New Treatment Paradigm for HCV and HCV/HIV Coinfection

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Nancy S. Reau, MD, The University of Chicago Medicine, Chicago, Illinois, USA, reviewed the current treatment regimens and guidelines for hepatitis C virus (HCV) and their indications. Dr Reau was a member of the panel that developed the web-based "Recommendations for Testing, Managing, and Treating Hepatitis C" for the American Society for the Study of Liver Disease/Infectious Diseases Society of America (AASLD/IDSA) [www.hcvguidelines.org. Accessed May 26, 2015].

Clinical evidence supports treatment for all patients with chronic HCV (class I, level A). According to the AASLD/IDSA guidelines, the aim is to reduce all-cause mortality and liver-related adverse events by achieving a virologic cure as evidenced by sustained virologic response (SVR). First priority should be given to persons who will derive the most benefit and have the greatest impact on further HCV transmission, including those with advanced fibrosis (F3) or compensated cirrhosis (F4), liver transplant recipients, patients with severe extrahepatic manifestations of HCV, and those in high-risk groups where there is a potential to spread HCV (eg, men who have sex with men with high-risk sexual practices, active injection drug users, incarcerated persons, and HCV-infected women of child-bearing potential wishing to get pregnant). There are several classes of HCV therapy, each with products that have been approved or are in review with the FDA (Table 1).

The choice of therapy for HCV is based on fibrosis stage (presence or absence of cirrhosis, compensated or decompensated), treatment experience (experienced or naïve and exposure to direct acting antiviral containing medications), and subtype of HCV genotype. All oral therapy is recommended, but the combination of agents and duration of treatment will vary by genotype 1 subtype and degree of fibrosis. Interferon-based regimens are not recommended for any genotype 1 patient population. Treatment outcomes based on SVR are shown in Table 2 for genotypes 1, 4, 5, and 6.

The FUSION study [Jacobson IM et al. *N Engl J Med.* 2013] showed that for patients with HCV genotype 2, treatment with sofosbuvir (SOF) plus ribavirin (RBV) for 12 weeks, with an extension to 16 weeks, was effective for those with cirrhosis and those who had failed prior therapy.

There are 2 options for patients with HCV genotype 3. Most patients should receive SOF plus RBV for 24 weeks (class I, level B), although an alternative could be SOF plus RBV plus peginterferon for 12 weeks (class IIa, level A).

Susanna Naggie, MD, MHS, Duke Clinical Research Institute, Durham, North Carolina, USA, discussed the current management strategy according to the AASLD/IDSA recommendations for

Peer-Reviewed Highlights From

Digestive Disease Week 2015

May 16–19, 2015
Washington, DC, USA

Table 1. Available Hepatitis C Virus Agents

Protease Inhibitors	Polymerase Inhibitors		NS5A Inhibitors	Immune Modulation	Other
	Nucleotide	Nonnucleotide			
Simeprevir	Sofosbuvir	Dasabuvir	Ledipasvir	Interferon	Ribavirin
Paritaprevir + ribavirin			Ombitasvir		
			Daclatasvir[a]		

NS5A, nonstructural protein 5A.

[a]Under review by the FDA.

Source: ASSLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C. www.hcvguidelines.org. Accessed May 26, 2015.

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Table 2. Treatments for HCV

Regimen	Wk	Study	SVR, %	Reference
HCV genotype 1, treatment naïve				
SOF/LDV				
Noncirrhotic[a]	8	ION-3	94	Kowdley KV et al. *N Engl J Med.* 2014
Noncirrhotic[b]	12	ION-3	95	Kowdley KV et al. *N Engl J Med.* 2014
Cirrhotic	12	ION-1	99	Afdhal N et al. *N Engl J Med.* 2014
Paritaprevir + ribavirin + dasabuvir + ombitasvir				
Genotype 1b				
Noncirrhotic	12	PEARL III	99.5	Ferenci P et al. *N Engl J Med.* 2014
Cirrhotic (+ RBV)	12	TURQUOISE II	100	Poordad F et al. *N Engl J Med.* 2014
Genotype 1a				
Noncirrhotic (+ RBV)	12	PEARL IV	97	Ferenci P et al. *N Engl J Med.* 2014
Noncirrhotic (+ RBV)	12	SAPPHIRE-I	95.3	Feld JJ et al. *N Engl J Med.* 2014
Cirrhotic (+ RBV)	24	TURQUOISE II	92.2	Poordad F et al. *N Engl J Med.* 2014
SMV + SOF				
Noncirrhotic	12	COSMOS	95	Lawitz E et al. *Lancet.* 2014
Noncirrhotic	12	OPTIMIST-1	97	Kwo P et al. EASL 2015 (abstr LP14)
Cirrhotic	24	COSMOS	100	Lawitz E et al. *Lancet.* 2014
Cirrhotic	12	OPTIMIST-2	84	Lawitz E et al. EASL 2015 (abstr LP04)
HCV genotype 1, treatment experienced				
SOF/LDV (PR or PI + PR)				
Noncirrhotic	12	ION-2	94	Afdahl N et al. *N Engl J Med.* 2014
Cirrhotic	24	ION-2	99	Afdahl N et al. *N Engl J Med.* 2014
Cirrhotic	12	SOLAR-I (+ RBV)	96	Reddy KR et al. AASLD 2014 (abstr 8)
Paritaprevir + ribavirin + dasabuvir + ombitasvir				
Genotype 1b				
Noncirrhotic	12	PEARL II	100	Andreone P et al. *Gastroenterology.* 2014
Noncirrhotic	12	SAPPHIRE-II	96.7	Zeuzem S et al. *N Engl J Med.* 2014
Cirrhotic	12	TURQUOISE-II	98	Poordad F et al. *N Engl J Med.* 2014
Genotype 1a				
Noncirrhotic (+ RBV)	12	SAPPHIRE-II	96	Zeuzem S et al. *N Engl J Med.* 2014
Cirrhotic (+ RBV)	24	TURQUOISE-II	95	Poordad F et al. *N Engl J Med.* 2014
SMV + SOF				
Noncirrhotic	12	COSMOS	95	Lawitz E et al. *Lancet.* 2014
Noncirrhotic	12	OPTIMIST-1	95	Kwo P et al. EASL 2015 (abstr LP14)
Cirrhotic	24	COSMOS	93	Lawitz E et al. *Lancet.* 2014
Cirrhotic	12	OPTIMIST-2	79	Lawitz E et al. EASL 2015 (abstr LP04)
HCV genotype 4				
SOF/LDV				
Treatment naïve	12	SYNERGY	95	Kohli A et al. CROI 2014 (abstr 27LB)
Treatment experienced	12	SYNERGY	95	Kohli A et al. CROI 2014 (abstr 27LB)
Paritaprevir + ribavirin + ombitasvir + RBV				
Treatment naïve	12	PEARL-I	100	Pol S et al. AASLD 2014 (abstr 19280)
Treatment experienced	12	PEARL-I	100	Pol S et al. AASLD 2014 (abstr 19280)
SOF + RBV				
Treatment naïve	24	n/a	92-100	NCT01713283
Treatment experienced	24	n/a		
SOF + PEG + RBV				
Treatment experienced	12	n/a	89	Esmat GE et al. AASLD 2014 (abstr 959)
HCV genotype 5 and 6				
SOF + PEG + RBV[c]	12	NEUTRINO	100	Lawitz E et al. *N Engl J Med.* 2013
SOF/LDV[d,e]	12	SYNERGY	96	Kohli A et al. CROI 2014 (abstr 27LB)

Studies are not head to head.
HCV, hepatitis C virus; LDV, ledipasvir; PEG, peginterferon; PI, protease inhibitors; PR, peginterferon ribavirin; RBV, ribavirin; SOF, sofosbuvir; SMV, simeprevir.
[a]HCV RNA < 6 000 000 (IU/mL).
[b]HCV RNA > 6 000 000 (IU/mL).
[c]Genotype 5, treatment experienced.
[d]Genotype 6, treatment naïve.
[e]Genotype 6, treatment experienced.

patients coinfected with HCV and HIV [www.hcvguidelines.org. Accessed May 26, 2015].

About 4 to 5 million individuals worldwide are coinfected with HCV/HIV [Rotman Y, Liang TJ. *J Virol.* 2009], and about 30% of patients in the United States with HIV also have HCV [Lo Re V III et al. *Ann Intern Med.* 2014]. According to Dr Naggie, there are excellent data to indicate that HIV is a risk factor for transmission of HCV. For this reason, the AASLD/IDSA HCV guidelines now recommend annual testing for high-risk HIV positive patients, such as those who inject drugs and for seropositive men who have unprotected sex with men (class IIA, level C).

In addition to clearly affecting the risk of sexual transmission of HCV, HIV affects the natural history of HCV. Despite receiving antiretroviral therapy, patients coinfected with HIV and HCV progress more quickly to decompensation than do HCV-monoinfected patients [Lo Re V III et al. *Ann Intern Med.* 2014]. Coinfected patients should receive the same treatment as those without HIV (class I; level B).

Dr Naggie noted that the treatment paradigm for HCV has changed in a very short period. New combinations are being developed based on the genetic barrier to resistance of the chosen regimen. Effectively stopping a rapidly replicating and mutating virus such as HCV requires a high genetic barrier. This can be achieved either by the drug (eg, nucleotide analog), which has a high genetic barrier because it binds to the conserved catalytic site of the enzyme, or by combining more direct-acting antivirals, thereby increasing the overall barrier of the regimen.

The effectiveness of therapy for coinfected patients has been shown in several studies using a variety of treatment regimens. SVR rates were high among coinfected patients treated with the 3D regimen (ie, 3 direct-acting antivirals) of ombitasvir, paritaprevir boosted with ritonavir, and dasabuvir for 12 or 24 weeks and regardless of treatment experience [Sulkowski MS et al. *JAMA*. 2015].

In what is perhaps the largest trial to date of all oral direct-acting antiviral regimens in coinfected patients, the once-daily treatment with the single-tablet regimen of ledipasvir (LDV)/SOF for 12 weeks was found to be highly effective and well tolerated in genotype 1 or 4 HCV/HIV coinfected patients who were treatment naïve and experienced, including those with cirrhosis [Naggie S et al. CROI 2015 (abstr 152LB)].

The ALLY-2 study found that once-daily oral daclatasvir plus SOF was associated with high SVR rates in coinfected patients with HCV genotypes 1 to 6. Although drug interactions exist with daclatasvir and HIV antiretrovirals, the lack of a fixed-dose combination with this regimen allows for the adjustment of the daclatasvir dose depending on the antiretroviral regimen used, making it a broadly compatible regimen in this population [Wyles D et al. CROI 2015 (abstr 151LB)].

In the ION-3 study [Kowdley KV et al. *N Engl J Med.* 2014], a fixed-dose combination tablet containing LDV/SOF for 8 weeks was associated with a high rate of SVR among previously untreated patients with HCV genotype 1 infection without cirrhosis; however, this arm did have significantly higher relapse rates as compared with the 12-week arm. Although a post hoc analysis suggested that patients with baseline HCV RNA < 6 000 000 IU/mL have a similarly low relapse rate regardless of length of treatment, this may not apply to other populations outside of this trial.

The ALLY-2 [Wyles D et al. CROI 2015 (abstr 151LB)] study also included an 8-week arm, and although this arm included cirrhotics and treatment-experienced patients, the SVR was significantly lower (75.6%) due to higher relapse than for those treated for 12 weeks (96.4%). Furthermore, the recent OPTIMIST-1 presentation at the 2015 meeting of the European Association for the Study of the Liver—which investigated another oral regimen of simeprevir and SOF for 8 vs 12 weeks in patients without cirrhosis who were treatment naïve and experienced—similarly reported higher relapse in the 8-week treatment arm, although in this case the most predictive baseline HCV RNA was < 4 000 000 IU/mL. Due to the higher relapse rates in 8-week treatments with current therapies and the lack of an accurate single baseline predictor, 8 weeks of LDV/SOF or daclatasvir/SOF is not recommended for HIV/HCV patients.

Recent data presented at the 2015 meeting of the European Association for the Study of the Liver showed similar rates of SVR among patients treated with grazoprevir plus elbasvir for 12 weeks who were cirrhotic and noncirrhotic, genotype 1a and 1b, and mono- and coinfected [Rockstroh JK et al. EASL 2015 (poster P0887); Zeuzem S et al EASL 2015 (abstr G07)].

Dr Naggie concluded that although SOF has few interactions, it is not sufficient alone to treat coinfected HCV/HIV patients; these patients need a regimen that is most compatible with their antiretroviral therapy. All direct-acting antivirals have drug interactions with HIV antiretrovirals; however, with similar efficacy and safety, there should be no coinfected patient without a safe HCV treatment option. For the rare patient where that might have been the case, the pending approval of daclatasvir should provide a bailout.