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Supplement: A CME CNE Approved Activity

Overcoming Challenges with Novel Therapies in the Management of Hepatitis C: An In-Depth Look at Genotype 1 and 4 HCV

This activity is supported by an educational grant from Merck & Co.

Overcoming Challenges with Novel Therapies in the Management of Hepatitis C: An In-Depth Look at Genotype 1 and 4 HCV

Mark Sulkowski, MD

Instructions for CME/CNE: Read the monograph, answer the post test, complete the evaluation form, and send completed post test and evaluation to:

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A score of 70% must be achieved on the post test to receive continuing education credits.

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Professor of Medicine at the Johns Hopkins School of Medicine in Baltimore, Maryland

Learning Objectives:

1. Review the efficacies, indications, and safety profiles of new and emerging direct-acting antiviral combinations in the management of HCV patients with genotype 1 or 4 infection.
2. Integrate guideline recommendations and clinical data of emerging HCV treatments to optimize individualized care for genotype 1 or 4 patients.
3. Assess factors that may lead to treatment failure in patients receiving direct-acting antiviral combinations.
4. Identify and overcome patients- and provider-related barriers to optimal HCV management.

Faculty Disclosure:
Dr. Sulkowski has been a principal investigator for research grants related to HCV with funds paid to Johns Hopkins University from AbbVie, BMS, Gilead, Janssen, and Merck. He has participated in Data and Safety Monitoring Board activities related to HBV for Gilead with funds paid to Johns Hopkins University. He has also been a scientific advisor related to HCV for AbbVie, Achillion, BMS, Cocrystal, Gilead, Janssen, and Merck. Terms of these arrangement are managed by the Johns Hopkins University in accordance with its conflict of interest policies.

This monograph was peer reviewed for potential bias.

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Jacquelyn Smith, RN, BSN, MA, CMCN has no real or perceived financial relationships to disclose.
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This activity has been approved by the American Board of Managed Care Nursing for 1.0 contact hours toward CMCN re-certification requirements.

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This activity is supported by an educational grant from Merck & Co.

Overcoming Challenge with Novel Therapies in the Management of Hepatitis C: An In-Depth Look at Genotype 1 and 4 HCV

Post-Test Questions

1. Which of the following hepatitis C virus (HCV) genotypes predominate in the U.S.?
   a. Genotype 4 b. Genotype 1
   c. Genotype 3 d. Genotype 5
2. Which of the following genotype subtypes is more difficult to eradicate?
   a. Subtype 1a
   b. Subtype 1b
3. Which of the following is an accurate statement about sustained virologic responses (SVR)?
   a. 100 percent of patients with chronic HCV can receive a SVR.
   b. Those who have undetectable virus in their blood 12 weeks after finishing therapy are 75 percent likely to remain free of HCV.
   c. A SVR is a cure for HCV.
   d. A SVR is long-term suppression of viral replication.
4. Which of the following patient factors allow a short course of therapy (8 weeks) with a direct-acting antiviral (DAA) to be considered?
   a. HCV RNA < 6 million IU/mL b. No evidence of liver ffibrosis
   c. Homeless d. History of good medication adherence
5. Which of the following scenarios would ribavirin be added to the DAA regimen?
   a. Paritaprevir/ritonavir/ombitasvir + dasabuvir [PrOD] for 1b genotype
   b. Daclatasvir + sofosbuvir for genotype 4
   c. Simeprevir + sofosbuvir for genotype 2 in patient with cirrhosis
   d. Grazoprevir/elbasvir for genotype 1a with a resistance associated variant (RAV) at position 28 (M28A/G/T)
6. For Genotype 1a, RAV testing is recommended before starting which of the following regimens?
   a. Grazoprevir/elbasvir b. Velpatasvir/sofosbuvir
   c. Daclatasvir + sofosbuvir d. Paritaprevir/ritonavir/ombitasvir
7. Worldwide, which of the following is a major barrier to effective treatment of genotype 4?
   a. Lack of effective regimens
   b. Socioeconomic factors limiting access to effective regimens
   c. High rate of adverse effects with the effective regimens
   d. High prevalence of coinfection with hepatitis B
8. Which of the following is a preferred regimen for use in those with kidney function less than 30ml/min?
   a. Simeprevir + sofosbuvir
   b. Daclatasvir + sofosbuvir
   c. Grazoprevir/elbasvir
   d. Paritaprevir/ritonavir/ombitasvir + dasabuvir + ribavirin
9. Patients who are coinfected with HIV and HCV require higher doses of DAAs to achieve SVR compared with someone not infected with HIV
   a. True b. False
10. Which DAA class should be avoided in those with cirrhosis because of potential for hepatic decompensation?
    a. NS5A inhibitors
    b. Nucleoside N25B polymerase inhibitors
    c. Non-nucleoside NS5B polymerase inhibitors
    d. NS3/4A protease inhibitors

Activity Evaluation and Improvement Process

(Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor)

1. Based on the content presented I am better able to:

   Review the efficacies, indications and safety profiles of new and emerging direct-acting antiviral combinations in the management of HCV patients with genotype 1 or 4 infection.

   4 3 2 1

   Integrate guideline recommendations and clinical date of emerging HCV treatments to optimize individualized care for genotype 1 or 4 patients.

   4 3 2 1

   Assess factors that may lead to treatment failure in patients receiving direct-acting antiviral combinations.

   4 3 2 1

   Identify and overcome patient- and provider-related barriers to optimal HCV management.

   4 3 2 1

2. The activity met my expectations. 4 3 2 1
3. The activity and presenter were free of bias. 4 3 2 1
4. The activity was applicable to my position. 4 3 2 1
5. Do you expect that the information you learned during this activity will help you improve your skills or judgement within the next six months? (4 definitely will change - 1 definitely will not change)

   4 3 2 1

6. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

7. What other topics interest you? _____
8. My goal of participating in this activity was: _____

   _____

9. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

10. Due to the content of this activity, I will change my practice patterns by:

    ☐ Identifying opportunities to improve treatment options for patients.
    ☐ Providing guidelines and resources on new therapies to providers.
    ☐ My practice patterns will not change.
    ☐ Other (specify): _____

11. Will the content presented increase your abilities in any of the following areas? Please check all that apply.

    ☐ Management and leadership skills
    ☐ Business and/or financial expertise to manage the medical loss ratio.
    ☐ Exchange ideas and network with colleagues to improve patient outcomes.
    ☐ Be aware of updates of Congress, pharmaceutical, Health and Human Services and other regulatory services.
    ☐ Clear knowledge of practice of medicine, especially common disease.
    ☐ Stay updated on clinical conditions.

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Introduction

HEPATITIS C VIRUS INFECTION (HCV) IS A worldwide problem and is a major cause of morbidity and mortality. It is estimated that worldwide over 180 million people are infected with HCV. [1,2] Across the world, five hundred million people die from HCV annually. East Asia, North Africa, and the Middle East are hot spots for HCV across the globe. The high rates in Egypt stem from a government campaign to eradicate Schistosomiasis with parenteral therapy that ended in the 1980s. In the United States (U.S.), HCV kills approximately 20,000 people per year, which surpasses the number who die from HIV or 60 other reportable infectious pathogens.

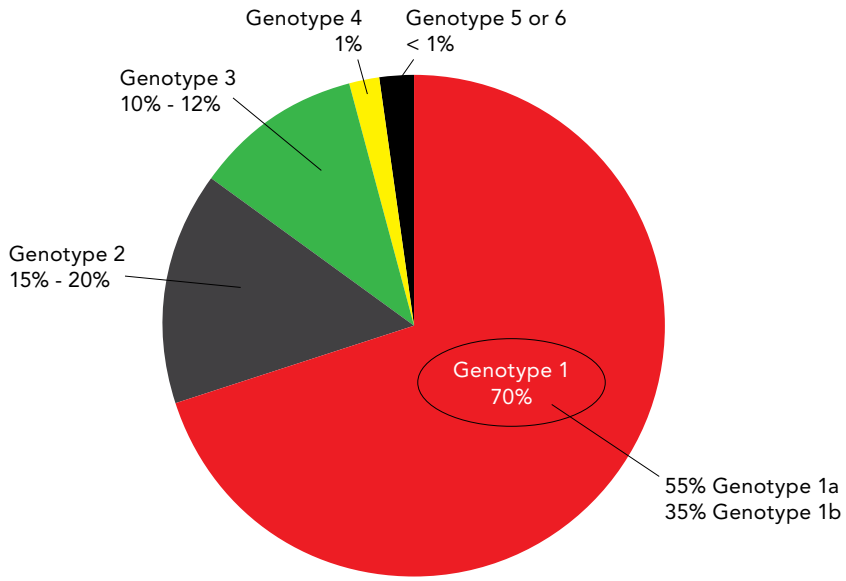
There are six known genotypes of HCV. In the U.S., genotype 1 predominates (Exhibit 1).[3,4] Genotype 1 predominates because it appears to have been the first one to arrive in the U.S., with studies of blood samples stored from as far back as the 1940s found genotype 1.[5] Subtype 1a is more common and more difficult to eradicate than 1b, which affects treatment selection.

Treatment of HCV

Identification of the hepatitis C virus life cycle was key to developing effective treatment. The virus locates and attaches itself to a liver cell and enters the cell. Once inside the cell, viral RNA is copied thousands of times, making the genetic material for new viruses which are released from the cell to infect other cells. Over time, this endless cycle of reproduction results in significant damage to the liver, as numerous cells are destroyed by viral reproduction or by the immune system's attacks on infected cells.[6]

Effective therapy focuses on various life cycle steps to halt multiplication of the HCV virus. The first antivirals developed directly against HCV (direct-acting antivirals, DAAs) were nonspecific protein 3/4A (NS3/4A) protease inhibitors which block translation and polyprotein processing. This class

Exhibit 1: Distribution of HCV Genotypes in the United States[3,4]



included grazoprevir, paritaprevir, and simeprevir. The nucleoside (sofosbuvir) and non-nucleoside (dasabuvir) non-specific 5B protein (NS5B) polymerase inhibitors block RNA replication. The NS5A inhibitors block both RNA replication and virion assembly. Available agents include daclatasvir, elbasvir, ledipasvir, ombitasvir, and velpatasvir. The NS5A agents very quickly decrease viral load and have become an important part of treatment. In general, the DAAs are well tolerated with minimal adverse effects.

Overall, with the new oral DAA regimens, 96 percent of patients can achieve a sustained virologic response (SVR), which is defined as undetectable virus in the blood 12 weeks after stopping therapy.[7] An SVR is a cure for HCV – those who achieve are 99 percent likely to remain free of hepatitis C. There are numerous health and financial benefits to curing HCV, including decreased rates of liver disease and liver cancer and reduced liver mortality. The goal is to deliver treatment to as many people as possible to prevent progression of HCV to cirrhosis and the clinical outcomes of chronic HCV.

Key information needed to decide how to treat a person with chronic HCV infection includes HCV genotype and, if genotype 1, subtype; HCV RNA level (viral load); presence of resistance-associated variants (RAVs) or substitutions (RASs) in those with genotype 1a; presence of cirrhosis; kidney function; hemoglobin; and prior HCV treatment.[8] Although there are some DAA regimens that are pangenotypic (cover all 6), for now, it is still the standard to approach care with genotype testing. Depending on the viral load, a shortened course of therapy (8 weeks) may be possible compared with the standard 12 weeks. RAVs are important because they make achievement of SVR more difficult. If a patient has cirrhosis, the degree of severity needs to be known. The more advanced cirrhosis is, the harder it is to eliminate HCV. Kidney function is important for medication selection and dosage of some medications. Patients who already have some anemia may not be able to take ribavirin which causes hemolytic anemia. Prior HCV treatment experience is important to know in order to learn from the prior course.

Genotype 1

There are multiple, highly effective, DAA regimens available to treat persons with HCV genotype 1 infection. Multidrug combinations combine multiple classes of drugs, each of which compensates for potential less favorable characteristics of a single drug and prevent the development of resistance. Interferon is no longer recommended for treating HCV in the U.S. because of a high rate of adverse effects and difficulty in completing the regimen.

Ribavirin is still used in some cases that are more difficult to eradicate. Ribavirin is a nucleoside analogue that has been available for many years. In addition to causing hemolytic anemia, this agent is teratogenic. Additionally, the dosage has to be adjusted in those with decreased renal function. Regi-

Exhibit 2: Example DAA Regimens[8]

	Antiviral				
	NS3[1]	NS5A	Non-Nuc NS5B	Nuc NS5B[2]	RBV[3-5]
Paritaprevir/ritonavir/Ombitasvir (Viekira) + Dasabuvir (Exviera) [PrOD]	●	●	●		●
Elbasvir /Grazoprevir (Zepatier, EBV/GZV)	●	●			●
Ledipasvir/Sofosbuvir (Harvoni, LDV/SOF) Velpatasvir/Sofosbuvir (Epclusa, VEL/SOF) Daclatasvir (Daklinza) + Sofosbuvir (Sovaldi) [DCV+SOF]		●		●	●
Simeprevir (Olysio) + Sofosbuvir (Sovaldi) [SMV+SOF]	●			●	

[1] Do not use NS3 containing regimens in patients with Class B and C cirrhosis

[2] Sofosbuvir is not recommended with estimated kidney function < 30 ml/min

[3] Ribavirin (RBV) is added to PrOD for 1a genotype

[4] Ribavirin is added to EBV/GZV for 1a if RAVs at 28, 30, 31, or 93

[5] Ribavirin is added for those with Class B or C cirrhosis or Class A with prior treatment failure

mens that contain ribavirin do cause a higher rate of adverse effects than regimens without it, but the increase is not major.

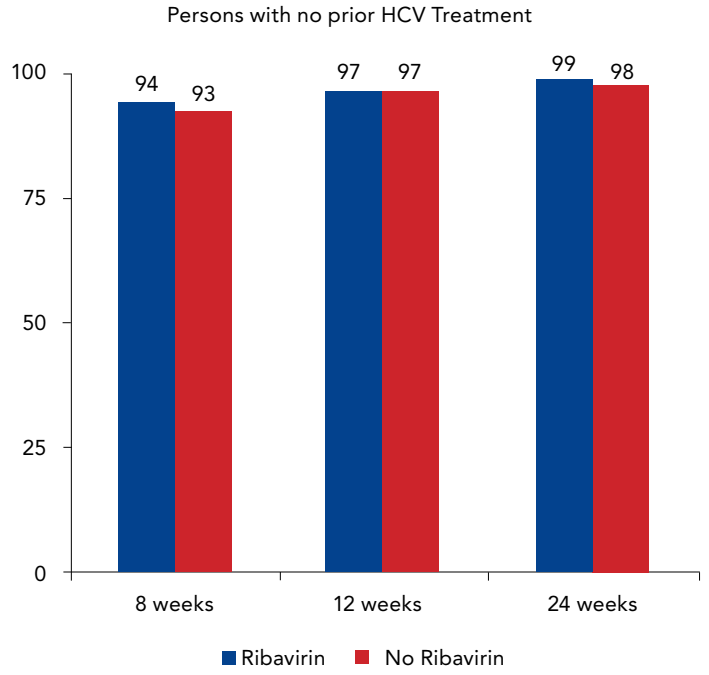
Exhibit 2 shows some example regimens and when ribavirin should be added.[8] Clinicians should always consult the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) guidelines online at hcvguidelines.org for the most up-to-date information on HCV treatment and recommended regimens.

Several of the DAA combinations are available as single dosage forms to make adherence with therapy easier. Ledipasvir/sofosbuvir (LDV/SOF, Harvoni®) is a single, once-a- day tablet regimen that is used for either eight, 12, or 24 weeks. The longer courses of treatment led to fewer relapses (0.2% and 0.6% for 24 and 12 weeks vs 4.6% for 8 weeks). In those with low viral load (HCV RNA < 6 million IU/mL), only 2 percent of those treated for eight weeks relapsed. There are now numerous studies that have found that a short course of eight weeks works effectively for those with low baseline levels of virus. In trials, this combination results in high SVR rates (Exhibit 3).[9-10] The efficacy of this regimen in the real world is very similar – 97 percent at eight and 12 weeks and 95 percent at 24 weeks.[11] In hard to treat patients, such as those with cirrhosis or prior failed treatment, there is still a question whether patients should be treated for 12 weeks with the addition of ribavirin or 24 weeks without. Ledipasvir/sofosbuvir plus ribavirin for 12 weeks compared with ledipasvir/sofosbuvir alone for 24 weeks produced similar SVR rates (97% in each) in persons with prior treatment experience and cirrhosis.[12] Thus, there are two equal options. In practice, if a patient can take ribavirin, they are put on the three-drug, 12-week regimen which is shorter and less expensive.

Simeprevir (Olysio®) and sofosbuvir (Solvaldi®) are two separate agents given as single daily doses. The two are given for 12 weeks in persons with genotype 1 with and without cirrhosis. SVR rates of 97 percent are achieved in all comers and 88 percent in those with cirrhosis.[13,14]

Another combination product is ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira XR®, Viekira Pak). This four-drug regimen is referred to as PrOD. Ribavirin is added to the regimen in patients with genotype 1a infection to prevent HCV virologic failure but is not required for 1b infection. Without ribavirin, those with genotype 1a only achieved a 90.2 percent SVR compared with 97 percent when ribavirin was added.[15] FDA labeling for this combination recommends 12 weeks with ribavirin for those with genotype 1a who have never been pre-

Exhibit 3: HCV Eradication with the Fixed-Dose Combination of Ledipasvir/Sofosbuvir[9,10]



viously treated. In another study, PrOD with ribavirin for 24 weeks was better than 12 weeks of the same regimen for treatment-experienced patients with compensated cirrhosis and HCV genotype 1a.[16] PrOD without ribavirin for 12 weeks is effective for treatment-experienced patients with compensated cirrhosis and HCV genotype 1b. In one trial, this regimen produced 100 percent SVR.[17]

Elbasvir/grazoprevir (EBV/GZV, Zepatier®) is the most recently approved combination therapy for HCV. This results in 99 percent SVR in those with genotype 1b and 92 percent in those with 1a.[18] The investigators found that those with certain RAVs (28,30,31,93) are those who require ribavirin to boost their SVR chances. One in 10 patients with genotype 1a will have one of these RAVSs. Patients with RAVs also need extended treatment (16 weeks).

Overall for genotype 1, subtype 1b is treated for 12 weeks in most patients and ribavirin does not need to be added to the treatment regimen. For genotype 1a, no RAV testing is recommended if LDV/SOF or PrOD is being used. LDV/SOF is given for eight or 12 weeks for most patients and 24 weeks for treatment-experienced patients with cirrhosis. PrOD is given for 12 weeks for most and 24 weeks for those with cirrhosis. RAV testing is recommended when EBV/GZV/ is used. Mutations at the 28, 30, 31, or 93 positions on the virus are known to be clinically significant. If no significant RAVs are detected, 12 weeks of treatment is given. Sixteen weeks of therapy with the addition of ribavirin is indicated when significant RAVs are detected. Resistance testing is also recommended for all patients who are not cured with first-line DAA regimens.

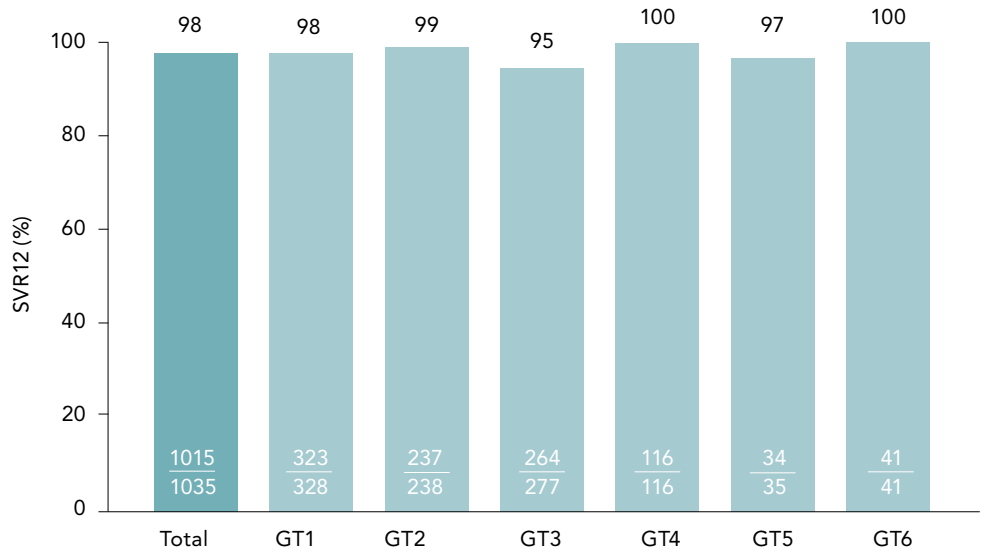
Genotype 2 and 3

Although the focus of this monograph is genotypes 1 and 4, regimens for the other genotypes are important. The recommended treatment for genotype 2 is the combination of sofosbuvir/velpatasvir, which produces higher SVR without anemia compared with the previous standard treatment of sofosbuvir/ribavirin.[19] Genotype 3 is the second most common genotype worldwide. It is recognized to cause a more aggressive disease course with higher rates of hepatocellular cancer and cirrhosis and is more difficult to treat than some of the other genotypes. All the first-generation DAAs did not work very well for this genotype. Daclatasvir/sofosbuvir and velpatasvir/sofosbuvir are the recommended regimens for genotype 3. The combination of daclatasvir/sofosbuvir and ribavirin is used for those with cirrhosis.

Genotype 4

Genotype 4 is the third most common HCV genotype worldwide. The good news is many different

Exhibit 4: Velpatasvir/Sofosbuvir: SVR by Genotype[20]



therapies can treat this one. Unfortunately, many of the people affected by this particular genotype live in the world where socioeconomic and political factors prevent them from receiving effective treatment. In many of the countries where genotype 4 predominates, it is about the only genotype seen. Several regimens including LDV/SOF, EBV/GZV, velpatasvir/sofosbuvir (VEL/SOF, Epclusa®) and ombitasvir/paritaprevir/ritonavir plus ribavirin are effective for this genotype. Dasabuvir, which is typically included with ombitasvir/paritaprevir/ritonavir, is not included because it is not effective for genotype 4. This four-drug regimen, although effective, can be difficult to use in developing countries because of the requirement to monitor for anemia with ribavirin.

Access to genotype testing is difficult in some countries. Treating everyone with a pangenotypic regimen may be the option. As shown in Exhibit 4, VEL/SOF is a regimen that will cover genotype 4, plus all the others.[20] The theoretical concern with using a pangenotypic regimen is, if patients are not monitored for adherence, there might be increased failure rates and development of resistance. American clinicians are unlikely to abandon genotype testing and begin using pangenotypic regimens in everyone. In countries where genotype testing may not be as common, a pangenotypic regimen could be selected.

Challenging Populations

In this age of highly effective antiviral regimens, there still are some challenges in managing HCV. Patients with renal dysfunction present a challenge for ribavirin dosing and if there is significant dysfunction, for many of the medications (Exhibit 5).[8] Sofosbuvir is not recommended if kidney function is less than 30 ml/min because of metabolite accumulation. Ribavirin will accumulate and lead to severe anemia. It can be difficult for those with end-stage renal disease to tolerate ribavirin and thus it will be more difficult to clear their HCV if they have genotype 1a. EBV/GZV is the most commonly used regimen in those with renal disease because neither medication has significant renal clearance.

Treatment of cirrhotic patients can also be challenging. It is important not to use NS3/4A protease inhibitors in this population because of potential for hepatic decompensation. The FDA issued a warning about serious liver injury risk with PrOD in 2015.[21] Since approval, 26 cases have been reported to the FDA, with most cases occurring one to four weeks after starting therapy. The recommended regimens for this population are LDV/SOF with or without ribavirin and daclatasvir and sofosbuvir with or without ribavirin. When treating patients with cirrhosis regardless of the regimen, they need to be monitored for increasing direct bilirubin and clinical signs of hepatic decompensation.

HIV and HCV coinfected persons suffer from more liver-related morbidity and mortality, nonhepatic organ dysfunction, and overall mortality than HCV mono-infected people.[8] Those coinfected should be treated and retreated the same as persons

Exhibit 5: Considerations in Patients with Renal Dysfunction[8]

- CrCl ≥ 30 mL/min: No dosage adjustments required with daclatasvir, sofosbuvir, ledipasvir/sofosbuvir, velpatasvir/sofosbuvir, simeprevir, paritaprevir/ritonavir/ombitasvir + dasabuvir
- CrCl < 30 mL/min/End stage renal disease: Consult the guidelines for recommended regimens
- Ribavirin Dosing

Creatinine Clearance	RBV Dose Daily
> 50 mL/min	< 75 kg = 1,000 mg ≥ 75 kg = 1,200 mg
30 - 50 mL/min	Alternate 200 mg and 400 mg QD
< 30 mL/min	200 mg QD
Hemodialysis	200 mg QD

without HIV infection, but concurrent antiretroviral therapy will have to be considered in selecting a DAA regimen. There are numerous drug interactions between the DAAs and antiretroviral medications that have to be recognized and managed (Exhibit 6).[8] Treating patients at high risk for transmitting HIV (high-risk sexual practices and active injection drug users) to others may decrease HCV transmission and HCV disease prevalence.

Hepatitis B (HBV) and C coinfection can occur. Patients coinfected with B and C have poor outcomes with progressive liver disease. These two viruses tend to antagonize each other. Several things can happen if someone is infected with both. There can be a high viral load of both but often one dominates in the viral load. In vitro works suggest that the innate immune response to virus in the liver to active HCV will suppress HBV. Years ago, the treatment of HBV and HCV was 24 weeks of interferon injections for either one. In the DAA era, the medications are only treating HCV. There is a theoretical concern that by treating C, the B virus can be released. The FDA recently reported 24 cases of hepatitis B reactivation.[22] This had led to heightened recommendations to screen all HCV patients for HBV before treatment with HBV surface antigen, core antibody, and surface antibody. Patients can then be classified as never or previously infected. Those previously infected can be further classified as chronic infected (surface antigen positive) or inactive (surface antigen negative). The chronically infected HBV patient needs to be treated, and all patients with prior HBV need to be monitored while undergoing HCV treatment.

Another challenging population are those with liver failure awaiting transplant. There is a concern among clinicians that if a patient's HCV is cured while waiting for transplant, their health may improve but they still have end-stage disease but may no longer be longer sick enough to qualify for a transplant. Most centers will assess the patient and decide that those sickest go ahead to transplant.

Dialysis patients are another conundrum because HCV is spread in dialysis centers. Treating all patients would eliminate transmission, but everyone would have to be treated to clearance, or those who got treated will get reinfected. Hepatitis C-positive kidneys are often not transplanted in the U.S. If a patient is willing to take a hepatitis C-positive organ, the wait time in some centers is as short as three months. It can take up to six years to get a hepatitis C infection-free organ from a deceased donor. Transplant centers are using these positive kidneys in already infected patients and then treating them post-transplant.

Follow-Up after SVR

After cure, patients should have viral loads checked for at least one year. If they don't have risks for reinfection, they don't necessarily need to be checked again. Two groups of patients need ongoing follow-up; those at risk for reinfection need an annual

Exhibit 6:Drug Interactions Between HIV Antiretrovirals and HCV Direct-Acting Antivirals[8]

	SMV + SOF	VEL/SOF	LDV/SOF	DCV + SOF	PrOD	EBV/GZV
Atazanavir + ritonavir						
Darunavir + ritonavir						
Lopinavir/ritonavir						
Tipranavir + ritonavir						
Efavirenz						
Rilpivirine						
Etravirine						
Raltegravir						
Elvitegravir + cobicistat						
Dolutegravir						
Maraviroc						
Tenofovir disoproxil fumarate						
Tenofovir alafenamide						

No Clinically significant interaction expected

Potential interaction may require adjustment to dosage, altered timing of administration, or additional monitoring

Do not coadminister

check and those with advanced liver disease need to be monitored for liver cancer development.

Conclusion

Hepatitis C virus infection can and should be cured. There are now numerous options for successful treatment, even in those who already have cirrhosis or who failed prior treatment. Some populations still provide challenges. Because the management of HCV continues to rapidly evolve, clinicians are encouraged to consult the online guidelines for the most recent recommendations.

Mark Sulkowski, MD, is a Professor of Medicine at the Johns Hopkins University School of Medicine in Baltimore, MD.

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