MINIREVIEWS

Hepatitis C: Treatment of difficult to treat patients

Eric G Hilgenfeldt, Alex Schlachterman, Roberto J Firpi

Eric G Hilgenfeldt, Department of Internal Medicine, University of Florida College of Medicine, Gainesville, FL 32610, United States

Alex Schlachterman, Roberto J Firpi, Department of Gastroenterology, Hepatology and Nutrition, University of Florida College of Medicine, Gainesville, FL 32610, United States

Roberto J Firpi, Section of Hepatobiliary Diseases and Transplantation, University of Florida, Gainesville, FL 32610, United States

Correspondence to: Roberto J Firpi, MD, MS, AGAF, Director of Hepatology and Liver Transplant, Section of Hepatobiliary Diseases and Transplantation, University of Florida, 1600 SW Archer Rd, MSB Rm M440, Gainesville, FL 32610, United States. roberto.firpi@medicine.ufl.edu
Telephone: +1-352-2739466
Fax: +1-352-3927393

Abstract

Over the past several years, more so recently, treatment options for hepatitis C virus (HCV) have seemed to exponentially grow. Up until recently, the regimen of pegylated interferon (peg-IFN) and ribavirin (RBV) stood as the standard of care. Direct acting antivirals, which target nonstructural proteins involved in replication and infection of HCV were first approved in 2011 as an addition to the peg-IFN and RBV regimen and with them have come increased sustained virological response rates (SVR). The previously reported 50%-70% SVR rates using the combination of peg-IFN and RBV are no longer the standard of care with direct acting antiviral (DAA) based regimens now achieving SVR of 70%-90%. Peg-IFN free as well as "all oral" regimens are also available. The current randomized controlled trials available show favorable SVRs in patients who are naive to treatment, non-cirrhotic, and not human immunodeficiency virus (HIV)-co-infected. What about patients who do not fit into these categories? In this review, we aim to discuss the currently approved and soon to be approved DAAs while focusing on their roles in patients that are treatment experienced, cirrhotic, or co-infected with HIV. In this discussion, review of the clinical trials leading to recent consensus guidelines as well as discussion of barriers to treatment will occur. A case will attempt will be made that social services, including financial support and drug/alcohol treatment, should be provided to all HCV infected patients to improve chances of cure and thus prevention of late stage sequela.

Key words: Hepatitis C virus; Direct acting antiviral; Human immunodeficiency virus; Cirrhosis; Treatment experienced

Core tip: The current randomized controlled trials available show favorable sustained virologic responses

in patients who are naive to treatment, non-cirrhotic, and not human immunodeficiency virus (HIV)-co-infected. What about patients who do not fit into these categories? In this review, we aim to discuss the currently approved and soon to be approved direct acting antivirals while focusing on their roles in patients that are treatment experienced, cirrhotic, or co-infected with HIV.

INTRODUCTION

In the most recent national health and nutrition examination survey the estimated prevalence of hepatitis C virus (HCV) infection was approximately 3.9 million in the United States alone, with an estimated 2.7 million with chronic infection[1]. Worldwide, the number living with chronic hepatitis C approaches 150 million[2]. These estimates likely fall significantly short given that nearly half of all infected patients have never been tested for HCV. This survey also excluded prisoners and the homeless; two well-known high-risk populations. Over the past several years, more so recently, treatment options for HCV have seemed to exponentially grow. Treatment for HCV began with Food and Drug Administration approval of interferon (IFN) in 1991, followed by combined IFN and ribavirin (RBV) in 1998, and later with pegylated IFN (peg-IFN) in 2001. Up until recently, the regimen of peg-IFN and RBV stood as the standard of care. Direct acting antivirals (DAAs), which target nonstructural proteins involved in replication and infection of HCV were first approved in 2011 as an addition to the peg-IFN and RBV regimen (Table 1).

Sustained virologic response (SVR), which is commonly defined as a lack of HCV detection 12-24 wk following treatment, with RBV and peg-IFN alone was marginal but has continued to improve. By understanding the genome of the HCV, scientists and researchers have been able to exploit its mechanism of transmission by creating inhibitors against several of the nonstructural proteins that are integral to HCV replication and function. As it currently stands, four classes of DAA exist which can be categorized according to the protein they inhibit. They include the NS3/4 protease, NS5A polymerase, and NS5B polymerases (nucleoside and non-nucleoside). The approval of telaprevir (TVR) and boceprevir (BOC) in 2011 marked the start of this new era. The approval of these NS3/4 protease inhibitors occurred following studies showing increased SVR, in comparison to IFN and RBV alone. Two years later this was followed by approval of sofosbuvir (SOF), a nucleoside NS5B inhibitor, and simeprevir (SIM), an NS3/4 protease inhibitor (Table 2).

Several other agents are currently undergoing late stage clinical trials and expected to be approved in the near future (Table 3).

The previously reported 50%-70% SVR rates using the combination of peg-IFN and RBV are no longer the standard of care (Figure 1). New guidelines clearly echo this[3]. IFN free as well as "all oral" regimens are already in place for genotype 2 and probably for genotypes 1 and 4 by the end of the year. RBV free regimens are also being explored[4]. The current randomized controlled trials available convincingly show favorable SVR in patients who are naïve to treatment, non-cirrhotic, and in non-human immunodeficiency virus (HIV)-co-infected, but what about patients who do not fit into these categories? Furthermore, concern for side-effect profile, unfamiliar practitioners and concern for drug-drug interaction has led to avoidance in all but treatment-naive and otherwise healthy patients.

In this review, we aim to discuss the currently approved and soon to be approved DAAs while focusing on their roles in patients that are treatment experienced, cirrhotic, or co-infected with HIV. In this discussion, particular attention will be paid to the continued barriers of treatment including ongoing psychological conditions such as addiction or depression, lack of access to care, poor social support, lack of financial resources, and many others. A case will attempt to be made that social services such as financial support and drug or alcohol treatment should be provided to all HCV infected patients in hopes that cure of hepatitis C will become a preventative measure for future development of HCV associated conditions; the most well-known being cirrhosis and hepatocellular carcinoma.

TREATMENT-EXPERIENCED PATIENTS

Treatment-experienced patients is perhaps the largest percentage of the patients to be discussed in this review. Patients who have been previously treated pose perhaps one of the most common dilemmas that practitioners face. This group can be divided into patients who have relapsed, those who partially responded to therapy, and to those who did not respond to treatment or null responders. Other variables to be considered are those that underwent incomplete treatment secondary to drop out and noncompliance.

TVR and BOC
REALIZE: Previous peg-IFN + RBV treated and peg-IFN + RBV failures: Non-responders, partial responders or those who have suffered a relapse were randomized into three treatment groups separated by treatment duration. An SVR rate of 66% was achieve in the 12-wk treatment arm utilizing TVR, peg-IFN, and RBV. Additionally, this study was also able to show a decreased relapse rate of 1% compared to 26% in the control group[5]. In a study published by the *Journal of Hepatology* treatment of prior non-responders, partial responders, and those with relapse using BOC

Table 1 Chronologically listed, Food and Drug Administration approved treatment regimens for hepatitis C virus

HCV (identified in 1989)
Approved drugs 1991-2001
Interferon (approved in 1991)
RBV + standard interferon (1998)
Peg-IFNs (approved in 2001)
Peg-IFN
Peg-IFN + RBV
DAAs 2011-present
Telaprevir and boceprevir
Increase SVR rates and provide the option of response-guided therapy and retreatment for genotype 1 patients
Telaprevir + peg-IFN + RBV, genotype 1 only (2011)
Boceprevir + peg-IFN + RBV, genotype 1 only (2011)
Sofosbuvir
Approved for use in all genotypes. High SVR rates with better tolerability, shorter duration, use in HIV-HCV co-infection, and first interferon-free all-oral regimen in genotype 2, 3 and certain other patients
Sofosbuvir + peg-IFN + RBV, in genotype 1 only (2013)
Sofosbuvir + RBV, without interferon, in genotype 2 and 3, in HIV-HCV co-infection, with any genotype, and in selected situations of genotype 1 (2013)
Simeprevir
High SVR rates with better tolerability and shorter duration for genotype 1
Simeprevir + peg-IFN + RBV, in genotype 1 only (2013)

Adapted from http://www.hepatitis.va.gov. DAAs: Direct acting antivirals; SVR: Sustained virological response; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; RBV: Ribavirin; Peg-IFN: Pegylated interferon.

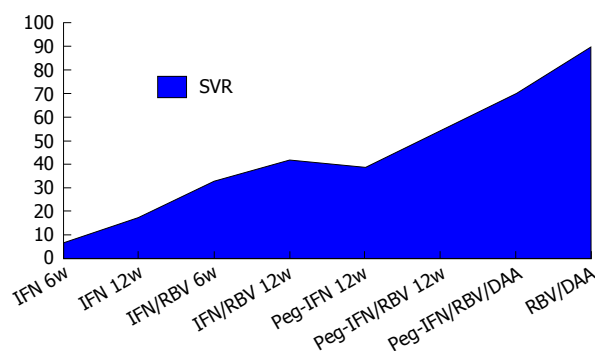| **Table 2 Currently available Food and Drug Administration approved pharmaceuticals for treatment of hepatitis C virus** |
|---|

Approved treatments for hepatitis C		
Brand name	**Generic names**	**Manufacturer name**
Sovaldi	SOF	Gilead Sciences
Olysio	SIM	Janssen
Incivek	TVR	Vertex
Victrelis	BOC	Merck and Co.
Pegasys	Peg-IFN	Roche
CoPegus	RBV	Roche
Pegintron	Peg-IFN alpha-2b	Schering
Intron A	IFN alpha-2b	Schering
Rebetol	RBV	Schering
Roferon	IFN alpha-2a	Roche
Infergen	IFN aphacon-1	Three Rivers Pharma

Adapted from http://www.fda.gov/. SOF: Sofosbuvir; SIM: Simeprevir; TVR: Telaprevir; BOC: Boceprevir; RBV: Ribavirin; Peg-IFN: Pegylated interferon.

Figure 1 Sustained virologic response of various treatment regimens. DAAs: Direct acting antivirals; RBV: Ribavirin; Peg-IFN: Pegylated interferon.

in combination peg-IFN and RBV was able to achieve rates of SVR of 63% percent of all treated followed by 38%, 67%, 93% respectively for each subgroup. The most commonly reported adverse events related to combination therapy utilizing BOC included anemia, fatigue, and dysgeusia[6].

RESPOND-2: Previous peg-IFN + RBV failure: In the RESPOND-2 trial conducted by Bacon *et al*[7] over 400 patients were randomized to receive treatment with BOC along with peg-IFN and RBV following previously failed treatment to peg-IFN and RBV alone. In this trial an SVR of 59%-66% in the BOC group, was achieved as compared with the control group SVR of 21%.

CUPIC: Previous peg-IFN + RBV failure: In this trial Hézode *et al*[8] looked at genotype-1, previously treated

with peg-interferon and RBV patients with a baseline MELD < 13 and Child-Pugh A compensated cirrhosis and examined SVR rates using TVR or BOC in combination with interferon and RBV. Compared with the REALIZE and RESPOND-2 trial, similar rates of SVR at 12 wk was achieved. In the TVR treatment arm an SVR of 75%, 40% and 20% were achieved in previously relapsed patients, partial responders, and null-responders, respectively. The BOC treatment group received slightly less encouraging results with rates of 54%, 38%, 0%, comparatively. Significant side effects occurred in almost half of all those treated in the study. Fifty patients (10%) experienced severe complications or death, with nearly half of these occurring during the first 12 wk of treatment. As has been previously noted in prior studies, severe anemia, requiring either discontinuation or reduction in dosing, as well as transfusion occurred in 134 and 78 of the 511 studied patients, respectively. Multivariate analysis suggested higher risk of side effects in patients with severe hypoalbuminemia and thrombocytopenia. Given the poor response of prior

Table 3 Food and Drug Administration approved and investigational drugs by mechanism of action

HCV NS3/4 protease inhibitors	Nucleos(t)ide HCV NS5B polymerase inhibitors	Non-nucleos(t)ide HCV NS5B polymerase inhibitors	HCV NS5A inhibitors
Telaprevir[1]	Sofosbuvir[1]	BI-207127	Daclatasvir
Boceprevir[1]	Mericitabine	VX-222	Ledipasvir
Danoprevir		ABT-333	ABT-267
Simeprevir[1]		BMS-791325	
ABT-450 (with ritonavir)		Tegobuvir	
Faldaprevir		GS-9669	
Asunaprevir			
GS-9451			

[1]Drugs have received Food and Drug Administration approval. Adapted from http://www.hepatitis.va.gov. HCV: Hepatitis C virus.

null responders, treatment utilizing BOC or TVR in combination with peg-IFN and RBV is not recommended. Due to adverse events, the authors also recommend considering not treating patients with platelet counts < 100000/mm^3 and serum albumin < 3.5 g/dL.

Simeprevir

In a phase Ⅱ clinic trial by Zeuzem *et al*[9], previously treated, genotype-1 infected patients underwent randomization to receive simeprevir in combination with peg-IFN and RBV for either 12, 24, or 48 wk or peg-IFN and RBV alone for 48 wk. The rate of overall SVR was significantly higher in the simeprevir group with 61%-80% *vs* 23% in the peg-IFN + RBV (PR) group. When examining prior null responders, an SVR rate of 38%-59% *vs* 19% was noted. Partial responders and relapsers achieved even higher rates; 48%-86% and 77%-89%, respectively. All groups had comparable numbers of adverse events.

In follow-up, a phase Ⅲ trial conducted by Forns *et al*[10] randomized genotype 1, PR failure patients into either a 12 wk course of SIM + PR (followed by either a 12 or 36 wk course of PR) or 48 wk of PR. SVR12 of 79.2% *vs* 36.1% was noted in the study groups, respectively. Similar adverse events were noted regardless of therapy.

SOF

FUSION: Previous PR + PR failures: Jacobson *et al*[11] looked at treatment with SOF and RBV in genotype 2 and 3 patients who previously failed peg-IFN based therapy. Patients were randomized to receive either 12 or 16 wk of treatment. Patients receiving 16 wk of therapy fared better than the 12 wk group and were able to achieve rates of SVR at 12 wk post therapy of 50% (50/100) and 73% (69/95), respectively. Breakdown of subgroups identified that genotype 2 patients had higher SVR rates than genotype 3. Additionally, non-cirrhotic patients had higher rates of response as compared with cirrhotic patients.

SOF/simeprevir

COSMOS: Previous PR failures: A phase Ⅱ clinical trial randomized 167 treatment naive and previously treated genotype 1 patients to receive both SOF and SIM alone or in combination with RBV[12]. Additionally, these patients were selected to receive either a 12 or 24-wk course of treatment. Among prior null responders with Metavir scores of F0-2 and without the Q80K mutation an SVR12 of 100% was achieved regardless of treatment regimen or duration. In patients with either F3-4 Metavir scores SVR12 fell slightly to 92% (38/41) in the 12 wk treatment arm regardless of treatment regimen. Among all subgroups, the presence of the Q80K mutation in genotype 1a patients conferred a decreased chance of achieving SVR. The extent of treatment resistance remains an area of future study but never the less should be noted when considering simeprevir-containing regimens.

SOF/ledipasvir

ION-2: Previous PR and DAA + PR failures: A trial by Afdhal *et al*[13] published in New England *Journal of Medicine* in 2014 looked at 440 patients who had failed previous peg-IFN and RBV therapy and treated them with SOF and ledipasvir (LED), a nucleoside 5A inhibitor, either with or without RBV. Treatment course was either 12 or 24 wk. In the 12 wk group, triple therapy with RBV resulted in a 96% SVR compared with a 94% in the dual treatment group. When the duration of treatment was extended to 24 wk both treatment arms had 99% SVR.

LONESTAR: Previous DAA + DAA failure: Lawitz *et al*[14] gathered 40 patients previously treated with BOC or TVR who then went on to fail therapy or have recurrence and randomized them to receive SOF and LED with or without RBV for a total of 12 wk. At 12 wk following therapy 95% (18/19) achieved SVR in the dual therapy group *vs* 100% (21/21) in the triple therapy group. Anemia was more common with those treated with RBV, occurring in 6 of the 21 patients, but did not lead to treatment failure or discontinuation.

SOF/daclatasvir

In a study by Sulkowski *et al*[4], 41 of 211 patients with genotype 1 were noted to have previously been treated with protease inhibitors, either BOC or TVR,

without achieving SVR. In this subgroup, randomization to daclatasvir, a nucleoside 5A inhibitor, and SOF with or without RBV for a total of 24 wk showed SVR12 of 100% (21/21) and 95% (19/20), respectively. Notable side effects included nausea, fatigue and headache and were reported in a majority of subjects. Side effects did not lead to discontinuation of treatment.

ABT-450/r/ombitasvir/dasabuvir/RBV

SAPPHIRE-Ⅱ: Previous PR failures: In a phase Ⅲ trial conducted by Zeuzem *et al*[15], 394 genotype 1 patients with prior treatment failure underwent randomization to receive 12 wk of treatment with the study drug regimen or placebo. SVR12 in the active regimen group was noted to be 96.3% (286/297). With only 1% drop out due to side effects and only 4.7% experiencing grade 2 or 3 anemia, this regimen shows some of the best results for HCV therapy to date. Additionally, SVR12 of prior null responders was 95.3% (139/146).

HIV/HCV CO-INFECTION

HIV-infected individuals with concomitant hepatitis C are known to have an increased morbidity and mortality[16]. They are also known to have relatively poor responses to peg-IFN and RBV therapy, as compared with mono-infected patients[17,18]. In a study by Benhamou *et al*[19] which examined HCV-related liver fibrosis progression, a CD4 count below 200/microliter, heavy alcohol consumption, and absence of protease inhibitor therapy were all identified as independent risk factors for progression to cirrhosis in HIV co-infected patients. Several mechanisms are described throughout the literature aiming to address this finding. On a molecular level, it has been noticed that when compared to the HCV mono-infected, HCV-HIV co-infected persons have higher levels of HCV RNA. The higher viral lode of HCV RNA is suspected to be secondary to an increased replication of HCV RNA by HIV proteins[20]. It is also thought that the overall state of immunodeficiency leads to an environment of rapid hepatocyte destruction and fibrosis progression[21].

Following the development of highly active anti-retroviral therapy (HAART) there has been an ever-increasing percentage of HIV infected patients who are dying from liver disease. In HIV infected patients, death from liver disease remains far more prevalent than death attributable to HIV-related complications[22,23]. The increased mortality from liver-related illness appears to be uniquely associated with co-infected patients only. In a large, multi-center, prospective trial examining HAART-related liver mortality in patients not infected with HCV or HBV the rate of death was 0.04/1000 person-years. Of the 12 recorded liver related deaths, seven were deemed to be due to excessive alcohol use while the other five were deemed to be related to HAART-related toxicity[24]. There also exists a mechanism by which HCV and HIV co-infection is thought to increase the risk for both HAART-related liver toxicity and cirrhosis. This mechanism consists of direct cell stress, mitochondrial dysfunction and immune reaction[25]. Though not completely clear, liver related deaths in HIV co-infected patients has been speculated to be the result of either of two reasons; increased lifespan from appropriately treated HIV (leading to the natural progression of HCV related cirrhosis and liver dysfunction) or HAART therapy induced liver toxicity[26]. Confound this with the potential drug-drug interactions, particularly with the newest of DAAs, and it is no wonder trepidation to providing treatment exists[27,28].

Prior to the creation of DAA, RBV and peg-IFN had been used with modest results. In a study published by Torriani *et al*[17] in the *New England Journal of Medicine*, 868 co-infected patients were randomized to receive either peg-IFN and RBV or peg-interferon and placebo for a total of 48 wk. Among the genotype-1 patients who received both peg-IFN as well as RBV an SVR of 29% compared with 62% in those with genotype 2 or 3 was achieved. In particular, a subgroup utilizing a higher dosing regimen proved to be the most efficacious, albeit with a greater prevalence of RBV associated anemia. Additional studies showing similar results exist[29-31].

TVR

With the approval of DAAs, subsequent studies looking at rates of SVR in the HIV co-infected population have shown promising results. In a study by Sulkowski *et al*[32] published in the Annals of Internal Medicine in 2013, a relatively small, yet randomized treatment population underwent combination therapy utilizing TVR in addition to peg-IFN and RBV. In this study 62 patients co-infected with both HCV and HIV were enrolled at multiple investigational sites. Genotype-1 infected patients, without cirrhosis, who had not had any previous HCV treatment and were noted to have "stable HIV disease" where eligible. Stable disease was classified as CD4 counts greater than 0.500×10^9 cells/L and HIV RNA levels < 100000 copies/mL. Antiretroviral regimens were allowed. SVR occurred in 74% (28/30) patients receiving TVR, peg-IFN and RBV *vs* 45% (10/22) of patients receiving peg-IFN and RBV alone. Side effects of pruritus, headache, rash and rectal pain were noted to be higher in the treatment group. Two patients were noted to have HCV breakthrough with TVR resistant variants. With these findings TVR in combination with peg-IFN and RBV improved upon previous rates SVR without appreciable drug-drug interaction or significant side effect.

BOC

In a phase Ⅱ trial by Sulkowski *et al*[33] 99 patients with co-infection of HIV and HCV were randomized in a 1:2 ratio to receive a 48-wk treatment course of either placebo or BOC in combination with RBV and peg-IFN. SVR in the triple therapy group was noted to be 63% compared with 29% in the control group. Adverse events were more common in the triple therapy arm

leading to significant amount of dropout (12 of 65). Reported adverse events included anemia, pyrexia, dysgeusia, vomiting and neutropenia. Additionally, HIV virological breakthrough occurred in seven patients; three receiving triple therapy and four in the control group. Considerable variability among patients that had breakthrough existed. In comparison to patients with HCV alone, co-infected patients who did not achieve SVR were noted to have significantly more (80% *vs* 53%) had resistant variants. Given some of the findings in this study, larger trials should be done to better characterize safety and efficacy of this regimen.

SOF
PHOTON-1: Genotype 1 patients with HIV infection: Sulkowski *et al*[34] conducted a trial utilizing an interferon sparing, 24-wk regimen comprised of SOF and RBV in genotype-1, 2 and 3. In the genotype 1 group an SVR of 76% regardless of antiretroviral regimen and with minimal drug-drug interactions was achieved. Based on this study, extrapolations of this data in co-infected patients with genotypes 2, 4, 5, and 6 current HCV guidelines recommend treatment with SOF in combination with RBV for 12 wk. Genotype 1 and 3 patients are recommended to undergo treatment with a 12 or 24-wk course of SOF, RBV and peg-IFN, respectively. Alternatives for patients who are peg-IFN intolerant exist. These regimens typically include combination therapy with SOF, simeprevir and RBV[3].

SOF/LED
NIAID ERADICATE: Genotype 1 patients with HIV infection: In the abstract presented by Osinusi *et al*[35], 50 HCV and HIV co-infected patients were given a 12-wk course of SOF and LED. Grouping based on HAART naive*vs* on HAART showed no difference in the 100% SVR rates achieved in both groups. No adverse events or discontinuations were noted during the treatment period.

CIRRHOTIC PATIENTS
Development of cirrhosis in patients with chronic hepatitis C infection occurs by molecular mechanisms involving inappropriate collagen deposition *via* the hepatic stellate cell. As described by Fontana *et al*[36] HCV infection is thought first to lead to release of metalloproteinases, which break down the surrounding low-density matrix within the sub-endothelial space. Then, recruitment and activation of stellate and Kupffer cells go on to deposit various forms of collagen within the extracellular matrix, forming what is termed fibrosis. More specifically, fibrosis is characterized by the presence of portal-central and portal-portal bands of this deposited collagen. With this change in the typical architecture, eventual disruption of normal processes of blood flow and nutrient exchange occurs, leading to the physiological manifestations of cirrhosis. Although new imaging modalities such as computed tomography,

magnetic resonance imaging, ultrasound and transient elastography remain promising noninvasive methods for diagnosing and grading cirrhosis, the ability to distinguish moderate, less advanced, disease is lacking. The gold standard for diagnosis and monitoring both the extent of fibrosis and portal hypertension remains liver biopsy and measurement of the hepatic venous portal gradient, respectively[37]. Of all patients with HCV, 80% are estimated to go on to developed chronic infection, 10%-15% of which will develop cirrhosis at 20 years after contracting the illness[38].

BOC
Cirrhosis, regardless of its level of compensation, has been documented on several occasions to result in decreased SVR in patients being treated for HCV. A meta-analysis done by Vierling *et al*[6] examined 5, phase Ⅲ, clinical trials of biopsy proven cirrhosis patients treated with either RBV and peg-IFN alone or in combination with BOC. Pooled estimates from these studies revealed a 55% SVR in the triple therapy group compared with 17% in the RBV and peg-IFN group. In terms of adverse side effects, anemia and diarrhea were significantly more prevalent in the triple therapy treatment arm. This postulated to be the result of either added side effects of BOC or the patient's underlying cirrhosis.

Simeprevir
PROMISE: Genotype 1, previous PR, with cirrhosis: In the trial by Forns *et al*[10] as mentioned above, a subpopulation of patients with cirrhosis/advanced fibrosis were studied and were able to achieve an SVR of 74%, compared to 79% when not taking into account presence of cirrhosis. Common adverse events included rash, flulike illness, pruritus and therefore had a better side effect profile than its predecessor's BOC and TVR. One factor that must be considered when using simeprevir is testing for the Q80K mutation prior to treatment initiation. Diminished responses were noted in genotype 1A with the mutation.

SOF
FISSION: Genotype 2 and genotype 3, treatment naïve, with and without cirrhosis: Four hundred and ninety nine genotype 2 and 3 patients were treated with either 12 wk of SOF and RBV or 24 wk of peg-IFN and RBV. Of the 499, 70% were genotype 3 and of these 20% were documented cirrhotic. The trial met the non-inferiority endpoint, showing an overall SVR rate of 67%, however analysis based on HCV genotype showed genotype 2 patients achieved 93% SVR, compared to only 56% in genotype 3 patients. Furthermore, liver fibrosis further decreased SVR to 34%. Cirrhosis in the genotype-2 patients did not influence SVR rates (91%) comparatively[14].

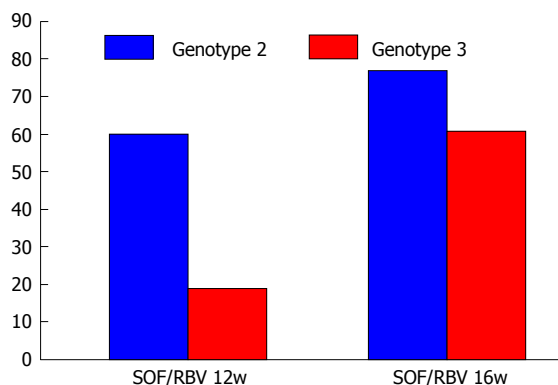**FUSION: Genotype 2 and genotype 3, previous PR, with and without cirrhosis:** In the FUSION trial,

Figure 2 Cirrhotic patients in the fusion trial. SOF: Sofosbuvir; RBV: Ribavirin.

subgroup analysis among cirrhotic patients with HCV treated with either 12 or 16 wk of SOF and RBV showed favorable results among genotype 2 patients treated for 16 wk. In this group an SVR of 78% was achieved. Less favorable results were noted in the 12-wk group with slightly better results occurring in those with genotype 2 (Figure 2).

SOF/LED
A recently published randomized trial by Gane *et al*[39] in Gastroenterology focusing on treatment with SOF in combination with LED with or without RBV for treatment of null responders with cirrhosis showed promising results. All patients (9/9) receiving triple therapy were able to achieve SVR. In the group of those receiving only SOF and LED, 7 of 10 achieved SVR. Both the unknown degree of cirrhosis and the small sample size remain limiting factors in this study. Adverse effects related to the RBV regimen are consistent with prior studies of cirrhotic patients showing a greater percentage of anemia in this group. In the RBV free regimen patients remained with stable hemoglobin levels suggesting that RBV and not cirrhosis itself contributes the anemia seen with typical treatment regimens.

LONESTAR: Previous DAA + DAA failure: In the trial by Lawitz *et al*[14], similar success rates in cirrhotic patients being treated with SOF based regimens *vs* non-cirrhotic patients was noted. Twenty two of 40 previously treated patients with compensated cirrhosis fared well overall, given that 39/40 of the patients achieved SVR, however this study is limited by its relatively small size.

It remains essential that we understand that development of cirrhosis in patients with hepatitis C leads to a potentially devastating disease. Once decompensation with either development of ascites, variceal hemorrhage, encephalopathy, coagulopathy, the probability of survival is only 50% at five years, with a median survival of only two years[40,41]. Therefore, pursuit of a cure using direct antiviral therapy should be pursued. Of the discussed DAAs, SOF-based regimens appear to provide the best chance of this and are consistent with the recommended treatment regimens of recently published consensus guidelines.

BARRIERS TO TREATMENT
Hepatitis C is a physical, mental, and social disease affecting not only the individual, but also the individual's loved ones and society as a whole. Considered a global disease, and for that matter the only currently curable chronic viral infection, the importance of pursuing treatment for hepatitis C remains paramount. Despite this, several barriers hindering this effort have been identified. These include: awareness of available therapy, financial constraints, and practitioners willing to prescribe treatment.

Comorbid psychiatric illness
It is well known the concomitant psychiatric illness plagues patients with hepatitis C. It is currently estimated that the largest at risk population for contracting hepatitis C is it that of intravenous (*iv*) drug users[42]. The problem is two-fold, in a study done by Johnson *et al*[43] in the American *Journal of Gastroenterology*, 309 current *iv* drug users undergoing substance abuse treatment were evaluated. In this group over 50% of test subjects were found to be positive for HCV antibodies and of the HCV positive patients, over half were noted to have concomitant depression. In addition to the pre-existing depression seen in this group, the treatment for HCV itself up until this point had also significantly contributed to depressive symptoms. Interferon in particular, has had a documented side effect profile consisting of fatigue, anxiety, and depression. Despite the black box warning associated with peg-IFN, studies show that patients with mood disorders currently in remission and receiving treatment should not be excluded from receiving interferon therapy[44]. Additionally, treatment of interferon associated depression and cognitive disorders can be achieved with the use of antidepressants and stimulators[45,46].

It is estimated that one in six incarcerated patients have hepatitis C and therefor the public perception remains that hepatitis C is acquired illness. As such, I anticipate continued difficulty obtaining social and financial support for concomitant *iv* drug use treatment, despite the fact that studies show co-administration of strict drug treatment program decreased risk of relapse and increase completion of treatment and monitoring.

Cost
Despite the excitement and promise these new therapies all hold, the cost-effectiveness of pursuing cure for hepatitis C has been a tougher pill to swallow than the actual treatment itself. SOF has been drawing attention recently. At around one thousand dollars per pill, 12 wk, a standard treatment course would run the patient and their insurance provider approximately $84000 with other DAA sharing similar price tags. The endeavor of validating coverage depends on the potential long-term savings from providing a cure. It is

difficult to estimate the exact savings per patient due to the various other factors involved, however rough estimates are possible. Consider this, the average annual health care costs for patients with chronic hepatitis C infection without cirrhosis is $17277. Once cirrhosis develops costs rise to $22752 among patients with compensated cirrhosis, and $59995 once end-stage liver disease develops[47]. Patients with compensated cirrhosis have been documented to live for at least a decade prior to development of decompensation[40]. This would amount to approximately $275000 in health care costs over this decade. Considering the median two-year survival for decompensated cirrhosis an additional $120000 would accrue. Lastly, if a candidate, liver transplantation with an average price tag ranging in upwards of $575000, per United Network for Organ Sharing, brings the total to over $1 million in health care costs[48]. Looking back at the treatment price tag of $84000 little hesitation should be had. This is not the case however because many variables play a part. Notably, incomplete treatment, unsuccessful treatment, and reinfection are always possible, particularly in patients with comorbid psychiatric illness, concomitant drug addiction, and poor social support; all known risks factors for contracting HCV[49]. In the long run this issue should continue to fade in its controversy given that minimum manufacturing costs for producing direct acting antivirals have been estimated at $100-$250 for a 12 wk course of treatment once patent expires and production of generic versions is available[50].

Aside from the cost savings achieved when no longer needing to treat the manifestations of chronic hepatitis C, cure of hepatitis C has been shown to provide additional benefits. Beside the improvement in psychological and social well-being which accompanies cure of hepatitis C, treatment also has been shown to decrease and potentially reverse cirrhosis, esophageal varices, and the risk for development of hepatocellular carcinoma[51-53].

Practitioner experience
In patients who are co-infected with HIV as well as HCV, the potential for complex drug interactions between HAART and direct antiviral agents can lead to trepidation among primary care providers when debating the initiation of treatment for HCV. Additionally, a practitioner's concerns about reinfection as well as their bias regarding *iv* drug users also represent barriers to engagement in treatment of HCV in patients[54]. Therefore, it is recommended, as outlined in the recent consensus article published in The Infectious Disease Society of America, that only practitioners who are comfortable in routine treatment of HIV, cirrhosis, and/or have familiarity with DAA should be involved in treatment for HCV. Therefor infectious disease specialists and hepatologists should be the providers responsible for initiating treatment of HCV for co-infected individuals, cirrhotic patients, and patients who have previously failed treatment.

Tolerability
Treatment for HCV had long been known to be as unpleasant as it was burdensome, leading to noncompliance and decreased quality of life during treatment. IFN based regimens, in particular, are riddled with adverse side effects[55]. For example, both the BOC and TVR regimens have complex dosing schedules and heavy pill burdens that will invariably lead to both incomplete compliance and treatment dropout[56]. As new treatments arise, the effect of the various regimens should not only be examined for response rates but should be evaluated for their tolerability. In several studies, Younossi *et al*[57,58] did just that. Examination of patient reported outcomes and health related quality of life data of patients in four different phase III clinical trials noted that patients who received treatment with the peg-IFN free regimen of SOF and RBV noted the smallest decline in quality of life scores among all treatment groups suggesting that INF free regimens lead to better tolerability and better adherence; both factors essential in increasing compliance. Aside from side effects, route of administration will surely have patients asking for IFN free regimens[59].

CONCLUSION
As indicated in several of the studies reviewed, SOF appears to currently be one of the best choices in all-comers. Further studies with larger populations of difficult to treat patients are warranted to fully assess the continued success, safety and side effects. Based on the studies examined, most of which included phase II and III trials, the current literature favors usage of a SOF-based regimen in patients with cirrhosis, HIV/HCV co-infection and prior treatment failure. As shown, SOF has proven efficacy in both cirrhotic and non-cirrhotic patients and also appears to span all genotypes. The limited drug-drug interactions make it a favorable option in patients co-infected with HIV. Additionally, the route of administration and the favorable side effect profile will lead to overall improvement in quality of life and compliance. Treatment and cure of hepatitis C is now probable, even in "difficult to treat" patients. Without financial assistance programs, practitioner awareness, and co-administered substance abuse treatment programs the potential gains these revolutionary drugs offer will fail to render an impact on prevention of long-term hepatitis C complications.

REFERENCES
1   **Denniston MM**, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, Holmberg SD. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med* 2014; **160**: 293-300 [PMID: 24737271 DOI: 10.7326/M13-1133]
2   **WHO**. Hepatitis C, Fact sheet N°164. [Updated 2014 April]. Available from: URL: http://www.who.int/mediacentre/factsheets/fs164/en/
3   **American Association for the Study of Liver Diseases and the**

Infectious Diseases Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C. Available from: URL: http://www.hcvguidelines.org

4   **Sulkowski MS**, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; **370**: 211-221 [PMID: 24428467 DOI: 10.1056/NEJMoa1306218]

5   **Zeuzem S**, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; **364**: 2417-2428 [PMID: 21696308 DOI: 10.1056/NEJMoa1013086]

6   **Vierling JM**, Zeuzem S, Poordad F, Bronowicki JP, Manns MP, Bacon BR, Esteban R, Flamm SL, Kwo PY, Pedicone LD, Deng W, Dutko FJ, DiNubile MJ, Koury KJ, Helmond FA, Wahl J, Bruno S. Safety and efficacy of boceprevir/peginterferon/ribavirin for HCV G1 compensated cirrhotics: meta-analysis of 5 trials. *J Hepatol* 2014; **61**: 200-209 [PMID: 24747798 DOI: 10.1016/j.jhep.2014.03.022]

7   **Bacon BR**, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1207-1217 [PMID: 21449784 DOI: 10.1056/NEJMoa1009482]

8   **Hézode C**, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva V, De Ledinghen V, Poynard T, Samuel D, Bourliere M, Alric L, Raabe JJ, Zarski JP, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Chazouilleres O, Abergel A, Guyader D, Metivier S, Tran A, Di Martino V, Causse X, Dao T, Lucidarme D, Portal I, Cacoub P, Gournay J, Grando-Lemaire V, Hillon P, Attali P, Fontanges T, Rosa I, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Carrat F, Bronowicki JP. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. *Gastroenterology* 2014; **147**: 132-142.e4 [PMID: 24704719 DOI: 10.1053/j.gastro.2014.03.051]

9   **Zeuzem S**, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, Hezode C, Hirschfield GM, Jacobson I, Nikitin I, Pockros PJ, Poordad F, Scott J, Lenz O, Peeters M, Sekar V, De Smedt G, Sinha R, Beumont-Mauviel M. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology* 2014; **146**: 430-41.e6 [PMID: 24184810 DOI: 10.1053/j.gastro.2013.10.058]

10 **Forns X**, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, Horban A, Brown A, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, Scott J, De La Rosa G, Kalmeijer R, Sinha R, Beumont-Mauviel M. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. *Gastroenterology* 2014; **146**: 1669-79.e3 [PMID: 24602923 DOI: 10.1053/j.gastro.2014.02.051]

11 **Jacobson IM**, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**: 1867-1877 [PMID: 23607593 DOI: 10.1056/NEJMoa1214854]

12 **Lawitz E**, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, DeJesus E, Pearlman B, Rabinovitz M, Gitlin N, Lim JK, Pockros PJ, Scott JD, Fevery B, Lambrecht T, Ouwerkerk-Mahadevan S, Callewaert K, Symonds WT, Picchio G, Lindsay KL, Beumont M, Jacobson IM. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet* 2014; **384**: 1756-1765 [PMID: 25078309 DOI: 10.1016/S0140-6736(14)61036-9]

13 **Afdhal N**, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herring R, Lalezari J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1483-1493 [PMID: 24725238 DOI: 10.1056/NEJMoa1316366]

14 **Lawitz E**, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, Symonds WT, McHutchison JG, Membreno FE. 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* 2014; **383**: 515-523 [PMID: 24209977 DOI: 10.1016/S0140-6736(13)62121-2]

15 **Zeuzem S**, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlière M, Sulkowski MS, Wedemeyer H, Tam E, Desmond P, Jensen DM, Di Bisceglie AM, Varunok P, Hassanein T, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014; **370**: 1604-1614 [PMID: 24720679 DOI: 10.1056/NEJMoa1401561]

16 **Zeremski M**, Martinez AD, Talal AH. Editorial commentary: Management of hepatitis C Virus in HIV-infected patients in the era of direct-acting antivirals. *Clin Infect Dis* 2014; **58**: 880-882 [PMID: 24336913 DOI: 10.1093/cid/cit804]

17 **Torriani FJ**, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-García J, Lazzarin A, Carosi G, Sasadeusz J, Katlama C, Montaner J, Sette H, Passe S, De Pamphilis J, Duff F, Schrenk UM, Dieterich DT. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; **351**: 438-450 [PMID: 15282351 DOI: 10.1056/NEJMoa040842]

18 **Opravil M**, Rodriguez-Torres M, Rockstroh J, Snoeck E, Chung RT, Tietz A, Torriani FJ. The dose-response relationship of peginterferon alfa-2a and ribavirin in the treatment of patients coinfected with HIV-HCV. *HIV Clin Trials* 2012; **13**: 33-45 [PMID: 22306586 DOI: 10.1310/hct1301-033]

19 **Benhamou Y**, Di Martino V, Bochet M, Colombet G, Thibault V, Liou A, Katlama C, Poynard T. Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy. *Hepatology* 2001; **34**: 283-287 [PMID: 11481613 DOI: 10.1053/jhep.2001.26517]

20 **Deng A**, Chen C, Ishizaka Y, Chen X, Sun B, Yang R. Human immunodeficiency virus type 1 Vpr increases hepatitis C virus RNA replication in cell culture. *Virus Res* 2014; **184**: 93-102 [PMID: 24589706 DOI: 10.1016/j.virusres.2014.02.017]

21 **Di Martino V**, Rufat P, Boyer N, Renard P, Degos F, Martinot-Peignoux M, Matheron S, Le Moing V, Vachon F, Degott C, Valla D, Marcellin P. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. *Hepatology* 2001; **34**: 1193-1199 [PMID: 11732009 DOI: 10.1053/jhep.2001.29201]

22 **Weber R**, Sabin CA, Friis-Møller N, Reiss P, El-Sadr WM, Kirk O, Dabis F, Law MG, Pradier C, De Wit S, Akerlund B, Calvo G, Monforte Ad, Rickenbach M, Ledergerber B, Phillips AN, Lundgren JD. Liver-related deaths in persons infected with the human immunodeficiency virus: the D: A: D study. *Arch Intern Med* 2006; **166**: 1632-1641 [PMID: 16908797 DOI: 10.1001/archinte.166.15.1632]

23 **Sherman KE**. Treatment of hepatitis C virus and human immunodeficiency virus co-infection. *Clin Gastroenterol Hepatol* 2005; **3**: S118-S121 [PMID: 16234058]

24 **Kovari H**, Sabin CA, Ledergerber B, Ryom L, Worm SW, Smith C, Phillips A, Reiss P, Fontas E, Petoumenos K, De Wit S, Morlat P, Lundgren JD, Weber R. Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of hepatitis B or C virus coinfection: the data collection on adverse events of anti-HIV drugs study. *Clin Infect Dis* 2013; **56**: 870-879 [PMID: 23090925 DOI: 10.1093/cid/cis919]

25 **Russmann S**, Kullak-Ublick GA, Grattagliano I. Current concepts of mechanisms in drug-induced hepatotoxicity. *Curr Med Chem* 2009; **16**: 3041-3053 [PMID: 19689281]

26 **Thomas DL**. The challenge of hepatitis C in the HIV-infected person. *Annu Rev Med* 2008; **59**: 473-485 [PMID: 18186707 DOI: 10.1146/annurev.med.59.081906.081110]

27 **Chen EY**, North CS, Fatunde O, Bernstein I, Salari S, Day B, Jain MK. Knowledge and attitudes about hepatitis C virus (HCV) infection and its treatment in HCV mono-infected and HCV/HIV co-infected adults. *J Viral Hepat* 2013; **20**: 708-714 [PMID: 24010645 DOI: 10.1111/jvh.12095]

28 **Karageorgopoulos DE**, El-Sherif O, Bhagani S, Khoo SH. Drug interactions between antiretrovirals and new or emerging direct-acting antivirals in HIV/hepatitis C virus coinfection. *Curr Opin Infect Dis* 2014; **27**: 36-45 [PMID: 24305043 DOI: 10.1097/QCO.0000000000000034]

29 **Carrat F**, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, Morand P, Goujard C, Pialoux G, Piroth L, Salmon-Céron D, Degott C, Cacoub P, Perronne C. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA* 2004; **292**: 2839-2848 [PMID: 15598915 DOI: 10.1001/jama.292.23.2839]

30 **Chung RT**, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, Peters MG, Koziel MJ, Bhan AK, Alston B, Colquhoun D, Nevin T, Harb G, van der Horst C. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004; **351**: 451-459 [PMID: 15282352 DOI: 10.1056/NEJMoa032653]

31 **Laguno M**, Murillas J, Blanco JL, Martínez E, Miquel R, Sánchez-Tapias JM, Bargallo X, García-Criado A, de Lazzari E, Larrousse M, León A, Loncá M, Milinkovic A, Gatell JM, Mallolas J. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS* 2004; **18**: F27-F36 [PMID: 15316335]

32 **Sulkowski MS**, Sherman KE, Dieterich DT, Bsharat M, Mahnke L, Rockstroh JK, Gharakhanian S, McCallister S, Henshaw J, Girard PM, Adiwijaya B, Garg V, Rubin RA, Adda N, Soriano V. Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV: a randomized trial. *Ann Intern Med* 2013; **159**: 86-96 [PMID: 23685940 DOI: 10.7326/0003-4819-159-2-201307160-00654]

33 **Sulkowski M**, Pol S, Mallolas J, Fainboim H, Cooper C, Slim J, Rivero A, Mak C, Thompson S, Howe AY, Wenning L, Sklar P, Wahl J, Greaves W. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. *Lancet Infect Dis* 2013; **13**: 597-605 [PMID: 23768747 DOI: 10.1016/S1473-3099(13)70149-X]

34 **Sulkowski MS**, Naggie S, Lalezari J, Fessel WJ, Mounzer K, Shuhart M, Luetkemeyer AF, Asmuth D, Gaggar A, Ni L, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Rodriguez-Torres M, Dieterich D. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA* 2014; **312**: 353-361 [PMID: 25038354 DOI: 10.1001/jama.2014.7734]

35 **Osinusi A**, Kohli A, Marti MM, Nelson A, Zhang X, Meissner EG, Silk R, Townsend K, Pang PS, Subramanian GM, McHutchison JG, Fauci AS, Masur H, Kottilil S. Re-treatment of chronic hepatitis C virus genotype 1 infection after relapse: an open-label pilot study. *Ann Intern Med* 2014; **161**: 634-638 [PMID: 25364884 DOI: 10.7326/M14-1211]

36 **Fontana RJ**, Everson GT, Tuteja S, Vargas HE, Shiffman ML. Controversies in the management of hepatitis C patients with advanced fibrosis and cirrhosis. *Clin Gastroenterol Hepatol* 2004; **2**: 183-197 [PMID: 15017601]

37 **Kim MY**, Jeong WK, Baik SK. Invasive and non-invasive diagnosis of cirrhosis and portal hypertension. *World J Gastroenterol* 2014; **20**: 4300-4315 [PMID: 24764667 DOI: 10.3748/wjg.v20.i15.4300]

38 National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C 2002 (June 10-12, 2002). *Gastroenterology* 2002; **123**: 2082-2099 [PMID: 12454863 DOI: 10.1053/gast.2002.1232082]

39 **Gane EJ**, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, Symonds WT, McHutchison JG, Pang PS. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. *Gastroenterology* 2014; **146**: 736-743.e1 [PMID: 24262278 DOI: 10.1053/j.gastro.2013.11.007]

40 **Fattovich G**, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens F, Solinas A, Mura D, Brouwer JT, Thomas H, Njapoum C, Casarin C, Bonetti P, Fuschi P, Basho J, Tocco A, Bhalla A, Galassini R, Noventa F, Schalm SW, Realdi G. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; **112**: 463-472 [PMID: 9024300]

41 **D'Amico G**, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; **44**: 217-231 [PMID: 16298014 DOI: 10.1016/j.jhep.2005.10.013]

42 **Aspinall EJ**, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, Goldberg DJ, Hellard ME. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clin Infect Dis* 2013; **57 Suppl 2**: S80-S89 [PMID: 23884071 DOI: 10.1093/cid/cit306]

43 **Johnson ME**, Fisher DG, Fenaughty A, Theno SA. Hepatitis C virus and depression in drug users. *Am J Gastroenterol* 1998; **93**: 785-789 [PMID: 9625128 DOI: 10.1111/j.1572-0241.1998.225_a.x]

44 **Malek-Ahmadi P**. Mood disorders associated with interferon treatment: theoretical and practical considerations. *Ann Pharmacother* 2001; **35**: 489-495 [PMID: 11302414]

45 **Valentine AD**, Meyers CA. Neurobehavioral effects of interferon therapy. *Curr Psychiatry Rep* 2005; **7**: 391-395 [PMID: 16216160]

46 **Angelino AF**, Treisman GJ. Evidence-informed assessment and treatment of depression in HCV and interferon-treated patients. *Int Rev Psychiatry* 2005; **17**: 471-476 [PMID: 16401545 DOI: 10.1080/02646830500381567]

47 **Gordon SC**, Pockros PJ, Terrault NA, Hoop RS, Buikema A, Nerenz D, Hamzeh FM. Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. *Hepatology* 2012; **56**: 1651-1660 [PMID: 22610658 DOI: 10.1002/hep.25842]

48 **Reau NS**, Jensen DM. Sticker shock and the price of new therapies for hepatitis C: is it worth it? *Hepatology* 2014; **59**: 1246-1249 [PMID: 24493069 DOI: 10.1002/hep.27039]

49 **Alter MJ**. Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 2007; **13**: 2436-2441 [PMID: 17552026]

50 **Hill A**, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. *Clin Infect Dis* 2014; **58**: 928-936 [PMID: 24399087 DOI: 10.1093/cid/ciu012]

51 **Morgan RL**, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med* 2013; **158**: 329-337 [PMID: 23460056 DOI: 10.7326/0003-4819-158-5-201303050-00005]

52 **Bruno S**, Crosignani A, Facciotto C, Rossi S, Roffi L, Redaelli A, de Franchis R, Almasio PL, Maisonneuve P. Sustained virologic response prevents the development of esophageal varices in compensated, Child-Pugh class A hepatitis C virus-induced cirrhosis. A 12-year prospective follow-up study. *Hepatology* 2010; **51**: 2069-2076 [PMID: 20196120 DOI: 10.1002/hep.23528]

53 **Poynard T**, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, Ling MH, Albrecht J. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002; **122**: 1303-1313 [PMID: 11984517]

54 **Zeremski M**, Zibbell JE, Martinez AD, Kritz S, Smith BD, Talal AH. Hepatitis C virus control among persons who inject drugs requires overcoming barriers to care. *World J Gastroenterol* 2013;

19: 7846-7851 [PMID: 24307778 DOI: 10.3748/wjg.v19.i44.7846]

55   **Marinho RT**, Barreira DP. Hepatitis C, stigma and cure. *World J Gastroenterol* 2013; **19**: 6703-6709 [PMID: 24187444 DOI: 10.3748/wjg.v19.i40.6703]

56   **Younossi ZM**, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. *J Hepatol* 2014; **60**: 530-537 [PMID: 24269472 DOI: 10.1016/j.jhep.2013.11.009]

57   **Younossi ZM**, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, Nelson D, Gerber L, Nader F, Hunt S. Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2014; **12**: 1349-1359.e13 [PMID: 24316172 DOI: 10.1016/j.cgh.2013.11.032]

58   **Younossi ZM**, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, Nelson D, Nader F, Hunt S. Minimal impact of sofosbuvir and ribavirin on health related quality of life in chronic hepatitis C (CH-C). *J Hepatol* 2014; **60**: 741-747 [PMID: 24333184 DOI: 10.1016/j.jhep.2013.12.006]

59   **Feld JJ**. The beginning of the end: what is the future of interferon therapy for chronic hepatitis C? *Antiviral Res* 2014; **105**: 32-38 [PMID: 24548815 DOI: 10.1016/j.antiviral.2014.02.005]

Baishideng®