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Probable Factors Impacting the Real-World Treatment Outcomes of Direct-Acting Antivirals for Hepatitis C Treated Populations: A Themed Review

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ABSTRACT

The therapeutics landscape of hepatitis C is changing expeditiously because of the inclusion of interferon-free antiviral regimens in the treatment strategies. Now, we have highly effective, safe and well-tolerated drugs to cure most patients while achieving higher sustained virologic response rates (SVRs: HCV RNA is undetectable in the serum after the 12 or more weeks of therapy) and hepatitis C recurrence will largely disappear. Such therapeutic regimens in combination or as co-formulated pills present highly efficient treatment options to overcome the hepatitis C related challenges with wide genotype (GT) coverage, short period of treatment and fewer side effects. Interferon-free direct-acting antivirals (IFN-free DAAs) are the drug of choice to triumph the health care burden of hepatitis C infection all over the world, but some challenges still must be met. The therapy costs, treatment access to low and middle-income countries (LMICs), differential routes of hepatitis C transmission and the emergence of treatment-associated adverse events are posing dilemmas too in the real-world clinical experiences. The availability of pan-genotypic DAAs to treat all HCV genotypes/subtypes infections, difficult-to-cure HCV populations and for previous treatment failure with first or second-generation DAAs have made it possible to treat everyone who needs treatment in this decade. The dosage algorithms of certain DAAs are also being evaluated in clinical trials for their administration in infants, children, women of reproductive age and pregnant females. The proposition of this pragmatic review article overviews the treatment based outcomes of these regimens in current clinical settings and highlights the challenges to overcome while achieving the prime objective of hepatitis C elimination by 2030.

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1. Introduction

Affecting around 71 million people worldwide and a half million deaths each year, hepatitis C has eclipsed the total number of morbidities and mortalities than HIV around the globe (Hsu et al., 2015; Zoratti et al., 2020). Acute hepatitis C infection is a multifaceted ailment and often asymptomatic which leads to chronic hepatitis C (CHC) in 80% of the infected individuals (Shahid, AlMalki, Hassan, & Hafeez, 2018). The sequences of serological events in acute hepatitis C vary from person to person. However, HCV RNA detection in a patient's serum is identified as the earliest marker of acute infection diagnosis (Shahid & Ibrahim, 2018). HCV RNA in the liver precedes the development of serum glutamic-pyruvic transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT) elevations, symptoms, or the appearance of anti-HCV antibodies (Shahid et al.,

2021). The studies also reveal that hepatitis C RNA may persist in acute infection for several years even if the biochemical resolution of the infection occurs (Cacoub et al., 2016). HCV RNA persists and is continuously detected throughout chronic hepatitis C (CHC) infection (Hellard & Doyle, 2014). HCV neutralizing antibodies are detected positive in affected patients for years although, in some patients, antibodies levels may decline spontaneously during the infection or after the treatment (Heffernan, Cooke, Nayagam, Thursz, & Hallett, 2019). Fluctuations in serum SGPT levels seem to be a salient feature of chronic infection and may reflect the progression of CHC to hepatic inflammation and necrosis (Wiktor, 2019). HCV replication may be increased in advanced hepatic diseases (hepatic fibrosis and cirrhosis) and plays a key role in their progression and ultimately leads to hepatocarcinogenesis (Moon & Erickson, 2019).

The overall cure rates with once known as the 'gold standard of care'; i.e. interferon (IFN) and nucleoside analog ribavirin (RBV) have been dismally poor with dual therapy completion in chronically infected HCV patients along with the emergence of severe adverse events (SAEs) (Abdel-Aziz et al., 2018). All oral IFN-free DAAs were awaited eagerly not only to avoid the administration of PEG-IFN α to intolerant interferon patients but also to decrease the frequency of associated adverse events and viral breakthroughs (a sudden raise in serum HCV RNA levels after a constant period of suppression during the treatment) in patients (Gutierrez, Lawitz, & Poordad, 2015). These therapies are very efficacious, well-tolerable and the relative ease of administration also allows for widespread use outside of a specialist's office. These drugs achieve SVR rates higher than 95% in treated individuals (Feld, Jacobson, Jensen, et al., 2015). These drugs are relatively safe in administration, albeit costly and still not accessible to treat everyone who is in need in many LMICs (Zoratti et al., 2020). These therapeutic regimens contain unrestricted hepatitis C genotype efficacy (pan-genotypic DAAs approved a couple of years ago to treat all HCV genotypes/subtypes) and result in excellent on-treatment virologic responses (Table 1) (Zoratti et al., 2020). However, the successful use of these therapeutic regimens would depend on various factors including previous patient history of treatment, HCV viral load monitoring during treatment (exemption for pan-genotypic DAAs as they achieve >95% SVR rates in treating populations), probable side effects, possible drug-drug interactions (DDIs) and the emergence of viral escape mutants (Zoratti et al., 2020). These treatment strategies were being investigated for HCV for many years by deriving some established findings in the treatment of HIV debility, where different drugs are used in combination; i.e. antiretroviral (ART) therapies with different antiviral efficacies and high genetic barrier to drug resistance that substantially decrease the risk of viral breakthroughs, viral relapse (during the therapy, the levels of HCV RNA decrease to undetectable limit; i.e. <50 IU/mL but becomes detectable after the discontinuation of therapy) and virologic failure in the treated individuals (Shahid et al., 2018).

Table 1

The most promising interferon-free DAA combinations along with pan-genotypic DAA regimens approved by the US FDA to treat the infections caused by hepatitis C virus (HCV)

Referenced clinical trials[a]	Drug Efficacy[b]	Drug Resistance Barrier[c]	Pan-genotypic coverage[d]	Severe Adverse effects[e]	Drug-drug Interactions[f]	Development Phase	Target site
Ledipasvir and sofosbuvir combination (Pan-genotypic regimen)							
NCT01701401 NCT01768286 NCT01851330 NCT02073656	+++	+++	+++	+	+	Approved	NS5A/NS5B active site
Sofosbuvir and simeprevir combination							
NCT01466790 NCT02114177 NCT02114151	+++	++	++	+	++	Approved	NS5B/NS3 serine protease active site
Daclatasvir and sofosbuvir combination (Pan-genotypic regimen)							
NCT02032875 NCT01359644 NCT02032888 NCT02032901	+++	+++	++	+	+	Approved	NS5A/NS5B active site + mRNA chain
Sofosbuvir and velpatasvir combination (Pan-genotypic regimen)							
NCT02201940 NCT02201953	+++	+++	+++	+	+		NS5B/NS5A active site +

NCT02220998 NCT02201901 NCT02480712						Approved	mRNA chain
Daclatasvir-asunaprevir and beclabuvir combination							
NCT01979939 NCT01973049	+++ +++	+++ ++	++ ++	+ ++	++ ++	Approved	NS5A/NS3-4A serine protease active site /NNIs
Paritaprevir-ombitasvir-ritonavir and dasabuvir combination							
NCT01716585 NCT01715415 NCT01704755 NCT01939197 NCT01674725 NCT01767116 NCT01833533	+++	+++	++	+	+	Approved	NS3-4A serine protease/NS5A active site/NNIs
Paritaprevir-ombitasvir and ritonavir combination							
NCT01685203 NCT02265237 NCT02247401	+++	++	+	+++	+	Approved	NS3-4A serine protease/NS5A active site
Elbasvir and grazoprevir combination							
NCT02105688 NCT02105662 NCT02105701 NCT02105467 NCT02092350	+++	++	+++	++	++	Approved	NS3-4A/NS5A serine protease active site
Daclatasvir and asunaprevir combination							
NCT01581203 NCT01573351	+++	+++	+	+	+++	Approved in Japan	NS5A/NS3-4A serine protease active site
Sofosbuvir, velpatasvir, and voxilaprevir combination							
NCT02607735 NCT02607800 NCT02639338 NCT02639247 NCT02745535	+++	++	+	+	+	Approved	N
Glecaprevir and Pibrentasvir combination (Pan-genotypic regimen)							
NCT02604017 NCT02640482 NCT02640157 NCT02636595 NCT02966795 NCT02642432 NCT02738138 NCT02651194 NCT03069365 NCT03089944 NCT02446717 NCT02243280 NCT02243280 NCT02243293	+++	+++	+	+	+	Approved	NS3-4A/NS5A active site

Note:

[a]Only those phase II/III clinical trials were mentioned in Table 1 which were reported to the US FDA for the approval of interferon-free DAA combination and were registered to clinicaltrials.gov website.

[b]Drug efficacy profile was presumed on the overall SVR rates compiled in phase II/III clinical trials where SVRs > 95% = high profile, SVRs > 90% = average profile and SVRs > 85-90% = low profile.

[c]Drug resistance barrier was postulated on all the data that is registered to clinicaltrials.gov.

[d]Pan-genotypic coverage was based on the fact that SVR was obtained with the DAA combination at the end of therapy. SVR 1 through 6 genotypes = high profile, two/three genotypes = average profile, and one genotype = low profile.

[e]Severe adverse event (SAEs) profile was compiled on the basis of percentage adverse effects that was occurred in phase II/III clinical trials which caused the cessatin of therapy in treated individuals, where 10% SAEs > high profile, 10→5% SAEs > average profile, and 5→0 % SAEs > low profile.

[f]Drug-drug interaction profile was established based on the DAA's ability to induce/inhibit hepatic cytochrome P450 system, P-glycoprotein (P-gp) and organic transporting polypeptide (OATP) induction/inhibition. CYP 450, P-gp and OATP induction/inhibition= high profile, P-gp and OATP induction/inhibition= average profile, and one or none of these CYP 450 or P-gp or OATP induction/inhibition = low profile.

High profile = +++, Average profile = ++ and low profile= +

Current direct acting antivirals (DAAs) target the 3 nonstructural proteins of hepatitis C virus (HCV) upon which they are classified accordingly as shown in the figure 1.

From the august 2020, DAAs (ombitasvir, grazoprevir, boceprevir, daclatasvir, dasabuvir, paritaprevir, elbasvir, simeprevir, and telaprevir) are no longer used for HCV treatment in the USA (Zoratti et al., 2020). Similarly, telaprevir and boceprevir are also absolute and no longer recommended in the rest of the world to treat HCV, but the resting DAAs are prescribed by clinicians to treat hepatitis C worldwide (Shahid & Ibrahim, 2018). The *in vitro* studies of nucleoside analog inhibitors (NIs: sofosbuvir) plus drug targeting viral host factors (cyclophilin inhibitors and alisporivir) demonstrate a high drug resistance barrier and represent the principal drugs as an all-oral interferon-free regimen (Chatterji et al., 2014). Analogously, NS3/4A and non-nucleoside analog inhibitors (NNIs: faldaprevir) discontinued because of SAEs and deleobuvir, which possess high antiviral efficacy (Chatterji et al., 2014), but the low genetic barrier of drug resistance may be valuable for NIs or cyclophilin inhibitors as an oral drug partner. Despite that, some NNIs have low efficacy against the HCV but due to the high genetic barrier to drug resistance are also in preclinical trials and would be a valuable part of IFN-free regimens (Hézode et al., 2015; Waked et al., 2016). Although, the current status of anti-HCV drug development and therapeutics is a wider subject in hepatitis C therapeutics and cannot be covered in one review. Even though the message from this matter-of-fact review is simple; i.e., "We have the drugs to cure hepatitis C". Figure 1 depicts the schematic presentation of most promising DAAs with their targeted active sites while table 1 demonstrates the salient features of the FDA-approved interferon-free DAAs combinations for hepatitis C treatment. The subsequent sections of the current review provide the patient and treatment-based outcomes of interferon-free antivirals in treated individuals and overview the challenges in real-world clinical experiences to be tackled not only to get high SVR rates in treated patients but also to cure the infection.

2. DAA's Efficacy and Their Impact on HCV Treatment

The practice-based individual treatment outcomes for DAAs may differ from those obtained in highly selected patients participating in phase III clinical trials. Thus, it is a prerequisite to recognizing the real-world clinical efficacy, safety and benefits of these "state of the art" IFN-free antiviral drugs are used to treat the hepatitis C in a broad spectrum of patients. Recently reported data from the various studies and clinical trial in real-world populations show that ledipasvir/sofosbuvir treated patients (eight weeks course) had 97% SVR12 rates (Zoratti et al., 2020). The cure rates were almost similar to phase III clinical trial results. SVR rates did not deviate significantly among those with the previous history of HCV treatment, hepatic cirrhosis, duration of therapy, or HCV/HIV co-infection. These outcomes support an 8-weeks course of ledipasvir/sofosbuvir combination for the treatment of infections caused by hepatitis C virus (genotype-1 non-cirrhotic) and untreated infected people with viral load < 6 million IU/mL (Heffernan et al., 2019; Zoratti et al., 2020).

Similarly, another study also examined a specific population to determine the SVR rates in the patients who were infected with hepatitis C virus genotype-1and were also coinfected with HIV-1 and treated with ledipasvir/sofosbuvir with or without ribavirin for 8, 12, or 24 weeks (Zoratti et al., 2020). Fifty-nine percent of patients were treated at a community site, 46% were HCV treatment-experienced, 35% had hepatic cirrhosis and 22% had 6 million IU/mL or greater baseline viral RNA levels. Only 6% of patients were treated for 8 weeks, 74% were administered to 12 weeks' therapy and 20% took 24 weeks of treatment. The overall SVR12 rate was 98% in this heterogeneous patient population. Virologic failure was reported only in one patient among the three patients who did not achieve SVR12. There was no significant impact of previous treatment history, cirrhosis or treatment duration on overall SVR rates (Wiktor, 2019).

Comparative efficacies of ledipasvir/sofosbuvir ± RBV combination and "3D" regimen e.g. Viekira Pak®; a combination of 3 DAAs (ombitasvir, paritaprevir and dasabuvir) ± RBV were also assessed in HCV GT-1 infected patients in routine medical practice (Bourlière et al., 2015). This intent-to-treat (ITT) cohort study used the Veterans Affairs' Clinical Case Registry of the USA to identify 6961 patients who initiated therapy for eight or twelve weeks with ledipasvir/sofosbuvir ± ribavirin or twelve weeks with 3D ± ribavirin at 126 facilities (Backus, Belperio, Shahoumian, Loomis, & Mole, 2016). Overall SVR rates were 91% for LDV/SOF recipients, 90% for LDV/SOF + ribavirin recipients, 95% for "3D regimen" recipients and 87% for 3D + ribavirin recipients who completed therapy for 8 weeks. SVR in

those with higher degrees of fibrosis (FIB-4 > 3.25) was 87% for LDV/SOF recipients, 88% for LDV/SOF + ribavirin, 93% for "3D regimen" and 86% for those who were treated with 3D + ribavirin (Backus et al., 2016; Bourlière et al., 2015). SVR rates were 94% for LDV/SOF, 92% for LDV/SOF + ribavirin, 98% for "3D regimen" and 95% for 3D + ribavirin after 12 weeks' treatment completion. These high SVR rates were equal to those attained in clinical trials. Reduced odds of reaching an SVR were noted for those with a high body mass index (BMI), those with prior decompensated cirrhosis, those receiving the 3D + ribavirin regimen and those who were black. These lower response rates were probably associated with early DAAs discontinuation because the negative predictors had no significant impact to achieve an SVR in patients with 12-weeks treatment completion. However, a fibrosis score of more than 3.25 (FIB-4 > 3.25) is always considered a significant negative predictor to achieve higher SVR rates (Backus et al., 2016; Bourlière et al., 2015).

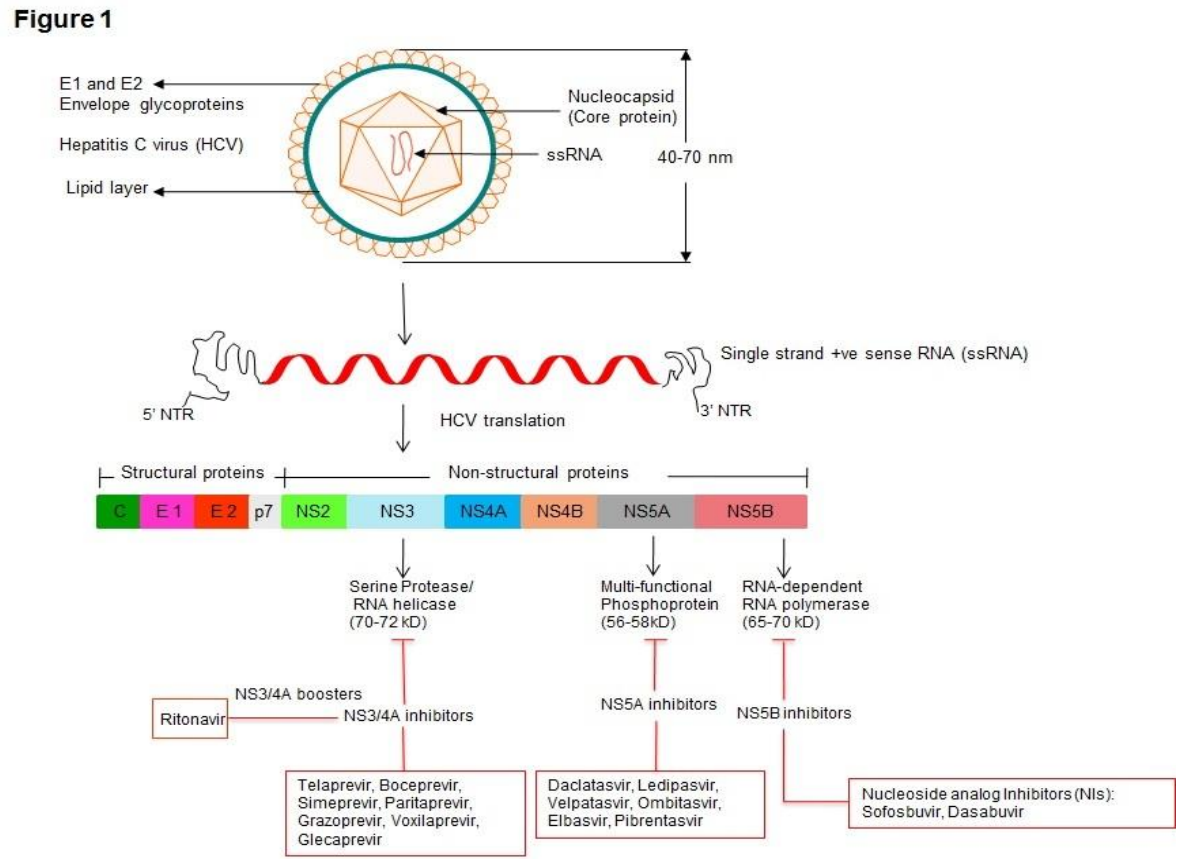

Figure 1: HCV genome organization and the most promising anti-hepatitis C direct-acting antivirals with targeted active sites.

Hepatitis C virus nonstructural proteins are core targeted sites for DAAs among which NS3 serine protease/helicase, NS5A (a phosphoprotein integral for the formation of viral replication complex), and RNA-dependent RNA polymerase (RdRp; NS5B) are the most important ones. The specific inhibitors of these targeted sites are shown in red rectangular boxes.

2.1. HCV GT-4 Resistance to Some DAA Combinations

HCV GT-4 accounts for the highest prevalence of active cases of hepatitis C in Egypt, the Middle East and sub-Saharan Africa (SSA). Viral infection with this genotype represents approximately 13% of clinical cases globally indicating an increasing spread elsewhere. In a phase 2b study, the ombitasvir/paritaprevir + ribavirin regimen achieved a 100% SVR12 rate in HCV GT-4 participants without cirrhosis (Abergel et al., 2016; Keating, 2016). AGATE-1 clinical trial authenticated the therapeutic efficacy of ombitasvir, paritaprevir and ritonavir plus RBV in HCV GT-4 patients with compensated cirrhosis (Keating, 2016). 59 out of 120 adult patients received 12-weeks active treatment and 61 were administered with 16 weeks of the same treatment regimen. 97 % (57/59) SVR rates were achieved in 12-weeks

treated patients and 98 % (60/61) in the 16-weeks group. However, the frequency of side effects (asthenia, anemia, pruritus, fatigue, nausea, headache and dizziness) was significantly higher in both patient arms (Keating, 2016). The AGATE-II clinical trials were conducted in the native Egyptian population with HCV GT-4 infection to assess the clinical potency and efficacy of 3D plus RBV for 12 weeks (Waked et al., 2016). 160 patients out of 182 were eligible for clinical study inclusion criteria including treated and untreated infected patients and cirrhosis had not observed in 100 patients. The active treatment (3D + RBV) was administered for 12 weeks. For the remaining 60, 31 with cirrhosis were randomly assigned for an active treatment to 12-weeks and 29 to 24-weeks. 94% SVR rates were achieved in the noncirrhotic patient arm (94/100) and 97 % in cirrhotic patients (30/31) for a 12-weeks treatment and 93 % (27/29) in cirrhotic patients administered with active treatment for 24-weeks. The AEs frequency was relatively higher in non-cirrhotics including headache and fatigue the most common (41 % and 35 %, respectively) ones than the cirrhotic ones (29–38 %) (Wakeed et al, 2016). The clinical efficacy of 3D plus RBV in the clinical trials (AGATE-I and AGATE-II) predicts assured cure for HCV GT-4 cirrhotic and non-cirrhotic infected patients. However, no surplus benefits in SVR rates were noticed while extending the treatment duration from 12 to 16 or even 24 weeks in cirrhotic patients in the treated population (Keating, 2016; Waked et al., 2016). Likewise, a small patient poll enrolled in the clinical trials could not be justified to calculate the frequency of severe AEs in treated patients. In addition to that, further clinical studies are eagerly desired to evaluate the clinical efficacy of 3D + RBV in cirrhotic infected large populations as most of the approved DAAs are still contraindicated to be administered in hepatitis C cirrhotic individuals in real-world clinical practice (Waked et al., 2016).

2.2. HCV GT-3: A Challenging Hepatitis C Genotype to Treat Yet

HCV GT-3 infected individuals are known to be the difficult-to-treat in the current clinical settings with IFN-free DAAs and become more challenging in patients with a history of decompensated cirrhosis and advanced fibrosis (Kohli et al., 2015). IFN-free DAAs as dual combinations are still not proven clinically effective for GT-3 infected populations. The molecular determinants behind this less treatment effectiveness are still elusive and are speculated that might HCV core antigen protein generates a high genetic barrier to DAA resistance and aggravate the chronic hepatitis C (CHC) infection progession to decompensated cirrhosis and hepatocarcinogenesis by complex interplay with host cellular pathways (Kohli et al., 2015; Zoratti et al., 2020). For this reason, separate clinical trials for HCV GT-3 infected patients are designed with a longer duration of therapy with triple or quadruple DAAs combination and some of those are in the progress (Kohli et al., 2015). Recent literature predicts that pan-genotypic DAAs would be the right approach to treat HCV GT-3 patients (Zoratti et al., 2020). IFN-free DAAs are considered to be equally effective in patients who were infected with genotype-1 & 2 of hepatitis C virus (either cirrhotics or non-cirrhotics). However, 10% SVR rates differ between cirrhotic and non-cirrhotic GT-3 infected patients, which signifies the criteria of fibrosis-prioritizing strategy to clinically evaluate these regimens in GT-3 infected patients (Innes, Goldberg, Dillon, & Hutchinson, 2015; Lawitz et al., 2014). Recently, some clinical studies administering sofosbuvir plus daclatasvir and RBV active regimen documented high SVR rates in HCV GT-3 treated patients after 16-week therapy(Sulkowski et al., 2014). However, SVR rates were not significantly higher in cirrhotic ones and treatment-experienced patients. Further, clinical studies are warranted in this prospect (Sulkowski et al., 2014).

3. Ribavirin-free Combinations

The approved IFN-free DAA regimens for HCV GT-2 and 3 infected individuals in the form of a combination of SOF plus RBV—achieve relatively higher SVR rates but at the cost of modest decrements in patient-reported outcomes (PROs). These adverse self-reported quality-of-life measures are directly or indirectly relevant to AEs of RBV. Such patient-reported outcomes (PROs) were compared in a study wher genptype-2 and 3 HCV infected patients were treated with velpatasvir/sofosbuvir, a fixed-dose combination (FDC) vs. sofosbuvir + RBV (Younossi et al., 2016). The data were analyzed for 2 phase III clinical trials including 818 patients. 99% SVR rates were achieved in VEL/SOF recipients with HCV GT-2 affected who were treated for 12 weeks and 95% in VEL/SOF recipients who were genotype 3; 94% in SOF + ribavirin recipients with genotype 2 for 12 weeks' treatment and 80% in SOF + ribavirin recipients who were genotype 3 and treated for 24 weeks. PRO

domain in 12 out of 23 patients was found significantly improved in patients at treatment week 4 and receiving VEL/SOF (Younossi et al., 2016). These improvements continued to increase during treatment. In contrast, some improvements in various PROs at treatment completion, PRO domains were noted to decrease for patients in the SOF + ribavirin group (Younossi et al., 2016). HCV cirrhotic patients that are treated with RBV containing regimen have higher SVR (Younossi et al., 2017). The investigators also compared the PROs associated with the regimens using RBV (SOF or VEL/SOF) in cirrhotic and non-cirrhotic patients. A total of 488 patients had received SOF/VEL + RBV for 12 weeks (all GTs) or SOF + ribavirin (12 weeks course) or (24 weeks course) for genotype-2 and 3. Regardless of the inclusions of cirrhotic patients, mild impairment in some aspects of PROs was noticed in patients administered with ribavirin-containing regimens which were substantially improved after treatment and became more impressive with longer follow-up (Younossi et al., 2017).

4. Pretty Mind-boggling Aspects of DAAs Efficacy in Real-world Clinical Practice

All-oral interferon-free DAAs regimens have shown spectacular clinical promise while treating difficult to treat HCV populations in clinical trials (Shahid & Ibrahim, 2018; Younossi et al., 2017; Zoratti et al., 2020). However, the question remains; Can this degree of success be replicated in a real-world application by these highly efficient though extremely expensive treatment strategies from well-organized clinical trials to real-world clinical practice? Until now only 10 million HCV-affected people receive the treatment worldwide since the approvals of DAAs to be used for the treatment of HCV since 2014 (Shahid et al., 2021; Shahid & Ibrahim, 2018). Moreover, will this level of success apply to all patients in clinical practice? Recent published clinical data reveal mixed findings and opinions in this context and address real-world outcomes of such innovative therapeutic regimens and the prospects for ensuring the best outcome for CHC infected patients including certain difficult-to-cure patient groups (HCV GT-3 infected patients, HCV/HBV, or HCV/HIV or HCV/CKD coinfected patients, HCV individuals infected with decompensated cirrhosis, patients previously treated with first-generation DAAs and who may require long duration treatment including RBV in active treatment or the use of new RBV free combinations like pan-genotypic DAAs; discussed below) (Grebely & Dore, 2014; H. A. Innes et al., 2015; Reig et al., 2016). There are also the possibilities of novel modalities, where more interferon-free regimens in the preclinical phase will be added to the expanding armamentarium of anti-HCV direct-acting antivirals and combination regimens. One example of this scenario is the next-generation investigational but recently approved pangenotypic, fixed-dose, once-daily combination tablet containing sofosbuvir/velpatasvir (400mg/100mg, Epclusa®) for chronic kidney disease (CKD) patients with HCV (Curry et al., 2015; Foster et al., 2015).

5. Challenges in HCV Treatment and Future Treatment Perspectives with DAAs

There are certain challenges associated with interferon-free DAAs which must be encountered not only to get high SVR rates in treated individuals but also to prevent the chances of HCV recurrence (Grebely & Dore, 2014). The existence of baseline viral escape mutants or emergence of resistance-associated substitutions during the treatment and the quasispecies nature of circulating HCV genome in HCV affected individuals may be a potential cause of treatment failure in treating patients and always remain a key area of concern for the researchers and investigators while developing these game-changer anti-HCV drugs (Gaudieri et al., 2009; Sarrazin & Zeuzem, 2010). The major advantages of new treatment approaches, most probably of the pan-genotypic DAAs seem to be non-overlapping resistance profiles that investigators demonstrated in clinical trials. However, it is too early to comment on their existence in real-world clinical practice because pan-genotypic DAAs are still not widely used in general CHC infected populations and require extensive research in this prospect. Therapy costs and access to treatment are also the main limitations to treat HCV patients in those regions where the infection is common (Egypt and some regions of South Asia, where HCV is almost an endemic) and even in resource-rich countries (USA) where certain states have refused to treat everyone instead to "prioritizing coverage to those who need it the most" (Hill, Khoo, Fortunak, Simmons, & Ford, 2014; Jayasekera, Barry, Roberts, & Nguyen, 2014). The subsequent section

highlights these harboring issues and their management supported by some recently conducted clinical trials, albeit; some studies are retrospective in nature and need further long-term follow-ups to elucidate the full benefits of DAAs against the emergence of resistance-associated substitutions (RAS).

5.1. Non-adherence to Treatment Diminishes Real-world DAA SVR Rates

The World Health Organization (WHO) has determined that 50% of hepatitis C infected individuals do not take medications for chronic conditions as prescribed (Shahid et al., 2021). The investigators assessed the effect of DAA nona-dherence on SVR rates at 12 weeks post-completion therapy to identify the predictors of non-adherence (Zoratti et al., 2020). Patients who missed more than an average of one dose/month or more than five total doses were defined as nonadherent (Zoratti et al., 2020). Non-adherent patients had 19% lower rate of SVR12 as compared to those with documented adherence. SVR12 rates were 67% in the nonadherent group and 86% in the adherent group, with a 25% relapse rate in the nonadherent group. Female gender, black race and psychosis were noticed to be the prime factors associated with nonadherence. Anorexia, fatigue, headache, nausea, diarrhea and rash are the common adverse events that did not impact the adherence significantly (Zoratti et al., 2020). The efforts must be directed to manage psychiatric illness in hepatitis C infected individuals specially to reduce the financial burden of current treatment regimens (H. A. Innes et al., 2015).

5.2. Pan-genotypic Regimens for Difficult-to-treat HCV GTs/subtypes

An investigational protease inhibitor (ABT-493) and NS5A inhibitor (ABT-530) demonstrated potent pangenotypic anti-HCV activity *in vitro* . The therapeutic regimen has a high barrier to drug resistance and promising clinical efficacy against common RASs. In clinical trials, ABT-493 + ABT-530 were taken (for twelve weeks) that was well tolerated and achieved SVR rates of 97%-100% in HCV (all GTs) infected noncirrhotic patients (Kwo et al., 2017). When coadministered once-daily ABT-493/ABT-530 (300/120 mg) for 8 weeks, the overall SVR rates were achieved by 97% of HCV GT-1 infected patients and 98% of GT-2 infected patients. There were no virologic failures regardless of the baseline viral load or prior treatment history (Kwo et al., 2017). HCV GT-3 accounts for about 30% of all HCV infections worldwide and is the most difficult to cure GT (Kwo et al., 2017). In phase II studies, ABT-493/ABT-530 combination (once in a day for 12 weeks) was well tolerated and SVR rates were attained in 96% of treatment-naive, noncirrhotic GT-3 infected patients, with no virologic failures. High SVR rates were noticed for the 8 weeks treatment in untreated infected (GT-3) patients without cirrhosis (Kwo et al., 2017). The therapeutic efficacy of ABT-493/ABT-530 was also evaluated for twelve weeks in noncirrhotic infected patients with HCV (genotype 4,5 and 6). The overall SVR4 rates were achieved by 100% of the patients (Kwo et al., 2017). Mild adverse events (AEs) such as headache, diarrhea and fatigue were predominate. However, no treatment discontinuation was attributed to treatment-emergent adverse events. The DAA combination was generally well tolerated and demonstrated high SVRs. These results establish the first potent clinical pangenotypic activity of this ribavirin-free once-daily regimen for HCV GT-3 affected populations (Kwo et al., 2017) and thereafter novel pan-genotypic DAA combinations have been developed, tested both in preclinical and clinical trials and in 2017 approved by the US FDA to be administered to treat all HCV GTs/subtypes affected patients, difficult-to-cure HCV populations and for previous treatment failure with 1st and 2nd generation DAAs (Zoratti et al., 2020).

With the advancement and an ample understanding of hepatitis C genome replication and polyprotein processing determinants, the design and development of pan-genotypic DAAs targeting specific hepatitis C proteins have revolutionized the treatment paradigms for HCV difficult-to-treat individuals and are being used in real-world clinical practice since 2017 (Zoratti et al., 2020). Now the treatments are available for all patients who are untreated or treated with various regimens (previous treatment failure with PEG-IFN/RBV or DAAs failure), who contain HCV with cirrhosis (either compensated or decompensated) or not, who are concomitantly suffering from co-infections (HCV/HBV, HCV/HIV, or HCV/CKD) or who are suffering from any HCV GTs/subtypes, or mixed GTs/subtypes or with "undetected" or "indeterminate" HCV GTs/subtypes. Before the availability of these promising DAAs to attain higher SVR rates (>95%) or cure of HCV

affected individuals, both the patients and clinicians were reluctant to initiate, adhere, or complete the treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) based therapies due to suboptimal SVR rates, significant rates of SAEs, potential drug toxicities and possible DDIs with pole frequency medications (Shahid et al., 2021). However, these concerns have been significantly reduced and are no longer applicable with current pan-genotypic DAAs. Interestingly, the current pan-genotypic DAAs are therapeutically active at virus life cycle by only targeting and inhibiting HCV nonstructural proteins that are potentially involved in virus replication and translation (Table 1) (Shahid et al., 2021; Zoratti et al., 2020). Data from real-life clinical situations explore that cure rates are found to be almost similar with pangenotypic DAAs administration across all HCV GTs/subtypes with some exceptions of GT-3 infected patients either treatment naïve or treated with PEG-IFN/RBV but received no therapeutic benefits or first and second-generation DAAs (Shahid et al., 2021; Zoratti et al., 2020). It seems that effective HCV treatment is now a reality provided that to surmount some cross-cutting barriers to provide these regimens to everyone who is diagnosed with HCV. Furthermore, the AEs associated with pan-genotypic DAAs administration are also mostly manageable. However, co-administration of RBV with these regimens may cause insomnia in treating patients, sleep disruption can be avoided by adjusting the timing of the dose (Zoratti et al., 2020).

5.3. HCV Treatment Failure with Baseline Resistance-associated Substitutions (RASs) and Pan-genotypic DAA

Baseline RAS testing is becoming almost irrelevant pangenotypic DAAs are found efficacious against almost all HCV GTs 1 through 6 infected patients (Shahid et al., 2021). Furthermore, the current treatment guidelines issued from the US FDA and AASLD-IDSA skip the resistance testing during or after the post-treatment completion of DAA therapy except in the cases of viral breakthrough, viral relapse, or treatment failure with a pangenotypic regimen. For example, NS5A RASs testing in HCV GT-1 patients with a previous treatment failure (an NS5A inhibitor) and with or without hepatic cirrhosis is recommended to initiate retreatment therapy with pan-genotypic DAA regimens (either to start LDV/SOF or EBR/GZR combination as retreatment option) (Zoratti et al., 2020). Similarly, HCV infected patients (GT-3) with compensated cirrhosis and who are previously treated (either with an NS3-4A PIs or an NS5B inhibitor with lower SVR rates) are recommended for RAS testing before initiating retreatment with a pan-genotypic regimen (Shahid et al., 2021; Zoratti et al., 2020). RAS testing is also recommended in HCV GT-3 patients for the inclusion of RBV in active DAA regimens while treating decompensated cirrhotic patients. Meanwhile, EASL recommendations about RAS testing raise concerns including the limited accessibility and affordability to reliable HCV RAS testing, sequencing analysis, data interpretations and reported results (Shahid et al., 2021). On the other hand, EASL does not enforce baseline RAS testing before treatment initiation while recommending only treatment-experienced and treatment-failure patients with SOF + RBV, PEG-IFN + RBV, PEG-IFN + RBV + SOF based regimens (Zoratti et al., 2020). As mentioned earlier that the AASLD guidelines somehow recommend RAS testing in all DAAs treatment failures before retreatment; however, the treatment strategies with current pan-genotypic DAAs regimens to overcome RAS are not assessed in large patient populations for retreatment settings (Shahid et al., 2021). For this reason, retreatment could be an emergency to manage the vulnerable HCV-infected populations with prior DAA-treatment failure as this fraction of populations would be a continuous reservoir of HCV transmission to general unaffected individuals if remain untreated (Shahid et al., 2021).

5.4. Treatment Paradigms for Special Populations

5.4.1. Decompensated Cirrhotic Patients

The SOF/VEL regimens show prominent efficacy rates in patients infected with HCV GTs 1 to 6 with decompensated cirrhosis (Feld, Jacobson, Hézode, et al., 2015; Wyles et al., 2017). One study explored higher SVR rates and also attempted to identify key clinical and laboratory profiles associated with changes in the model for end-stage liver disease (MELD) scores in patients who achieve SVRs (Huang et al., 2021). SVR rates in 267 patients who were randomly assigned and treated were 83% (SOF/VEL for twelve weeks), 94% (SOF/VEL + ribavirin for twelve weeks) and 86% (SOF/VEL for twenty-four weeks), respectively (Huang et al., 2021). It was noticed that SOF/VEL had pronounced efficacy

rates in patients with decompensated cirrhosis. As the study documented Patients with higher MELD scores, lower BMI, or the absence of ascites and encephalopathy at the time of enrollment achieved higher SVR rates (Huang et al., 2021).

5.4.2. Cirrhotic Patients awaiting Liver Transplantation

Hepatic cirrhosis is a major cause of liver transplantation (LT) among adults in the United States (Njei, McCarty, Fortune, & Lim, 2016). In one study, the investigators evaluated the comparative cost-effectiveness of treating HCV pre-LT versus post-LT in the event of HCV recurrence (Njei et al., 2016). In this base-case analysis, the investigators found that treatment of HCV post-LT led to US dollars 70,224 more in spending per quality-adjusted-life-year (QALY) (Njei et al., 2016). One QALY equates to one year in perfect health compared with pre-LT treatment. In a sensitivity analysis, the post-LT treatment led to US dollars 98,275 more spent per QALY for patients without hepatocellular carcinoma (HCC) and US dollars 41,040 more spent per QALY for those with HCC compared with pre-LT treatment. The researchers estimated that treating 100,000 patients with HCV before liver transplantation would prevent 182 cases of liver failure, 139 cases of HCC, 194 transplantations and 858 liver-related deaths. They also concluded that treatment of HCV before liver transplantation is more economical and improves liver-related outcomes as compared to delay in treatment until post-LT HCV recurrence (Njei et al., 2016).

5.4.3. Treatment option for Prior DAA Therapy Failure

Optimal treatment plans for the retreatment of the HCV infected patients with prior DAA treatment failure are still inconclusive. However, the researchers conducted clinical efficacy of 3D regimen ± RBV in GT-1 treatment-experienced patients (Poordad et al., 2019). High SVR rates were recorded with this multitargeted regimen in DAA treatment failure, including those who had failed three DAA regimens and those with NS5A resistance-associated variants (Poordad et al., 2019). Recently reported studies explored that pan-genotypic DAAs would be a key option for the previous HCV treatment failures with an NS3-4A serine/protease or NSA5A inhibitor DAAs (Poordad et al., 2019).

Currently, the efficacy data of multiple salvage therapies administered to DAA-based treatment failure patients with RASs achieved excellent SVR rates that suggest their potential use in real-life situations rather than to be treated such patient populations with existing therapies or addition of RBV in active regimens (Shahid et al., 2021; Zoratti et al., 2020). However, weight-based RBV may be added for 24 weeks to retreat from SOF-based treatment failure unless contraindicated. SOF-based dual or triple DAA combination including an NS5A inhibitor (velpatasvir: VEL) or the inclusion of an NS3-4A PIs (voxilaprevir: VOX) along with RBV for 12 or 24 weeks are also good choices for the retreatment of previous treatment failures with first or second-generation NS3-4A PIs or NS5A inhibitors containing pre-existing or treatment-emergent RASs (Shahid et al., 2021; Zoratti et al., 2020). Likewise, for SOF and SMV failure, LDV/SOF or SOF/DCV administration for 24 weeks may achieve higher SVR rates in cirrhotic patients and including RBV, the treatment duration may shorten up to 12 weeks. For SOF-RBV treatment failure, the retreatment strategies can be the inclusion of PEG-IFN (SOF/ plus PEG-IFN plus RBV) for twelve weeks or with SOF/RBV for twenty-four weeks. PEG-IFN plus RBV along with SOF is also suggested for LDV/SOF treatment failure with NS5B associated RAS for 12 weeks (Shahid et al., 2021; Zoratti et al., 2020).

RASs associated with NS5A inhibitors show maximum virus fitness and persist for a long time after treatment failure(Shahid et al., 2021). Recently published data suggest retreatment strategies for the treatment failure of first-generation NS5A inhibitor regimens (e.g. daclatasvir; DCV). In POLARIS-1 clinical trials, treatment-failure patients with an NS5A inhibitor have retreated with a combination of SOF/VEL/VOX for twelve weeks. Overall SVR rates were achieved 96%, from which 83% of patients had NS3/NS5A RASs (SVR rates were achieved 97%) and 17% had no RAS (SVR rates were 98%) (Zoratti et al., 2020). SVR rates were achieved 99% in non-cirrhotics, 93% in cirrhotics, and 95% in GT3 patients. In contrast to POLARIS-1, POLARIS-4 studies were conducted in T.E patients who did not respond to NS3 and/or NS5B inhibitors and were retreated with a combination of SOF/VEL/VOX or SOF/VEL for twelve weeks (Zoratti et al., 2020). Overall SVR rates were achieved 98% with SOF/VEL/VOX combination versus 90% with SOF/VEL. However, these

SVR rates were not impacted by HCV GTs/subtypes, patient cirrhotic status, and NS3/ or NS5A associated RASs (Zoratti et al., 2020). In MAGELLAN-1 clinical trials, 16 weeks administration of GLE/PIB combination achieved high SVR rates (100%) in GT-1 patients who had a previous treatment failure with an NS5A and/or NS3-4A PIs (Zoratti et al., 2020). However, the EASL guidelines recommend that this DAAs combination does not possess a high genetic barrier-to-resistance against previous treatment failures with an NS5A inhibitor and fails to achieve optimal SVR rates in treated (NS5A-associated RASs) patients (Zoratti et al., 2020). In parallel to that, cirrhotic and non-cirrhotic HCV patients and treatment-failure with a PI and/or/NS5A inhibitor must be retreated with SOF/VEL/VOX combination for twelve weeks (Zoratti et al., 2020). SOF plus the fixed-dose combination of GLE/PIB should be administered for 12 weeks in patients who are predictors of lower treatment responses (advanced hepatic disease, treatment-failure with multiple courses of DAA-based regimens and having complex NS5A-associated RAS profile) (Zoratti et al., 2020). For very difficult-to-cure populations based on complex RAS profiles (patients with NS5A RASs who failed twice to achieve SVR rates with a PI and/or an NS5A inhibitor), the combination of SOF/VEL/VOX or SOF plus GLE/PIB can be given for 12 weeks with weight-based RBV and/or treatment duration can be prolonged from 12 to 16 or 24 weeks while excluding RBV (Zoratti et al., 2020).

5.4.4. Asian American Patients

An ongoing clinical study characterizes the rate of cirrhosis progression and hepatic decompensation in patients of various ethnicities that were diagnosed with CHC infections (Nguyen & Nguyen, 2013). According to the study demographics, out of a total of 9451 patients, 972 were Asian. Asian patients were significantly older than non-Asian patients with the chance of at least two comorbidities; a higher proportion had diabetes mellitus (DM), hypertension, coronary artery disease and chronic kidney disease (CKD) (Nguyen & Nguyen, 2013). The 10-year cumulative occurance of cirrhosis and hepatic decompensation was significantly higher in Asian patients. On multivariate analysis, ethnicity, older age, male sex, no SVR, and Asian ethnicity were significant independent predictors of cirrhosis and failure to achieve an SVR. Hepatic decompensation was noticed much higher in Asian ethnicity (Nguyen & Nguyen, 2013). Early treatment with DAAs that result in successful SVR may decrease the rate of progression to cirrhosis and hepatic decompensation for all patients with hepatitis C, but especially for those who are at the highest risk (Nguyen & Nguyen, 2013).

6. Adjuvant Therapies Significance

Some conclusive studies suggest that caffeine might have hepatoprotective properties in a variety of hepatic parenchymal disorders, including nonalcoholic fatty liver disease (NAFLD) and HCV. Various studies reported that, higher consumption of caffeine caused lower risk of liver enzyme elevation, cirrhosis, and HCC (Setiawan et al., 2017). The investigators evaluated the protective effect of coffee drinking in black, Native Hawaiian, Japanese-American, Latino, and white patients with chronic liver diseases in one study (Setiawan et al., 2017). Regular coffee intake was associated with reduced risks for NAFLD-related progression in a dose-dependent manner. For example, compared with non–coffee drinkers, those who reported drinking two to three cups and four or more cups of coffee per day had a 14% and a 34% reduction, respectively, in the risk for the NAFLD-related disease. High consumption (four or more cups per day of regular coffee) was linked with a reduced risk for HCV-related chronic liver disease (Setiawan et al., 2017).

Similarly, a meta-analysis and systematic review also predict that caffeine intake can decreased the risk for of hepatic fibrosis in patients with CHC infections (Jaruvongvanich, Sanguankeo, Klomjit, & Upala, 2017). It is unclear whether caffeine or other metabolites of coffee are the responsible ameliorative agent. However, it is postulated that the presumed hepatoprotective effect may be due to the antioxidant properties of caffeine or to the reduced expression of CYP1A2, which correlates with fibrosis progression (Jaruvongvanich et al., 2017; Setiawan et al., 2017). Future studies might assess the optimal dose and preparation of caffeinated beverages for the prevention of hepatic fibrosis in patients with CHC infection.

7. Therapy Cost and Treatment Access

7.1. Health Care Expenditures and Trends in Healthcare Utilization

Chronic hepatic diseases are the 12th leading cause of death in the United States (Hirode, Saab, & Wong, 2020). Affected patients, such as those with chronic HCV infection, experience a financial burden due to their disease, including substantial healthcare expenses, a negative impact on employment, and a significant impairment in quality of life (Hirode et al., 2020; Zoratti et al., 2020).

One study conducted by Wadhwa and colleagues evaluated the current health care burden of hospitalizations due to hepatitis C infection by using the National Inpatient Sample Database (NISD) to find all subjects for whom hepatitis C was the discharge diagnosis from 1997 to 2012 (Grant, Jhaveri, McHutchison, Schulman, & Kauf, 2005). In 1997, there were 134,161 hospitalizations due to hepatitis C, which rose to 607,056 in 2012. In addition, hospital charges for HCV-related admission increased an average of US dollars 2182 per year, while the average length of stay decreased by a small amount each year. In-hospital deaths during HCV admissions decreased an average of 4% per year. Of note, the number of admissions for HCV-related cirrhosis increased by 342%, and the number of admissions for HCV-related hepatocellular carcinoma increased by 645% during the study period (Grant et al., 2005; Zoratti et al., 2020).

7.2. Cost-mapping Study

Telaprevir regimens for CHC GT-1 treatment were associated with an average cost of US dollars 189,000 per SVR (Stahmeyer et al., 2016). Newer DAAs regimens along with pan-genotypic combinations are well tolerated and thus may not engender costs related to AEs management, which was often necessary with previous drugs. This predisposing factor, along with higher DAAs clinical efficacies, suggests lower SVR costs for the new DAAs compared with prior drugs(Stahmeyer et al., 2016). One study conducted by Nyberg and colleagues used detailed cost mapping to determine the cost per SVR for individuals treated with LDV/SOF ± RBV (Chhatwal, Kanwal, Roberts, & Dunn, 2015). Cost codes associated with each patient undergoing HCV treatment either inpatient or outpatient with this regimen for 1 year was determined. Derived costs were then mapped to each unique code and all codes were linked to 1262 patients who underwent treatment during the study period (Chhatwal et al., 2015). This detailed cost-mapping study included total inpatient and outpatient costs associated with all medical care given to each unique patient during treatment. Thus, it included costs over and above the expense of medications (Chhatwal et al., 2015). The average cost per SVR was US dollars 75,502 for noncirrhotic patients and US dollars 100,518 for patients with cirrhosis. Due to well tolerability and higher SVR rates, the cost per SVR using LDV/SOF ± RBV is lower than the cost previously reported for IFN-based treatment with and without first-generation DAAs (Chhatwal et al., 2015).

The improved SVR rates associated with the new DAA regimens, as well as the availability of pan-genotypic regimens, allow highly cost-effective treatment; however, still, the 'sticker shock' prices of these innovative therapeutic regimens have made the treatment out of reach in LMICs and limited access to care even in resource replete nations (Shahid et al., 2021). One study conducted in the USA discussed disparities in access to care in a real-world setting, where HCV GT-1 infected patients had been prescribed 8, 12, or 24 weeks of currently approved DAA regimens (Chhatwal et al., 2015). The data were collected from 2878 HCV GT-1 infected patients who were commenced for all-oral treatment between October 2014 and June 2015. It was noticed that un-anticipation increases of non-start rates to double-digit levels in commercial and Medicare groups. The theme of denied access was observed for Medicaid patients, and the magnitude of denial was higher and continued with newer DAA regimens. Unfortunately, the denial ratio was higher for stage 3 or 4 fibrosis patients infected with HCV, or who were at risk for liver-related complications, and accounted for more than 33% of patients who were described as the most urgent candidates for therapy (Chhatwal et al., 2015).

In summary, the FDA-approved DAA combinations and pan-genotypic regimens work to cure HCV-infected individuals in real-world clinical practice. Although still expensive; however, hopefully very shortly, clinicians will be able to select and administer a DAA combination or pan-genotypic DAA regimen that they deem fit to be an optimal cure for

their patients. Now that we have the hepatitis C virus on the run, can a universal cure be attained? The aim of the global health sector strategy (GHSS) on viral hepatitis is to eradicate the viral hepatitis by 2030, saving 7.1 million lives (Shahid et al., 2021). Enhanced HCV diagnostics in premises where the HCV infection is almost an endemic and linkage to care of those who are diagnosed HCV positive are important steps in improving global elimination outcomes related to the HCV epidemic (Shahid et al., 2021). Furthermore, choosing the optimal drug combination for each patient and ensuring adherence to the recommended regimen is also important to scale up HCV treatment. Targets of the HCV elimination strategies must also include raising awareness and increasing access to treatment. We have the way. Do we have the will?

8. Conclusion

All oral interferon-free DAAs combinations and pangenotypic regimen present highly successful therapeutic approaches and treatment outcomes against hepatitis C in real-life clinical situations. The treatment strategies based on such therapeutic regimens are highly efficient to cure HCV GT 1 to 6 infected patients excluding the use of IFN and in some situations RBV from the active regimen combination. Some of these coformulated pills and their use in combination with other DAAs have also simplified the treatment paradigms for difficult-to-treat HCV GT-1 infected individuals, difficult to treat HCV infected populations, and previous treatment failure with IFN-based regimens. pan-genotypic DAA regimens are clinically promising with their excellent efficacy, superb safety and the emergence of minimal SAEs during or post-completion therapy and would be the drug of choice for women of reproductive age (WORA), pregnant females, infants and children in the future. However, extensive studies would be required to determine which therapeutic regimen is the most advantageous for an individual patient regarding higher efficacy, well tolerability and having a strong drug resistance genetic barrier. However, the story is not over with the cure of the virus but there are certain challenges to encounter to win this uphill battle against hepatitis C. The drug costs and accessibility of the treatment to HCV diagnosed patients who need the drugs most are two significant concerns in this context. In most countries, drug cost is one of the leading barriers to treating chronic hepatitis C infection. However; generic DAAs treatment will likely reduce the cost without affecting cure rates as shown in multiple recently published clinical data. Similarly, deficiencies in HCV screening and infection diagnosis and lack of ideal disease burden simulation models also pose hurdles to treating hepatitis C infection. By analogy, despite the therapeutic advances in hepatitis C, the care continuum is still experiencing some significant barriers, namely in the form of a lack of trained and hepatic disease specialists who traditionally administer hepatitis C therapy. Widening the care model for HCV patients with active or ongoing infection to include non-specialists, general physicians, clinicians, and primary healthcare providers to administer DAAs even for traditionally harder-to-treat subpopulations, could significantly elaborate the scale of therapy and bridge the existing gaps in the hepatitis C cascade of care. High throughput anti-HCV screening, cost-effective analysis of the treatment, applications of risk prediction tools, and implementation of controlled HCV health care policies will also help to eliminate hepatitis C from the globe.

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Imran Shahid designed the whole study, searched and analyzed the data and wrote the whole manuscript.

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References

Abdel-Aziz, A. M., Ibrahim, M. A., El-Sheikh, A. A., Kamel, M. Y., Zenhom, N. M., Abdel-Raheim, S., & Abdelhaleem, H. (2018). Effect of Sofosbuvir Plus Daclatasvir in Hepatitis C Virus Genotype-4 Patients: Promising Effect on Liver Fibrosis. *J Clin Exp Hepatol, 8*(1), 15-22. doi:10.1016/j.jceh.2017.06.006

Abergel, A., Metivier, S., Samuel, D., Jiang, D., Kersey, K., Pang, P. S., . . . Asselah, T. (2016). Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. *Hepatology, 64*(4), 1049-1056. doi:10.1002/hep.28706

Backus, L. I., Belperio, P. S., Shahoumian, T. A., Loomis, T. P., & Mole, L. A. (2016). Comparative effectiveness of ledipasvir/sofosbuvir ± ribavirin vs. ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin in 6961 genotype 1 patients treated in routine medical practice. *Aliment Pharmacol Ther, 44*(4), 400-410. doi:10.1111/apt.13696

Bourlière, M., Bronowicki, J. P., de Ledinghen, V., Hézode, C., Zoulim, F., Mathurin, P., . . . Pol, S. (2015). Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis, 15*(4), 397-404. doi:10.1016/s1473-3099(15)70050-2

Cacoub, P., Comarmond, C., Domont, F., Savey, L., Desbois, A. C., & Saadoun, D. (2016). Extrahepatic manifestations of chronic hepatitis C virus infection. *Ther Adv Infect Dis, 3*(1), 3-14. doi:10.1177/2049936115585942

Chatterji, U., Garcia-Rivera, J. A., Baugh, J., Gawlik, K., Wong, K. A., Zhong, W., . . . Gallay, P. A. (2014). The combination of alisporivir plus an NS5A inhibitor provides additive to synergistic anti-hepatitis C virus activity without detectable cross-resistance. *Antimicrob Agents Chemother, 58*(6), 3327-3334. doi:10.1128/aac.00016-14

Chhatwal, J., Kanwal, F., Roberts, M. S., & Dunn, M. A. (2015). Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med, 162*(6), 397-406. doi:10.7326/m14-1336

Curry, M. P., O'Leary, J. G., Bzowej, N., Muir, A. J., Korenblat, K. M., Fenkel, J. M., . . . Charlton, M. (2015). Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. *N Engl J Med, 373*(27), 2618-2628. doi:10.1056/NEJMoa1512614

Feld, J. J., Jacobson, I. M., Hézode, C., Asselah, T., Ruane, P. J., Gruener, N., . . . Zeuzem, S. (2015). Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. *N Engl J Med, 373*(27), 2599-2607. doi:10.1056/NEJMoa1512610

Feld, J. J., Jacobson, I. M., Jensen, D. M., Foster, G. R., Pol, S., Tam, E., . . . Yetzer, E. S. (2015). Randomized study of danoprevir/ritonavir-based therapy for HCV genotype 1 patients with prior partial or null responses to peginterferon/ribavirin. *J Hepatol, 62*(2), 294-302. doi:10.1016/j.jhep.2014.09.013

Foster, G. R., Afdhal, N., Roberts, S. K., Bräu, N., Gane, E. J., Pianko, S., . . . Sulkowski, M. (2015). Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *N Engl J Med, 373*(27), 2608-2617. doi:10.1056/NEJMoa1512612

Gaudieri, S., Rauch, A., Pfafferott, K., Barnes, E., Cheng, W., McCaughan, G., . . . Lucas, M. (2009). Hepatitis C virus drug resistance and immune-driven adaptations: relevance to new antiviral therapy. *Hepatology, 49*(4), 1069-1082. doi:10.1002/hep.22773

Grant, W. C., Jhaveri, R. R., McHutchison, J. G., Schulman, K. A., & Kauf, T. L. (2005). Trends in health care resource use for hepatitis C virus infection in the United States. *Hepatology, 42*(6), 1406-1413. doi:10.1002/hep.20941

Grebely, J., & Dore, G. J. (2014). Can hepatitis C virus infection be eradicated in people who inject drugs? *Antiviral Res, 104*, 62-72. doi:10.1016/j.antiviral.2014.01.002

Gutierrez, J. A., Lawitz, E. J., & Poordad, F. (2015). Interferon-free, direct-acting antiviral therapy for chronic hepatitis C. *J Viral Hepat, 22*(11), 861-870. doi:10.1111/jvh.12422

Heffernan, A., Cooke, G. S., Nayagam, S., Thursz, M., & Hallett, T. B. (2019). Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. *Lancet, 393*(10178), 1319-1329. doi:10.1016/S0140-6736(18)32277-3

Hellard, M. E., & Doyle, J. S. (2014). Interferon-free hepatitis C treatment: one pill to fit all? *Lancet, 383*(9916), 491-492. doi:10.1016/S0140-6736(13)62151-0

Hézode, C., Asselah, T., Reddy, K. R., Hassanein, T., Berenguer, M., Fleischer-Stepniewska, K., . . . Pol, S. (2015). Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. *Lancet, 385*(9986), 2502-2509. doi:10.1016/s0140-6736(15)60159-3

Hill, A., Khoo, S., Fortunak, J., Simmons, B., & Ford, N. (2014). Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. *Clin Infect Dis, 58*(7), 928-936. doi:10.1093/cid/ciu012

Hirode, G., Saab, S., & Wong, R. J. (2020). Trends in the Burden of Chronic Liver Disease Among Hospitalized US Adults. *JAMA Netw Open, 3*(4), e201997. doi:10.1001/jamanetworkopen.2020.1997

Hsu, Y. C., Ho, H. J., Huang, Y. T., Wang, H. H., Wu, M. S., Lin, J. T., & Wu, C. Y. (2015). Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut, 64*(3), 495-503. doi:10.1136/gutjnl-2014-308163

Huang, Y. T., Hsieh, Y. Y., Chen, W. M., Tung, S. Y., Wei, K. L., Shen, C. H., . . . Chang, T. S. (2021). Sofosbuvir/velpatasvir is an effective treatment for patients with hepatitis C and advanced fibrosis or cirrhosis in a real-world setting in Taiwan. *BMC Gastroenterol, 21*(1), 259. doi:10.1186/s12876-021-01837-y

Innes, H., Goldberg, D., Dillon, J., & Hutchinson, S. J. (2015). Strategies for the treatment of Hepatitis C in an era of interferon-free therapies: what public health outcomes do we value most? *Gut, 64*(11), 1800-1809. doi:10.1136/gutjnl-2014-308166

Innes, H. A., McDonald, S. A., Dillon, J. F., Allen, S., Hayes, P. C., Goldberg, D., . . . Hutchinson, S. J. (2015). Toward a more complete understanding of the association between a hepatitis C sustained viral response and cause-specific outcomes. *Hepatology, 62*(2), 355-364. doi:10.1002/hep.27766

Jaruvongvanich, V., Sanguankeo, A., Klomjit, N., & Upala, S. (2017). Effects of caffeine consumption in patients with chronic hepatitis C: A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol, 41*(1), 46-55. doi:10.1016/j.clinre.2016.05.012

Jayasekera, C. R., Barry, M., Roberts, L. R., & Nguyen, M. H. (2014). Treating hepatitis C in lower-income countries. *N Engl J Med, 370*(20), 1869-1871. doi:10.1056/NEJMp1400160

Keating, G. M. (2016). Ombitasvir/Paritaprevir/Ritonavir: A Review in Chronic HCV Genotype 4 Infection. *Drugs, 76*(12), 1203-1211. doi:10.1007/s40265-016-0612-1

Kohli, A., Kattakuzhy, S., Sidharthan, S., Nelson, A., McLaughlin, M., Seamon, C., . . . Kottilil, S. (2015). Four-Week Direct-Acting Antiviral Regimens in Noncirrhotic Patients With Hepatitis C Virus Genotype 1 Infection: An Open-Label, Nonrandomized Trial. *Ann Intern Med, 163*(12), 899-907. doi:10.7326/m15-0642

Kwo, P. Y., Poordad, F., Asatryan, A., Wang, S., Wyles, D. L., Hassanein, T., . . . Mensa, F. J. (2017). Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. *J Hepatol, 67*(2), 263-271. doi:10.1016/j.jhep.2017.03.039

Lawitz, E., Poordad, F. F., Pang, P. S., Hyland, R. H., Ding, X., Mo, H., . . . Membreno, F. E. (2014). Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet, 383*(9916), 515-523. doi:10.1016/s0140-6736(13)62121-2

Moon, S., & Erickson, E. (2019). Universal Medicine Access through Lump-Sum Remuneration - Australia's Approach to Hepatitis C. *N Engl J Med, 380*(7), 607-610. doi:10.1056/NEJMp1813728

Nguyen, L. H., & Nguyen, M. H. (2013). Systematic review: Asian patients with chronic hepatitis C infection. *Aliment Pharmacol Ther, 37*(10), 921-936. doi:10.1111/apt.12300

Njei, B., McCarty, T. R., Fortune, B. E., & Lim, J. K. (2016). Optimal timing for hepatitis C therapy in US patients eligible for liver transplantation: a cost-effectiveness analysis. *Aliment Pharmacol Ther, 44*(10), 1090-1101. doi:10.1111/apt.13798

Poordad, F., Bennett, M., Sepe, T. E., Cohen, E., Reindollar, R. W., Everson, G., . . . Younes, Z. (2019). Ombitasvir/paritaprevir/ritonavir and dasabuvir with or without sofosbuvir for patients with hepatitis C virus genotype 1 infection who failed a prior course of direct-acting antiviral therapy. *J Med Virol, 91*(7), 1307-1312. doi:10.1002/jmv.25448

Reig, M., Mariño, Z., Perelló, C., Iñarrairaegui, M., Ribeiro, A., Lens, S., . . . Bruix, J. (2016). Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol, 65*(4), 719-726. doi:10.1016/j.jhep.2016.04.008

Sarrazin, C., & Zeuzem, S. (2010). Resistance to direct antiviral agents in patients with hepatitis C virus infection. *Gastroenterology, 138*(2), 447-462. doi:10.1053/j.gastro.2009.11.055

Setiawan, V. W., Porcel, J., Wei, P., Stram, D. O., Noureddin, N., Lu, S. C., . . . Noureddin, M. (2017). Coffee Drinking and Alcoholic and Nonalcoholic Fatty Liver Diseases and Viral Hepatitis in the Multiethnic Cohort. *Clin Gastroenterol Hepatol, 15*(8), 1305-1307. doi:10.1016/j.cgh.2017.02.038

Shahid, I., AlMalki, W. H., Hassan, S., & Hafeez, M. H. (2018). Real-world challenges for hepatitis C virus medications: a critical overview. *Crit Rev Microbiol, 44*(2), 143-160. doi:10.1080/1040841X.2017.1329277

Shahid, I., Alzahrani, A. R., Al-Ghamdi, S. S., Alanazi, I. M., Rehman, S., & Hassan, S. (2021). Hepatitis C Diagnosis: Simplified Solutions, Predictive Barriers, and Future Promises. *Diagnostics (Basel), 11*(7). doi:10.3390/diagnostics11071253

Shahid, I., & Ibrahim, M. M. (2018). All Oral Interferon-free Direct-acting Antivirals as Combination Therapies to Cure Hepatitis C. *Curr Mol Med, 18*(7), 409-435. doi:10.2174/1566524019666190104110439

Stahmeyer, J. T., Rossol, S., Bert, F., Böker, K. H., Bruch, H. R., Eisenbach, C., . . . Krauth, C. (2016). Outcomes and Costs of Treating Hepatitis C Patients in the Era of First Generation Protease Inhibitors - Results from the PAN Study. *PLoS One, 11*(7), e0159976. doi:10.1371/journal.pone.0159976

Sulkowski, M. S., Gardiner, D. F., Rodriguez-Torres, M., Reddy, K. R., Hassanein, T., Jacobson, I., . . . Grasela, D. M. (2014). Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med, 370*(3), 211-221. doi:10.1056/NEJMoa1306218

Waked, I., Shiha, G., Qaqish, R. B., Esmat, G., Yosry, A., Hassany, M., . . . Doss, W. (2016). Ombitasvir, paritaprevir, and ritonavir plus ribavirin for chronic hepatitis C virus genotype 4 infection in Egyptian patients with or without compensated cirrhosis (AGATE-II): a multicentre, phase 3, partly randomised open-label trial. *Lancet Gastroenterol Hepatol, 1*(1), 36-44. doi:10.1016/s2468-1253(16)30002-4

Wiktor, S. (2019). How feasible is the global elimination of HCV infection? *Lancet, 393*(10178), 1265-1267. doi:10.1016/S0140-6736(18)32750-8

Wyles, D., Bräu, N., Kottilil, S., Daar, E. S., Ruane, P., Workowski, K., . . . Sulkowski, M. (2017). Sofosbuvir and Velpatasvir for the Treatment of Hepatitis C Virus in Patients Coinfected With Human Immunodeficiency Virus Type 1: An Open-Label, Phase 3 Study. *Clin Infect Dis, 65*(1), 6-12. doi:10.1093/cid/cix260

Younossi, Z. M., Stepanova, M., Feld, J., Zeuzem, S., Sulkowski, M., Foster, G. R., . . . Hunt, S. (2017). Sofosbuvir and Velpatasvir Combination Improves Patient-reported Outcomes for Patients With HCV Infection, Without or With Compensated or Decompensated Cirrhosis. *Clin Gastroenterol Hepatol, 15*(3), 421-430.e426. doi:10.1016/j.cgh.2016.10.037

Younossi, Z. M., Stepanova, M., Sulkowski, M., Foster, G. R., Reau, N., Mangia, A., . . . Hunt, S. (2016). Ribavirin-Free Regimen With Sofosbuvir and Velpatasvir Is Associated With High Efficacy and Improvement of Patient-Reported Outcomes in Patients With Genotypes 2 and 3 Chronic Hepatitis C: Results From Astral-2 and -3 Clinical Trials. *Clin Infect Dis, 63*(8), 1042-1048. doi:10.1093/cid/ciw496

Zoratti, M. J., Siddiqua, A., Morassut, R. E., Zeraatkar, D., Chou, R., van Holten, J., . . . Druyts, E. (2020). Pangenotypic direct acting antivirals for the treatment of chronic hepatitis C virus infection: A systematic literature review and meta-analysis. *EClinicalMedicine, 18*, 100237. doi:10.1016/j.eclinm.2019.12.007