAA with a low genetic barrier to resistance require only one or two amino acid substitutions for high resistance. DAA with a high barrier to resistance usually require three or more amino acid substitutions in the same region to confer loss of activity. Second generation PIs have a higher barrier to resistance, better potency against multiple genotypes, more convenient dosing schedules and improved safety and tolerability. In combination with DAAs with different mechanisms of action, these new PIs appear to achieve greater SVR rates than the first-generation PIs.

Polymerase inhibitors

Nucleoside polymerase inhibitors in their 5'-triphosphate form interfere with viral replication by binding to the NS5B RNA-dependent RNA polymerase. There are two different classes of NS5B RNA polymerase inhibitors: nucleoside inhibitors (NI) and non-nucleoside inhibitors (NNI).

NI mimic the natural substrates of the polymerase and are therefore incorporated into the RNA chain, leading to direct chain termination.⁴⁰ NI require bioconversion to an active triphosphate form in the hepatocyte. Since the active site of NS5B is highly conserved, NI are usually pan-genotypic. However, single amino acid substitutions in every position of the active site may result in loss of function of the NI, but resistance to nucleoside analogue inhibitors is rare since these substitutions reduce fitness.

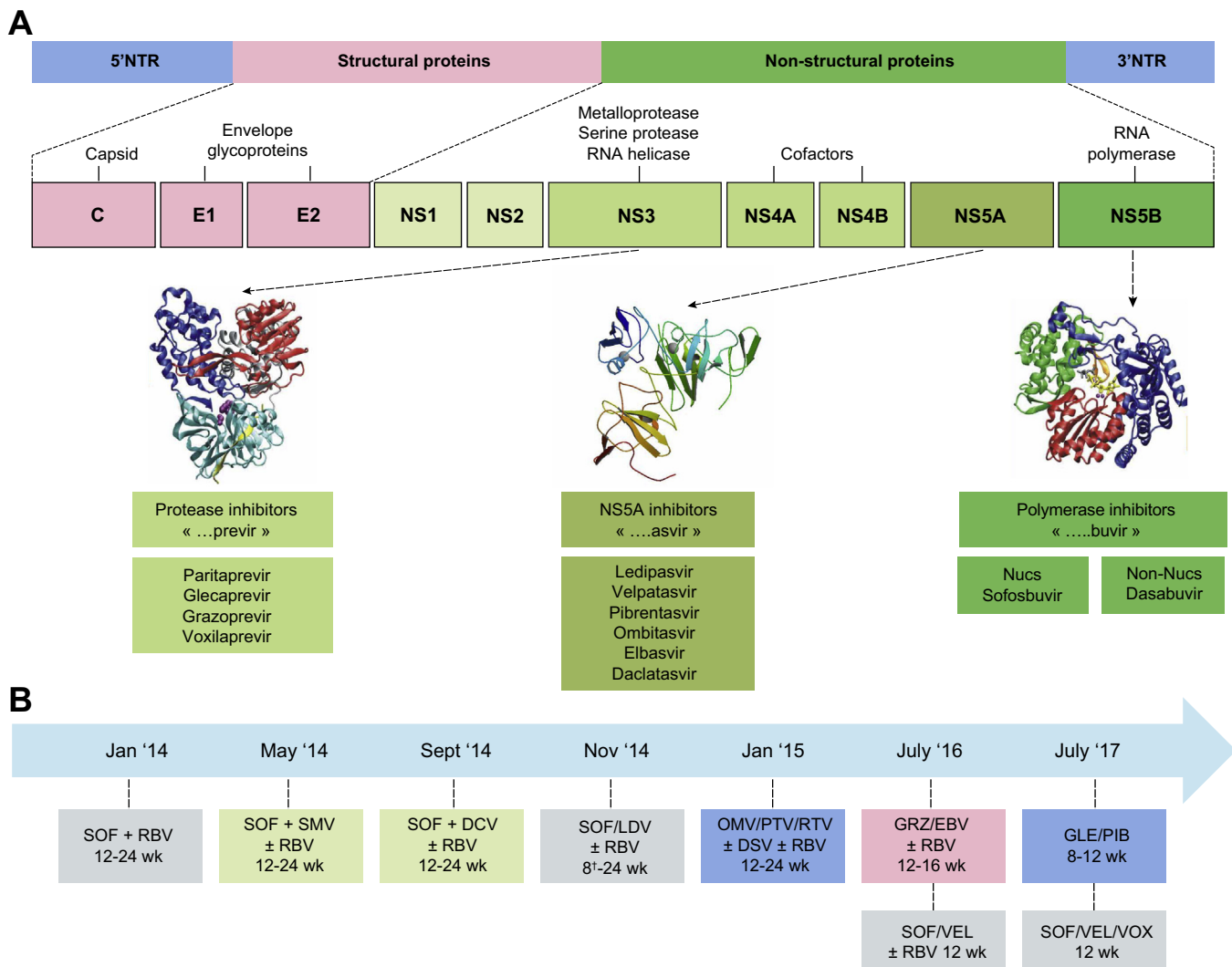


Fig. 2. Mode of action of DAAs and developmental milestones of approved direct-acting antivirals. (A) DAA with different viral targets (NS3 protease inhibitors, nucleoside/nucleotide analogues and non-nucleoside inhibitors of the RNA-dependent RNA polymerase and NS5A inhibitors) have been developed in combination and leads to high efficacy, reduced risk of resistance and shorten treatment duration. (B) Development milestones of approved DAAs. DAA, direct-acting antiviral; NS, non-structural protein.

In contrast, allosteric NNI bind to several discrete sites outside of the HCV polymerase active site, which results in conformational protein change before the elongation complex is formed.⁴⁰ NS5B is structurally organised in a characteristic 'right-hand motif', containing finger, palm and thumb domains, and offers four main NNI-binding sites (benzimidazole [thumb 1], thiophene [thumb 2], benzothiadiazine [palm 1] and benzofuran [palm 2]). Resistance is more frequent with NNI than NI treatment. Moreover, mutations at NNI-binding sites do not necessarily lead to impaired function of the enzyme.

NS5A inhibitors

The NS5A is a membrane-associated phosphoprotein present in basally phosphorylated (p56) and hyperphosphorylated (p58) form.^{35,41} It has been reported that only p58-defective mutants could be complemented in *trans*, and NS5A is involved in HCV virion production, suggesting that different forms of NS5A exert multiple functions at various steps of the viral replication cycle.^{35,41}

The N terminus of NS5A (domain I) has been crystallised in alternative dimeric forms and contains both zinc- and RNA-binding domains, properties that have been demonstrated *in vitro*. NS5A has been shown to interact with a number of host proteins and plays a role in interferon resistance *in vivo*.^{35,41} Furthermore, NS5A inhibitors could block hyperphosphorylation of NS5A, which is believed to play an essential role in the viral replication cycle.

Development milestones of approved DAAs are provided (Fig. 2B).

Efficacy of direct-acting antivirals in genotype 4-5-6

Direct-acting antivirals for HCV genotype 4 infection

The efficacy of different DAAs in the treatment of HCV GT4 infection is summarised (Table 1).

Historical perspectives: DDAs in HCV genotype 4

In the early development phases of DAAs, daclatasvir in a daily dose of 60 mg in combination with PegIFN and RBV led to an SVR24 rate of 100% in 12 patients with HCV GT4 infection,⁴² and sofosbuvir plus PegIFN and RBV for 12 weeks resulted in a 96% SVR rate in 28 treatment-naïve patients with GT4 infection.⁴³ The addition of simeprevir to PegIFN and RBV, in a response-guided therapy, has also increased SVR.⁴⁴

Interferon-free sofosbuvir-RBV was used for 12 or 24 weeks in clinical trials in Egyptian patients with GT4 infection, in the US⁴⁵ and Egypt.⁴⁶ Twelve-week treatment was associated with suboptimal response (SVR at 12 weeks [SVR12] 68%–77%) and treatment for 24 weeks was associated with SVR rates of 90%–93%. Real-world results from patients treated in the national

treatment programme in Egypt showed lower response rates in patients treated with sofosbuvir-RBV for 24 weeks (78.7% of 5,667 patients) and a 94% SVR12 among 8,742 patients treated with sofosbuvir and PegIFN plus RBV for 12 weeks.⁴⁷ These regimens are no longer recommended, and no longer in use because of interferon-related adverse events or suboptimal response rates.

Clinical trials of interferon-free sofosbuvir-simeprevir for 12 weeks showed SVR12 rates of 100% in patients with HCV GT4, with or without compensated cirrhosis in Spain⁴⁸ and Egypt,⁴⁹ whereas shortening treatment to eight weeks in patients without cirrhosis reduced response to only 75%.⁴⁹ Real-world results of using this combination for 12-weeks resulted in an overall SVR12 rate of 94%.⁵⁰

Although very limited data was available on the combination of sofosbuvir-daclatasvir in patients with HCV GT4 (four patients in the ALLY-1 trial,⁵¹ three with HIV co-infection in ALLY-2⁵² and 19 with advanced liver disease in a real-world report from Europe⁵³) all achieved SVR12. The national treatment programme in Egypt has treated large number of patients using sofosbuvir-daclatasvir for 12 weeks (with added RBV for treatment-experienced patients or patients with advanced fibrosis). Real-world results from the first 18,378 patients treated with this combination showed an overall SVR12 rate of 95% (95.4% in patients treated without RBV and 94.7% in patients treated with RBV).⁵⁴

Sofosbuvir-ledipasvir

The HCV NS5B uridine nucleotide polymerase inhibitor, sofosbuvir, has nanomolar *in vitro* activity against all HCV genotypes. It has a favourable safety profile, and a high genetic barrier to resistance. The HCV NS5A inhibitor, ledipasvir, has nanomolar *in vitro* activity against HCV GT1, 4, 5 and 6. In a phase II, open-label study, 44 patients (22 treatment-naïve and 22 treatment-experienced) received ledipasvir and sofosbuvir orally once daily for 12 weeks.⁵⁵ Among study participants, HCV GT4 subtypes were well represented. Ten patients (23%) had compensated cirrhosis. All 44 patients completed the full 12 weeks of dosing. The SVR12 rate was 93% (41 of 44; 95% CI 81–99). SVR12 rates were similar between treatment-naïve (95%; 21 of 22) and treatment-experienced (91%; 20 of 22) patients. All three patients who did not achieve SVR12 had virological relapse within four weeks of the end of treatment; all three had baseline HCV RNA >800,000 IU/ml, a non-CC IL-28B genotype, and pretreatment NS5A resistance-associated variants. None of the patients who relapsed had cirrhosis.

Phenotypic assessment of 56 HCV NS5A patient isolates from various GT4 subtypes indicated that ledipasvir had high potency for the common subtypes 4a/d, and subtypes 4c/f/k/l/m/n/o/p/r/t, despite the presence of resistance-associated

Table 1. Trials of direct-acting antivirals for HCV GT4, GT5, and GT6.

HCV GT4 infection					
Regimen	Type	Population	Duration (wks)	SVR12	Ref.
SOF-LDV	Phase II, open label	44	12	93%	⁵⁵
SOF-LDV	Phase II, open label	21	12	95%	⁵⁷
SOF-LDV	Phase III	255	8/12	95/98%	⁵⁸
SOF-VEL	Phase III, randomised	116	12	100%	⁵⁹
SOF-VEL-VOX	Phase III, randomised	63/53	8/12	92/100%	⁶¹
OBV-PTV	Phase IIb, randomised	42 (with RBV)	12	100%	⁶²
		44 (without RBV)		91%	
OBV-PTV-RBV	Phase III, randomised	59 cirrhotics	12	97%	⁶³
		61 cirrhotics	16	96%	
OBV-PTV-RBV	Phase III, randomised	100 non-cirrhotics	12	94%	⁶⁴
		60 cirrhotics	12/24	97/93%	
GLE-PIB	Phase II/phase III	46	8	93%	⁶⁶
		76	12	99%	
EBV-GRZ	Pooled analysis	111 naïve	12	96%	⁶⁸
		8 experienced	16	100%	
HCV GT5 infection					
Regimen	Type	Population	Duration (wks)	SVR12	Ref.
SOF-LDV	Phase II, open-label	21 naïve	12	95%	⁷²
		20 experienced		95%	
SOF-VEL	Phase III, assigned to SOF/VEL	24 naïve	12	96%	⁵⁹
		11 experienced		100%	
SOF-VEL/VOX	Phase III,	18	8	94%	⁶¹
GLE-PIB	Phase III, phase II	2	8	100%	⁶⁶
		26	12	100%	
HCV GT6 infection					
Regimen	Type	Population	Duration (wks)	SVR12	Ref.
SOF-LDV	Phase II, open label	25	12	96%	⁷³
SOF-LDV	Phase II	45	8/12	95/100%	⁷⁴
SOF-VEL	Phase III, randomised	38	12	100%	⁵⁹
SOF-LDV-VOX	Phase III, randomised to 12 wks of SOF/LDV	30/9	8/12	100/100%	⁶¹
GLE-PIB	Phase III; phase II	10/19	8/12	90/100%	⁶⁶

DCV, daclatasvir; DSV, dasabuvir; EBV, elbasvir; GLE, glecaprevir; GRZ, grazoprevir; GT, genotype; LDV, ledipasvir; OMV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; RTV, ritonavir; SOF, sofosbuvir; SVR12, sustained virological response at 12 weeks; VEL, velpatasvir; VOX, voxilaprevir.

Key point

Data regarding these specific patient populations are now available, although the number of patients remains low.

substitutions (RASs).⁵⁶ For the rare GT4b, ledipasvir median EC₅₀ was higher, but with a broad range of individual values. Importantly, all GT4b isolates tested had 2–4 NS5A RASs, some including Y93H. Similarly, the two patients infected with HCV GT4r who had virologic relapse had rare triple RASs. Reversion of these substitutions to the consensus residue significantly increased ledipasvir susceptibility.

Another study performed in the US, showed similar results; in 21 treatment-naïve and experienced patients infected with HCV GT4, 12 weeks of ledipasvir and sofosbuvir resulted in an SVR rate of 95% (20 of 21).⁵⁷

A study performed in Egypt included 255 patients infected with GT4, where 170 treatment-naïve patients were randomised to sofosbuvir-ledipasvir treatment for 8 or 12 weeks, with or without RBV, and 85 treatment-experienced patients to treatment for 12 weeks with or without RBV.⁵⁸ Among treatment-naïve patients treated for 12 weeks, SVR12 rates were 98%, irrespective of RBV intake, and among those treated for eight weeks, SVR12 rates were 95% without RBV, and 90% with RBV. All treatment-experienced patients treated for 12 weeks with

RBV (including 11 sofosbuvir-experienced patients), and 34 of 36 patients treated without RBV responded to treatment.

Sofosbuvir-velpatasvir

Velpatasvir is a new pan-genotypic HCV NS5A inhibitor with picomolar *in vitro* antiviral activity against HCV GT1–6 and most NS5 resistance-associated variants. In the phase III ASTRAL-1 trial, treatment-naïve and treatment-experienced patients with chronic HCV GT1, GT2, GT4, GT5, or GT6 infections were randomised in a 5:1 ratio to receive a 12-week course of either sofosbuvir-velpatasvir or placebo.⁵⁹ All 116 patients with HCV GT4 treated with sofosbuvir-velpatasvir achieved SVR.

We recently analysed 501 patients from three large phase III trials (ASTRAL-1, -2, and -3) with compensated cirrhosis (Metavir F4) or advanced fibrosis (F3) who received sofosbuvir-velpatasvir for 12 weeks. Again all 60 patients with HCV GT4 infection achieved SVR.⁶⁰ In GS-US-342-1138, all patients achieved SVR12, regardless of their subtype or presence of RASs. *In vitro* data confirmed that velpatasvir is potent against all GT4 isolates tested.⁵⁶

Sofosbuvir-velpatasvir-voxilaprevir

Voxilaprevir is a macrocyclic, pan-genotypic inhibitor of the NS3/4A protease with picomolar antiviral activity against HCV GT1–6 and an improved resistance profile in comparison to earlier protease inhibitors.

The POLARIS-2 trial enrolled patients infected with all HCV genotypes. Compensated cirrhosis was allowed except for patients with HCV GT3 infection.⁶¹ Patients received either a fixed-dose combination of 400 mg of sofosbuvir, 100 mg of velpatasvir, plus 100 mg of voxilaprevir once daily for eight weeks or a fixed-dose combination of 400 mg of sofosbuvir plus 100 mg of velpatasvir once daily for 12 weeks. The overall SVR rate was 95% for the eight week three-DAA regimen and 98% for the 12 week two-DAA regimen. Hence, the primary efficacy endpoint of non-inferiority (5% margin) was not met.

The SVR rate for GT4 was 94% for the eight week three-DAA regimen and 98% for the 12 week two-DAA regimen.

Paritaprevir-ritonavir-ombitasvir

Ombitasvir is a potent NS5A inhibitor and is co-formulated with paritaprevir, a potent NS3/4A protease inhibitor; paritaprevir is co-dosed with ritonavir to increase drug exposures. In a phase IIb study (Pearl study), 100% of patients (n = 91) with HCV GT4 infection, without cirrhosis, achieved SVR when treated with ombitasvir, paritaprevir, and ritonavir plus RBV for 12 weeks.⁶² In this study of patients with GT4 infection, 100% of patients (n = 42) and 91% of patients (40 out of 44) achieved SVR when treated with paritaprevir-ritonavir-ombitasvir for 12 weeks plus RBV or without RBV, respectively. In a phase III, multicentre, randomised open-label trial, (Agate-I study) 120 patients with HCV GT4 infection and compensated cirrhosis in North America and Europe received paritaprevir-ritonavir-ombitasvir with weight based RBV for 12 weeks or 16 weeks; 97% of patients achieved SVR in the 12-week group and 98% achieved SVR in the 16-week group.⁶³ With high proportions of patients achieving SVR12, no posttreatment relapses, and a similar adverse event profile for the 12-week and 16-week treatment groups, 16-week treatment seems to provide no added benefit for patients with HCV GT4 infection and compensated cirrhosis.

The companion AGATE-II study provides additional evidence of high efficacy (94–97%) of paritaprevir-ritonavir-ombitasvir plus RBV in patients with HCV GT4 infection, with or without cirrhosis, in Egypt.⁶⁴

Glecaprevir-pibrentasvir

Glecaprevir is a potent NS3/4A protease inhibitor with nanomolar antiviral activity against HCV GT1–6 and most known NS3 RASs. Pibrentasvir is an NS5A inhibitor with picomolar antiviral activity

against HCV GT1–6 and most NS5A RASs. This fixed-dose combination demonstrates synergistic antiviral activity and a high barrier to resistance.⁶⁵

The efficacy and safety of eight-week and 12-week glecaprevir-pibrentasvir treatment in non-cirrhotic patients with HCV GT4, GT5 or GT6 infections were reported recently (Surveyor-II, Part 4 and Endurance-4).⁶⁶

The SVR12 rate (intention-to-treat population) in patients with GT4 infection treated for 12 weeks and eight-weeks was 99% (75/76) and 93% (43/46), respectively, with no virologic failures. The SVR12 rate (modified intention-to-treat population) was 100% (75/75) for 12 weeks, and 100% (43/43) for eight-weeks.

Elbasvir-grazoprevir

Elbasvir, an NS5A inhibitor, and grazoprevir, an NS3/4A protease inhibitor, have demonstrated high *in vitro* potency against HCV GT4 replicons, as well as RASs that confer resistance to first-generation protease inhibitors and RASs related to treatment failures on daclatasvir and ledipasvir.⁶⁷

We conducted an integrated analysis to assess the efficacy of the once-daily combination of elbasvir 50 mg and grazoprevir 100 mg, with and without RBV in patients with HCV GT4 infections, enrolled in the phase II/III clinical programme with elbasvir-grazoprevir.⁶⁸

Overall, among patients treated with 12 or 16 weeks of elbasvir-grazoprevir ± RBV, the SVR12 efficacy rates were 96.4% (107/111) in treatment-naïve patients and 88.6% (39/44) in treatment-experienced patients. The SVR12 rates were 96.0% (97/101) in treatment-naïve patients treated with 12 weeks of elbasvir-grazoprevir, and 100% (8/8) in treatment-experienced patients treated with 16 weeks of elbasvir-grazoprevir plus RBV.⁶⁸ Efficacy was not impacted by subtype. Finally, the regimens of 12 weeks of elbasvir-grazoprevir without RBV, and 16 weeks of elbasvir-grazoprevir plus RBV were efficacious in treatment-naïve and treatment-experienced patients with HCV GT4 infection, respectively. Baseline NS5A RASs did not affect the efficacy of elbasvir-grazoprevir in patients with GT4 infections.

We must recall that elbasvir-grazoprevir for 12 weeks had a low rate of adverse events and was effective in patients infected with HCV who had stage 4–5 chronic kidney disease.⁶⁹ Effectiveness and safety of elbasvir-grazoprevir in patients with chronic hepatitis C and chronic kidney disease has recently been confirmed in a real-world setting, with results from the Veterans Affairs System.⁷⁰

An ongoing multi-site, open-label, partially randomised trial of the efficacy and safety of elbasvir-grazoprevir in French subjects with chronic HCV GT4 infection is evaluating an eight-week treatment duration (NCT03111108).

Ravidasvir

To date, only one trial has been performed with ravidasvir. Carried out in Egypt, it concluded that treatment with ravidasvir plus sofosbuvir, with or without RBV, was well-tolerated and associated with high SVR rate for patients infected with HCV GT4, with and without cirrhosis, regardless of previous interferon-based treatments.⁷¹ Confirmatory studies are needed.

Direct-acting antivirals for HCV genotype 5 infection

The efficacy of different DAAs in HCV GT5 infection is summarised (Table 1).

Sofosbuvir-ledipasvir

In a phase II, open-label study conducted in France, 21 treatment-naïve and 20 treatment-experienced patients with HCV GT5 infection were enrolled to receive a 12-week course of ledipasvir-sofosbuvir.⁷² For the treatment-naïve patients with GT5 infection, 20 of 21 (95%) achieved an SVR12. For the treatment-experienced patients with GT5 infection, 19 of 20 (95%) achieved an SVR12. Ten patients had compensated cirrhosis and all achieved SVR12.

Sofosbuvir-velpatasvir

In the phase III ASTRAL-1 trial, because of the low prevalence of GT5 in the study regions, patients with GT5 did not undergo randomisation but were assigned to the sofosbuvir-velpatasvir group.⁵⁹

Among the treatment-naïve patients treated with sofosbuvir-velpatasvir, 23 of 24 (96%) with GT5 infection achieved an SVR12. Among the treatment-experienced patients treated with sofosbuvir-velpatasvir, 11 of 11 (100%) achieved an SVR12.⁵⁹

Sofosbuvir-velpatasvir-voxilaprevir

In the POLARIS-2 trial, for the patients with GT5 infection treated for eight weeks, 17 of 18 (94%) achieved an SVR12. No patients were treated in the 12-week arm.⁶¹

Glecaprevir-pibrentasvir

Efficacy of eight-week glecaprevir/pibrentasvir treatment and 12-week treatment in non-cirrhotic patients with HCV GT4, GT5 or GT6 infections were reported recently (Surveyor-II, Part 4 and Endurance-4).⁶⁶

Eight weeks of treatment led to SVR in 2/2 patients (100%); and twelve weeks of treatment led to SVR in 26/26 patients (100%).⁶⁶

Direct-acting antivirals for HCV genotype 6 infection

The efficacy of different DAAs in HCV GT6 infection is summarised (Table 1).

Sofosbuvir-ledipasvir

In an open-label, phase II study (LEPTON) performed in New Zealand, 25 treatment-naïve and

treatment-experienced patients with HCV GT6 infection received ledipasvir-sofosbuvir for 12 weeks.⁷³ Overall, 24 of the 25 patients (96%) achieved an SVR12. The one patient in this cohort who did not achieve an SVR12 dropped out of the study at week 8. Only two of the treatment-naïve patients with GT6 had cirrhosis.

In a US study, 45 patients with HCV GT6 infection without cirrhosis were treated with ledipasvir-sofosbuvir for either eight or 12 weeks. All 25 patients treated for 12 weeks and 19/20 treated for only eight weeks achieved SVR. In the same study, 15 patients with HCV GT6 infection and cirrhosis were treated with ledipasvir-sofosbuvir for 12 weeks and 13 achieved SVR.⁷⁴

Sofosbuvir-velpatasvir

In the phase III ASTRAL-1 trial, among the treatment-naïve patients treated with sofosbuvir-velpatasvir, all 38 patients with GT6 infection achieved an SVR12, including all three treatment-experienced patients.⁵⁹ Treatment history, cirrhosis status and GT6 subtype (6a/b vs. 6c-l vs. 6 other) did not affect SVR rate.

Sofosbuvir-velpatasvir-voxilaprevir

In the Polaris II study, all 30 patients with GT6 infections treated with sofosbuvir-velpatasvir-voxilaprevir for eight weeks achieved SVR, as did all nine GT6 patients treated with sofosbuvir-velpatasvir for 12 weeks.⁶¹

Glecaprevir-pibrentasvir

In Surveyor-II, Part-4, 9 of 10 patients (90%) with HCV GT6 infection, treated with glecaprevir-pibrentasvir for eight weeks achieved an SVR12.⁷⁵ In Surveyor-1 and in Endurance-4, all 30 patients without cirrhosis with HCV GT6 infection treated with glecaprevir-pibrentasvir for 12 weeks achieved SVR.⁶⁶

To increase the body of data for GT5 and GT6, an open-label, multicentre study is evaluating the safety and optimum duration of glecaprevir-pibrentasvir in 80 patients with HCV GT5 and GT6 infections (NCT02966795). This phase IIIb study included patients with or without compensated cirrhosis and both treatment-naïve and treatment-experienced patients (who had failed either PegIFN with or without RBV or sofosbuvir plus RBV with or without PegIFN).

Finally, what are the clinical benefits obtained by achieving SVR?

A remarkable revolution has recently been achieved with the availability of DAAs offering a high chance of cure and good tolerability. The primary goal of treatment is to achieve an SVR defined as undetectable serum HCV RNA 12 weeks after the end of treatment.⁷⁶ An SVR has been shown to be durable on long-term follow-up and associated with the eradication of HCV infection, confirmed by undetectable HCV RNA in serum

Key point

The availability of pan-genotypic DAAs with excellent efficacy and good tolerability offers the unique opportunity to achieve HCV elimination worldwide.

and the liver.⁷⁷ An SVR indicates that viral infection has been cured.

In addition, viral eradication is associated with the regression of fibrosis, arresting of the progression of cirrhosis to decompensated cirrhosis, and significant improvement in clinical outcome and survival with a decreased incidence of complications, especially hepatocellular carcinoma (HCC).

Protease inhibitors are contra-indicated in patients with decompensated cirrhosis. Treatment with sofosbuvir-velpatasvir with or without RBV for 12 weeks resulted in high rates of SVR in patients with HCV infection and decompensated cirrhosis, and tolerability is favourable.⁷⁸ Moreover, patients with HCV chronic infection and compensated or decompensated cirrhosis who achieve SVR can have clinically meaningful reductions in hepatic venous pressure gradient at long-term follow-up.⁷⁹ The survival benefit conferred by DAAs in patients with decompensated cirrhosis was recently confirmed. Observed incidence of deaths in patients with hepatic decompensation in the SOLAR studies was compared with mortality predicted by survival models derived from patients with HCV and hepatic decompensation in the pre-DAA era. It showed that DAAs significantly reduced mortality risk in patients with decompensated HCV cirrhosis, by as much as 60% within the first year of therapy.⁸⁰

Treating the underlying disease with newly developed DAAs often improves perceived fatigue and patient-reported outcomes.⁸¹ Healthy lifestyle changes are the cornerstone of treatment. The impact of SVR on morbidity and mortality are well recognised, although the true economic and social benefits can only be estimated on the assumption that HCV cure is not complicated by progression of the disease.

Staging of disease either clinically or by laboratory analysis or radiologic approaches remains a key part of HCV management. Diagnostic tools are under development to better diagnose advanced fibrosis.⁸² Patients with advanced cirrhosis will require continued care despite viral cure. The risk of HCC in patients with cirrhosis is reduced but not eliminated; patients treated with DAAs should continue to be closely monitored for HCC (ultrasound every six months). Surveillance is also advocated in patients who achieve SVR with any histological stage of hepatitis C who carry comorbidities such as alcohol consumption, diabetes and obesity, which are independent risk factors for HCC. Given the current controversy, until controlled clinical trials provide evidence of benefit or possible detriment, treatment is recommended for patients with cirrhosis to reduce the risk of progression of the underlying liver disease.

Conclusion: what are the gaps to achieve HCV elimination worldwide?

HCV GT4, GT5 and GT6 infections constitute almost one-quarter of all HCV infections globally

and are the predominant infections in the Middle East, Africa and South-East Asia, respectively. However, development of non-IFN therapies which are active against HCV GT4, GT5, and GT6 has been slow, reflecting not only the lack of *in vitro* replication models, but also the low (<5%) prevalence of these genotypes in high-income countries where the pharmaceutical companies have targeted GT1. However, the greatest unmet medical need in high-income countries is now patients infected with GT3. This has driven the recent development of pan-genotypic DAA regimens, which also provide safe and effective treatment for patients infected with GT4, GT5 or GT6.

HCV GT4, GT5 and GT6 have been neglected in the past, for many reasons, including the low prevalence in high-income countries where the DAAs have been developed. Data regarding these specific patient populations are now available, although the number of patients remains low. Guidelines will help the physicians to manage patients. The American Association for the Study of Liver Diseases/Infectious Diseases Society of America and the European Association for the Study of the Liver guidelines for HCV GT4, GT5 and GT6 are updated regularly.^{83,84} For HCV GT5 and GT6 infection, sofosbuvir-velpatasvir, sofosbuvir-ledipasvir, for 12 weeks are recommended. Glecaprevir-pibrentasvir has recently been approved as a pan-genotypic therapy for eight weeks in non-cirrhotic patients, and 12 weeks for compensated cirrhotic patients.

Treatment with DAAs result in high rates of cure in people who injects drugs (PWID) (Fig. 3). A first study has demonstrated that patients with HCV infection who were receiving opioid agonist therapy and treated with DAAs (elbasvir-grazoprevir) had high rates of SVR12, regardless of ongoing drug use.⁸⁵ In these studies, 0–3% of patients discontinued treatment because of adverse events. Compliance was excellent, even in patients taking illicit drugs while on treatment. Risk of reinfection appears low. These results support the removal of drug use as a barrier to interferon-free HCV treatment for patients receiving opioid agonist therapy. Since then, different DAAs have demonstrated high efficacy and good compliance in PWID.^{86–88} HCV reinfection was analysed in patients on opioid agonist therapy and following elbasvir-grazoprevir therapy.⁸⁹ Reinfection rates remained low in at risk populations. The reinfection rate was 2.3/100 person-years, with a persistent reinfection rate of 1.6/100 person-years.

The availability of pan-genotypic DAAs with excellent efficacy and good tolerability offers the unique opportunity to achieve HCV elimination worldwide. IFN-free DAA combinations are now able to cure HCV in more than 95% of HCV-infected individuals after 8–12 weeks of treatment.

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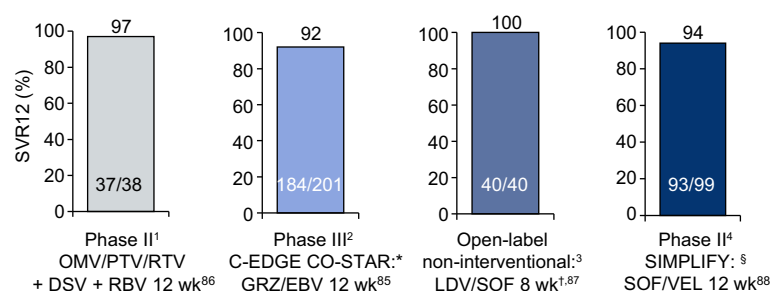


Fig. 3. Treatment with DAAs results in high rates of cure in people who inject drugs.^{85–88}

Although national programmes are the goal for every country, we have yet to see a comprehensive and effective programme anywhere around the world, even in wealthier countries. However, Australia and Iceland are two examples where elimination strategies are well advanced.

To date, 194 different countries have signed up to the World Health Organization 2011 resolution recognising viral hepatitis as a global health issue. In 2014, these countries accepted the ambitious targets for 2030 – 90% reduction in incidence and 65% reduction in mortality. Part of the strategy includes the formation of a national plan to increase testing and linkage to care.

Programmes to eliminate HCV must include increased screening (risk based and universal), linkage to care, as well as increased access to treatment worldwide. The accuracy, affordability and acceptability of testing must be improved through the provision of HCV antigen or RNA testing. Point-of-care testing in countries with a high prevalence of HCV could also improve linkage to care through community-based “test and treat” programmes. Reducing the cost of DAAs will also be important. In low-income countries the combination of generic sofosbuvir and daclatasvir or sofosbuvir and velpatasvir could be considered for economic reasons, to enhance treatment rates across all HCV genotypes. Real-life data on treatment efficacy, tolerability and adherence are mandatory. Compliance to drug regimens will become a major issue to avoid failure. It will be mandatory to control the quality of generic drugs. Shortening treatment duration, removing the need for RBV and on-treatment monitoring should enhance treatment uptake and SVR. Patients who failed previous treatment and developed resistance-associated variants of NS5A, should be rescued with the newly approved

sofosbuvir-based triple therapy or future combinations.^{90,91} Finally, the availability of affordable, efficient and safe DAAs with short treatment durations is paving the way for viral eradication.

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Conflict of interest

Professor Tarik Asselah is a speaker and investigator for AbbVie, Bristol-Myers Squibb, Janssen, Gilead, Roche and Merck. Professor Tarek Hassanein has received grants from AbbVie, Bristol-Myers Squibb, Eisai, Gilead Sciences, Ikaria, Janssen, La Jolla Pharmaceuticals, Merck, Mochida, NGM BioPharmaceuticals, Roche, Ocera, Sundise, Salix, Taigen, Takeda, Tobria, Vertex, and Vital Therapies, has served on advisory boards for AbbVie and Bristol-Myers Squibb, and is a speaker for Baxter, Bristol-Myers Squibb, Gilead, and Salix. Professor Imam Waked has been speaker for Roche, Merck, Bristol-Myers Squibb, Gilead Sciences, and Janssen, is an advisor for Janssen, Roche, Merck, and AbbVie, and has been a study investigator for Roche, Bristol-Myers Squibb, Gilead, Janssen, Pharco, and AbbVie. Doctor Abdellah Mansouri has nothing to declare. Professor Dusheiko currently acts as an advisor to Gilead Sciences, Bristol-Myers Squibb, Janssen and Merck. He has received speaking honoraria from Gilead Sciences, AbbVie, Bristol-Myers Squibb, Merck and Janssen in the past 2 years. He has received grant support from Gilead Sciences, AbbVie, Glaxo Smith Kline, Bristol-Myers Squibb, Janssen and Merck. Professor Edward Gane is a clinical investigator, or a member of Advisory Board or Speakers Bureau for Gilead Sciences, Merck, AbbVie, Roche, Janssen.

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

Authors' contributions

TA designed, prepared and supervised the manuscript. All the authors contributed to the drafting of the review, the critical revision of the manuscript and the final approval of the version to be published.

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