

The Role of Direct Acting Anti-Virals in Chronic Hepatitis C Treatment-2016 Update

Andrew Ofosu* and Raja K Dhanekula

Thomas Jefferson University, Philadelphia, PA. 19107, USA

*Corresponding author: Andrew Ofosu, Clinical Instructor, Thomas Jefferson University Hospital, Philadelphia, PA, USA, Tel: (800-533-3669); E-mail: andrew.ofosu@jefferson.edu

Received date: April 22, 2016; Accepted date: May 18, 2016; Published date: May 28, 2016

Copyright: © 2016 Ofosu A. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Chronic hepatitis C continues to be a major public health concern due to complications including liver cirrhosis and hepatocellular cancer. Prior to the development of direct acting antiviral drugs, chronic hepatitis C was primarily treated with interferon-based therapy. Treatment regimens were faced with challenges including limited efficacy, less tolerability and limited usage in decompensated liver cirrhosis.

The introduction of Direct Antiviral Agents (DAA) has changed the landscape of chronic hepatitis C treatment. Currently, the use of DAA has improved the sustained virologic response rates (SVR), with availability of genotype specific treatment and increased patient tolerability. Further, the availability of newer DAAs, have helped expand the treatment eligibility pool to include chronic hepatitis C (HCV) patients with advanced cirrhosis, patients with End Stage Renal Disease and post-liver transplant patients.

The development of new and improved generations of DAAs is ongoing and rapidly enhancing our armamentaria to achieve cure for patients with chronic hepatitis C infection. This short communication reviews the ongoing development, genotype specific treatment regimens, and current use of DAA in chronic hepatitis C patients including special patient populations such as HIV/HCV coinfections, patients with advanced liver cirrhosis, severe renal impairment and recurrent HCV post-liver transplant.

Keywords Chronic hepatitis C; Direct acting antivirals; Interferon-free therapy; Liver cirrhosis; Sustained virologic response; Treatment

Abbreviations

ABT-267: Ombitasvir; **ABT-333:** Dasabuvir; **ABT-450/r:** Paritaprevir with ritonavir; **CME:** Continuing Medical Education; **DAA:** Direct Antiviral Agents; **DCV:** Daclatasvir; **EBR:** Elbasvir; **GZP:** Grazoprevir; **HCV:** Hepatitis C Virus; **HIV:** Human Immunodeficiency Virus; **LDV:** Ledipasvir; **PEG-IFN:** Pegylated interferon; **PI:** Protease inhibitor; **RBV:** Ribavirin; **SOF:** Sofosbuvir; **SVR:** Sustained Virologic Response.

Introduction

It is estimated that over 170 million people worldwide are affected with chronic hepatitis C infection [1]. The estimated prevalence of HCV was found to be 1.3 percent of the non-institutionalized population (3.6 million people) in US, based on HCV antibody testing as reported by a recent survey [2]. A vast majority of these persons being aged 40 to 59 years, are unaware that they have Hepatitis C infection. Among this cohort, the estimated prevalence of current chronic infection using HCV RNA positivity was 1 percent (representing about 2.7 million people living with chronic HCV [2].

Chronic hepatitis C left untreated potentially leads to liver fibrosis, and liver cirrhosis in 14-19% of chronic hepatitis C patients over a period of 20 years [3]. The risk of hepatic decompensation among compensated cirrhosis is 3.9 percent per year and hepatocellular

carcinoma 3 percent per year [4]. This underscores the importance of treating chronic hepatitis C infection early in the course of disease. Early diagnosis remains a challenge, as most patients are asymptomatic for several years.

Treatment of Hepatitis C is a rapidly moving target. The introduction of direct acting antiviral (DAA) agents for HCV has shown great efficacy with a sustained virologic response (SVR) >90%, and better tolerance with less side-effects among users [5]. A recent predictive model envisions that hepatitis C will be a rare disease by 2036 with the use of DAA and screening for chronic HCV cases [6].

Despite the availability of DAA, there is a gap in knowledge in screening patients, appropriately referring them to specialist when warranted, and management particularly in HCV patients with comorbidities such as HCV/HIV co-infection and renal impairment. This review is an update on the current treatment options available for chronic hepatitis C, with focus on the use of DAA in treating Hepatitis C.

The goal of anti-viral therapy

The ultimate goal of therapy in HCV infection is the achievement of virologic cure, which is characterized by the absence of detectable HCV RNA at 12 weeks or more after completion of therapy; known as SVR [7]. This correlates with improved outcomes such as reduced risk of liver transplantation, all-cause mortality, hepatic decompensation and liver related mortality compared to non-responders [8,9].

Direct acting antivirals

Prior to the approval of DAA for treatment of Hepatitis C, the standard treatment of chronic Hepatitis C was a 24-48 week combination therapy of Pegylated interferon (Peg-IFN) and ribavirin (RBV) based on HCV genotype [10,11].

DAAs target molecular protein structures specific to HCV thereby hindering viral replication. Currently there are four categories of DAAs based on specific pharmacodynamics and role in hindering specific targets in HCV replication [12]. These are NS5A inhibitors, protease inhibitors (PIs) for specific target proteins, the RNA polymerase inhibitors (NPIs), and NS5B non-nucleoside polymerase inhibitors (NNPIs) [12].

NS5A inhibitors: Phosphorylation of NS5A is thought to aid in HCV particle production by its interaction with core protein. Mutation of the C-terminal serine cluster of NS5A required in basal phosphorylation inhibits NS5A-core protein interaction [13]. Currently, NS5A inhibitors available include Ledipasvir (LDV), Ombitasvir (ABT-267) and Daclatasvir (DCV) which are in fixed dose combinations with other DAA. The use of NS5A inhibitors with other direct-acting antivirals have been shown to achieve high SVR in HCV genotype 1 patients such as the use of LDV and Sofosbuvir (SOF) [14]. Recent trials have shown Elbasvir (EBR) in a fixed-dose combination with the protease inhibitor Grazoprevir (GZP) achieve high SVR in treatment-naïve patients (genotypes 1,4 and 6) [15].

NS3/4A Protease inhibitors: NS3/4A protease inhibitors inhibit NS3/4A serine protease, which is involved in viral processing and HCV replication [16]. The first generation NS3/4A inhibitor, telaprevir and boceprevir, are gradually being replaced by second-generation protease inhibitors which have greater efficacy and fewer side-effects such as Simeprevir (SIM) [17]. In the OPTIMIST-1 trial, HCV genotype 1 patients with and without cirrhosis attained SVR 12 rates of 95% and 97% in treatment-naïve and experienced patients respectively in patients treated with SIM and SOF [18]. Other second generation NS3/4A inhibitors include Paritaprevir which is available in fixed dose combination with ritonavir (ABT-450r) and ombitasvir (ABT-267) is

frequently given with dasabuvir (ABT-333) a non-nucleoside NS5B inhibitor. Faldaprevir is a new NS3/4A inhibitor that has shown favorable results in a phase 2b trial in HCV genotype 1 patients when used with deleobuvir with or without ribavirin [19].

NPIs: The NPIs cause premature HCV nascent RNA termination thereby inhibiting HCV replication. NPIs are usually pan-genotypic with high antiviral efficacy [20]. SOF an NPI, has been used in combination with other DAA, particularly as a fixed dose combination of LDV/SOF in treatment-naïve HCV genotype 1 patients [21].

NNPIs: Non-nucleoside polymerase inhibitors bind to one of the four allosteric sites inhibiting the RNA-dependent RNA-polymerases via the interruption of conformational changes in enzymatic function [22]. NNPI tend to be less efficacious and have a less to moderate resistance profile [23]. NNPIs serve primarily as adjuncts to other DAAs with a high resistance profile. A recent clinical trial involving the use of Dasabuvir, an NNPI, in combination with ombitasvir-paritaprevir-ritonavir with RBV in HCV genotype 1 patients resulted in an SVR of 95%-98% [24].

Genotype based treatment

HCV Genotype 1: Currently there are 5 recommended highly efficacious DAA oral combinations in HCV genotype 1 patients, determined by the existence of cirrhosis or its absence, type of HCV 1 genotype subtype, and the existence of NS5A resistance-associated variants detected by testing for resistance [25]. LDV/SOF combination is approved for 12 weeks in patients that were not previously treated, with either addition of RBV for 12 weeks or 24 weeks without the use of RBV in previously treated patients that failed or relapsed after prior treatment [26].

Other combinations include 12 weeks of SIM/SOF combination (OPTMIST-2 trial), 12 weeks of ombitasvir/ABT-450r plus ABT-333 with or without RBV (SAPPHIRE-I trial) or 12 weeks of EBR/GZP (C-EDGE trial) [24,27,28]. The current treatment recommendations in HCV Genotype 1 patients in both treatment-naïve and treatment-experienced patients have been summarized in Table 1 [25,29].

Genotype 1a Treatment Naïve Patients, No cirrhosis	Duration of Treatment
LDV/SOF	12 weeks
EBR/GZP	12 weeks
ABT-450/r+ABT-267+ABT-333+RBV	12 weeks
SIM+SOF	12 weeks
*DCV+SOF	12 weeks
Genotype 1a Treatment-naïve Patients + Compensated cirrhosis	
EBR/GZP	12 weeks
LDV/SOF	12 weeks
ABT-450/r+ABT-267+ABT-333+RBV	24 weeks
SIM+SOF ± RBV	24 weeks
*DCV+SOF ± RBV	24 weeks
*EBR/GZP+RBV	16 weeks

Treatment Failure: PEG-IFN and RBV	
LDV/SOF	12 weeks
ABT-450/r+ ABT-267+ABT-333	12 weeks
SOF+SIM ± RBV	12 weeks
Genotype 1a:	Defer treatment
Treatment Failure: SOF without advanced fibrosis:	
Genotype 1a:Treatment Failure: PEG-IFN and RBV+Cirrhosis	
LDV/SOF	24 weeks
LDV/SOF+RBV	12 weeks
ABT-450/r+ABT-267+ABT-333+RBV	24 weeks
Genotype 1a:	
Treatment Failure: SOF+Cirrhosis	
Advanced fibrosis: LDV/SOF ± RBV	24 weeks
Genotype 1b :Treatment-naïve Patients with no Cirrhosis	
EBR/GZP	12 weeks
LDV/SOF	12 weeks
ABT-450/r+ABT-267+ABT-333+RBV	12 weeks
SIM+SOF	12 weeks
*DCV+SOF	12 weeks
Genotype 1b :Treatment-naïve Patients+Compensated Cirrhosis	
GZP/EBR	12 weeks
LDV/SOF	12 weeks
ABT-450/r+ABT-267+ABT-333+RBV	12 weeks
SIM+SOF ± RBV	24 weeks
*DCV+SOF ± RBV	24 weeks
Genotype 1b:Treatment Failure: PEG-IFN+RBV	
LDV/SOF	12 weeks
ABT-450/r+ ABT-267+ABT-333+RBV	12 weeks
SOF+SIM ± RBV	12 weeks
Treatment Failure: SOF With No advanced fibrosis:	Defer treatment
Treatment Failure: PEG-IFN, RBV, PI	
LDV/SOF	12 weeks
Treatment Failure: PEG-IFN and RBV+Cirrhosis	
LDV/SOF	24 weeks
LDV/SOF+RBV	12 weeks
ABT-450/r+ABT-267+ABT-333+RBV	12 weeks

Treatment Failure: SOF+Cirrrosis	
Advanced fibrosis: LDV/SOF ± RBV	24 weeks
Treatment Failure: PEG-IFN, RBV, PI+Cirrrosis	
LDV/SOF	24 weeks
LDV/SOF+RBV	12 weeks

Table 1: [25,29] Treatment guidelines for HCV Genotype 1a and 1b.

HCV Genotype 2 and 3: Sofosbuvir with weight-based RBV for 24 weeks in patients with genotype 2 and 3 achieved SVR at 12 weeks; 93% in HCV genotype 2 and 85% at 24 weeks in genotype 3 (VALENCE HCV treatment study) [30]. Higher SVR 12 rates were

achieved in patients with HCV genotype 3 in the 24-week regimen compared to the 12 week and 16 week regimen reported in subsequent trials [31,32]. The current treatment recommendations in HCV Genotype 2 and 3 patients have been summarized in Table 2 [25,29].

Genotype 2 (Treatment-naïve Patients, no cirrhosis)	Duration of Treatment
SOF+RBV	12 weeks
*DCV+SOF	12 weeks
Genotype 2:Treatment-naïve+Compensated cirrhosis	
*DCV+SOF	16 weeks to 24 weeks
Genotype 3 (Treatment-naïve, no cirrhosis)	
DCV+SOF	12 weeks
SOF+RBV+weekly PEG-IFN	12 weeks
Genotype 3 (Treatment-naïve+ Compensated cirrhosis)	
SOF+RBV+weekly PEG-IFN	12 weeks
*DCV+SOF ± RBV	24 weeks
Genotype 4 (Treatment-naïve , no cirrhosis)	
ABT-450/r+ABT-267+ RBV	12 weeks
Genotype 4 (Treatment-naïve+Compensated cirrhosis)	
* ABT-450/r+ABT-267+RBV	12 weeks
*LDV/SOF	12 weeks
*EBR/GZP	12 weeks
Genotype 5/6 (Treatment-naïve ± Cirrhosis)	
* LDV/SOF	12 weeks
*SOF+RBV+weekly PEG-IFN	12 weeks

Table 2: [25,29] Treatment guidelines for HCV genotypes (2,3,4, 5/6).

HCV Genotype 4: Hezode et al. in a randomized, open-label trial (PEARL-I) evaluated the use of once-daily ABT-267 plus ABT-450r with or without RBV for 12 weeks. A high SVR 12 (100% versus 90.9%) in the ribavirin containing regimen and ribavirin-free regimen respectively were achieved [33]. Recent study by Asselah et al. among treatment-naïve genotype 4 patients treated with daily EBR /GZP with weight-based RBV achieved an overall SVR 12 of 97% (64/66) [34].

Treatment recommendations for HCV Genotype 4 patients have been summarized in Table 2 [25,29].

HCV Genotype 5 and 6: Data is limited in the treatment of HCV genotype 5 and 6 patients due to few studies. LDV/SOF combination for 12 weeks is recommended due to high SVR 12 (95%) achieved in HCV genotype 5 in a study conducted in France by Abergel et al. [35]. Treatment recommendations for HCV Genotype 5 and 6 patients have been summarized in Table 2 [25,29].

Unique subgroup of HCV patients

HIV/HCV co-infection: HIV infection in HCV patients increases the risk of cirrhosis and advanced fibrosis [36]. LDV/SOF combination, over 12 weeks can be used with most antiretroviral therapy, however its concomitant use with tenofovir requires frequent evaluation of creatinine clearance due to increased risk of tenofovir – associated renal toxicity [25]. There is data to suggest the effectiveness and safety of DAA in HIV/HCV-co-infected patients with HCV genotype 1 who were on antiretroviral therapy [37]. Other trials, namely the C-EDGE trial and TURQUOISE-1 study that evaluated the safety and effectiveness of Elbasvir/grazoprevir and Paritaprevir/ritonavir/ombitasvir+dasabuvir respectively in HIV/HCV-co-infected patients had favorable outcomes [38]. It is important to review the drug to drug interactions while selecting the appropriate treatment regimen in patients with HIV/HCV co-infection.

HCV with decompensated cirrhosis: The SOLAR-2 study examined the use of LDV/SOF with low initial dose of RBV (600 mg, increased as tolerated) for 12 weeks and 24 weeks in HCV genotype 1 and 4 patients with decompensated cirrhosis. SVR at 12 weeks was 87% and 89% at 24 weeks, however more adverse outcomes were observed at 24 weeks, compared to the 12 weeks duration of therapy [39]. An SVR 12 rate of 83% was demonstrated in patients with advanced cirrhosis treated with DCV with daily SOF in combination with low initial dose of RBV for 12 weeks in the ALLY-1 study [40].

Patients with recurrent HCV infection post-liver transplantation: The ALLY-1 also evaluated the use of daclatasvir administered with daily SOF and RBV for 12 weeks in patients with recurrent HCV infection post transplant. An SVR 12 rate of 94% was achieved among those with recurrent HCV infection post transplant [39]. Kwo et al. evaluated a fixed-dose combination of ABT-450r, and ombitasvir plus ABT-333 with RBV given for 24 weeks. An SVR24 rate of 96% was achieved among liver-transplant recipients with recurrent HCV genotype 1 [41].

Patients with severe renal impairment or ESRD requiring hemolysis: Results from the C-SURPER study showed that EBR/GZP given for 12 weeks achieved an SVR 12 of 99% in patients with HCV genotype 1 infection with severely compromised renal function(stage 4-5 chronic kidney disease) [42] The ongoing HCV-TARGET study evaluating the use of sofosbuvir-containing regimens (PEG-IFN, RBV and SOF; SIM and SOF with or without RBV; or SOF and RBV) in patients with less to severe renal dysfunction, has reported high response rates , comparable to patients without renal dysfunction [43].

Drug-drug interactions (DDIs): Some DAA such as simeprevir, daclatasvir, elbasvir and grazoprevir are metabolized through the CYP3A metabolism pathway [44]. Co-administration with strong inducers and inhibitors of CYP3A are invariably not recommended. Other DAA such as Sofosbuvir, Ledipasvir are substrates of the P-glycoprotein (P-gp) drug transporter. Co-administration of potent intestinal P-gp inducers such as rifampin, cambazepine , phenobarbital and phenytoin is not recommended. A recent review of drug to drug interactions in administration of DAA and other prescription medications reported most significant interactions with combination of ombitasvir/ritonavir/paritaprevir with or without dasabuvir [45].

Conclusion

The introduction of DAA has revolutionized the treatment of chronic hepatitis C. The use of DAA offers higher SVR, with high

levels of safety and efficacy. As new and improved DAAs are continually being developed, the prospects of achieving cure for all types of chronic HCV including prior treatment failures, patients with decompensated cirrhosis and transplant recipients is feasible. Potential DDIs should be considered in the use of DAA. Primary care providers ought to be educated through CME programs regarding screening tests, available treatment regimens, getting access to treatment for patients and indications for patients referral to a specialist. We recommend extensive programs utilizing print, electronic and social media aimed at increasing public awareness to risk factors for transmission, available screening tests as well as treatment advances.

However, high health care costs involved in successfully treating patients with DAA are the next major barrier to overcome, in providing access to treatment.

References

1. WHO (2015) index4.html- incidence.
2. Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T (2015) Toward a more accurate estimate of the prevalence of hepatitis C in the United States. *Hepatology* 62: 1353-1363.
3. Thein HH, Yi Q, Dore GJ, Krahn MD (2008) Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 48: 418-431.
4. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, et al. (1997) Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 112: 463-472.
5. Gutierrez JA, Lawitz EJ, Poordad F (2015) Interferon-free, direct-acting antiviral therapy for chronic hepatitis C. *J Viral Hepat* 22: 861-870.
6. Kabiri M, Jazwinski AB, Roberts MS, Schaefer AJ, Chhatwal J (2014) The Changing Burden of Hepatitis C Virus Infection in the United States: Model-Based Predictions. *Ann Intern Med* 161: 170-180.
7. Swain MG, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, et al. (2010) A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology* 139: 1593-1601.
8. Smith-Palmer J, Cerri K, Valentine W (2015) Achieving sustained virologic response in hepatitis C: a systematic review of the clinical, economic and quality of life benefits . *BMC Infect Dis* 15: 19.
9. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, et al. (2013) Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med* 158: 329-337.
10. Ghany MG, Strader DB, Thomas DL, Seeff LB (2009) American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 49: 1335-1374.
11. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB (2011) American Association for Study of Liver Diseases. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 Practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 54: 1433-1444.
12. Poordad F, Dieterich D (2012) Treating hepatitis C: current standard of care and emerging direct-acting antiviral agents. *J Viral Hepat* 19: 449-464.
13. Masaki T, Suzuki R, Murakami K, Aizaki H, Ishii K, et al.(2008) Interaction of Hepatitis C Virus Nonstructural Protein 5A with Core Protein Is Critical for the Production of Infectious Virus. *J Virol* 82: 7964-7976.
14. Kowdley KV, Gordon SC, Reddy KR, Rossaro L , Bernstein DE, et al. (2014) Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 370: 1879-1888.
15. Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ben Ari Z, et al. (2015) Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus

- Genotype 1, 4, or 6 Infection: A Randomized Trial. *Ann Intern Med.* 163: 1-13.
16. Pockros PJ (2010) New direct-acting antivirals in the development for hepatitis C virus infection. *Therap Adv Gastroenterol* 3: 191-202.
 17. Hunt D, Pockros P (2013) What are the promising new therapies in the field of chronic hepatitis C after the first-generation direct-acting antivirals?. *Curr Gastroenterol Rep* 15: 303.
 18. Kwo P, Gitlin N, Nahass R, Bernstein D, Etzkorn K, et al. (2016) Simeprevir Plus Sofosbuvir (12 and 8 Weeks) in HCV Genotype 1-Infected Patients Without Cirrhosis: OPTIMIST-1, a Phase 3, Randomized Study. *Hepatology*.
 19. Zeuzem S, Soriano V, Asselah T, Bronowicki JP, Lohse AW, et al. (2013) Faldaprevir and deleobuvir for HCV genotype 1 infection. *N Engl J Med* 369: 630-639.
 20. Bertino G, Ardiri A, Proiti M, Rigano G, Frazzetto E, et al. (2016) Chronic hepatitis C: This and the new era of treatment. *World J Hepatol* 8: 92-106.
 21. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, et al. (2014) Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 370: 1889-1898.
 22. Gerber L, Welzel TM, Zeuzem S (2013) New therapeutic strategies in HCV: Polymerase inhibitors. *Liver Int* 1: 85-92.
 23. Au J, Pockros PJ (2014) Novel Therapeutic Approaches for Hepatitis C. *Clin Pharmacol Ther* 95: 78-88.
 24. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, et al. (2014) Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 370: 1594-1603.
 25. AASLD/IDSA (2016) Recommendations for testing, managing, and treating hepatitis C.
 26. Bourlière M, Bronowicki JP, de Ledinghen V, Hézode C, Zoulim F, et al. (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: 397-404.
 27. Lawitz E, Matusow G, DeJesus E, Yoshida EM, Felizarta F, et al. (2015) Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: A Phase 3 study (OPTIMIST-2). *Hepatology*.
 28. Zeuzem S, Rockstroh JK, Kwo PY, Roth D, Lawitz E, et al. (2016) Predictors of Response to Grazoprevir/Elbasvir Among HCV Genotype 1 (GT1)-Infected Patients: Integrated Analysis of Phase 2-3 Trials. *AASLD*.
 29. Pockros PJ, Kardashian AA (2015) New Direct-Acting Antiviral Therapies for Treatment of Chronic Hepatitis C Virus Infection. *Gastroenterology & Hepatology* 11: 459.
 30. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, et al. (2014) Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 370: 1993-2001.
 31. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, et al. (2013) Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 368: 1878-1887.
 32. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, et al. (2013) Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 368: 1867-1877.
 33. Hézode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, et al. (2015) Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naïve and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomized, open-label trial. *Lancet* 385: 2502-2509.
 34. Asselah T, Reesink H, Gerstoft J, de Ledinghen V, Pockros P, et al. (2015) High Efficacy of Elbasvir and Grazoprevir with or without Ribavirin in 103 Treatment-Naïve and Experienced Patients with HCV Genotype 4 infection: A Pooled Analysis. *AASLD*.
 35. Abergel A, Loustaud-Ratti V, Metivier S (2015) Ledipasvir/sofosbuvir for the treatment of patients with chronic genotype 4 or 5 HCV infection. 50th Annual Meeting of the European Association for the Study of the Liver (EASL) Austria.
 36. Kirk GD, Mehta SH, Astemborski J, Galai N, Washington J, et al. (2013) HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study. *Ann Intern Med* 158: 658-666.
 37. Naggie S, Cooper C, Saag M, Workowski K, Ruane P, et al. (2015) Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med* 373: 705-713.
 38. Sulkowski MS, Eron JJ, Wyles D, Trinh R, Lalezari J, et al. (2015) Ombitasvir, Paritaprevir Co-dosed With Ritonavir, Dasabuvir, and Ribavirin for Hepatitis C in Patients Co-infected With HIV-1: A Randomized Trial. *JAMA* 313: 1223-1231.
 39. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, et al. (2015) Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. *Gastroenterology* 149: 649-659.
 40. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, et al. (2016) Daclatasvir With Sofosbuvir and Ribavirin for HCV Infection With Advanced Cirrhosis or Post-Liver Transplant Recurrence. *Hepatology* 63: 1493-1505.
 41. Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, et al. (2014) An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med* 371: 2375-2382.
 42. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, et al. (2015) Grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet* 386:1537-1545.
 43. Saxena V, Koraihy FM, Sise ME, Lim JK, Schmidt M, et al. (2016) Safety and Efficacy of Sofosbuvir-Containing Regimens in Hepatitis C Infected Patients with Impaired Renal Function. *Liver Int*.
 44. Williams JA, Ring BJ, Cantrell VE, Jones DR, Eckstein J, et al. (2002) Comparative metabolic capabilities of CYP3A4, CYP3A5, and CYP3A7. *Drug Metab Dispos* 30: 883-891.
 45. Honer Zu Siederdisen C, Maasoumy B, Marra F, Deterding K, Port K, et al. (2016) Drug-Drug Interactions With Novel All Oral Interferon-Free Antiviral Agents in a Large Real-World Cohort. *Clin Infect Dis* 62: 561-567.