Introduction

The more than 300 attendees at the 2015 "HEPATITIS C MANAGEMENT - STATE OF THE ART" conference listened as 17 faculty members discussed some of the serious concerns that remain in the fight against HCV: patient groups who present treatment challenges, which patients should be treated when, the treatment cascade, the costs of HCV care, liver cancer, and a host of other issues. Faculty also presented findings on an array of completed and ongoing trials of direct-acting antivirals (DAAs) designed to cure hepatitis C virus (HCV) infection, some of which had received approval since last year's HEPATITIS C MANAGEMENT - STATE OF THE ART conference. During panel discussions, the faculty members engaged in lively discussions, and each plenary session left time for audience members to ask for the faculty members' thoughts on key questions that have arisen in their own practices.

Attendees' years of experience in treating HCV infection:
- *<10 years—48%*
- *11–20 years—31%*
- *>20 years—21%*

At the end of this report, you will find a list of faculty-suggested readings on the topics discussed during the course.

For a full discussion of the topics covered in this report and to earn CME credit, please review the complete presentations and complete the post-tests available on this website: www.impactid.com.

Hepatology for the Non-hepatologist

With increasing numbers of Americans learning that they are infected with the hepatitis C virus (HCV), many will initially seek care and counsel from their primary care physician. Therefore the need to optimize these clinicians' knowledge of the liver, HCV, and HCV management will also increase, particularly with the availability of more effective and more tolerable treatments. In "Hepatology for the Non-hepatologist," **Kenneth E. Sherman, MD, PhD**, of the University of Cincinnati College of Medicine, reviewed the structure and function of the liver, how liver injury can occur, the conditions arising from liver injury, and basics of how to manage liver injury.

Hepatic fibrosis: natural history and staging

Hepatic fibrosis results from the liver's healing response following any of a variety of chronic injuries, some of which are shown in Figure 1. Acute liver injury, Dr. Sherman said, is typically defined as resolution within the 6 months following the onset of injury, vs chronic injury, which persists beyond 6 months. Laboratory measurements used to assess liver damage include:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Bilirubin
- Alkaline phosphatase (ALP)
- Gamma glutamyl transferase (GGT)

The degree of injury is assigned a grade of 0 through 4, depending on how far above normal the level of these substances is. A higher grade is indicative of a more urgent need for further assessment. Employing 2 measurements, Hy's Rule postulates that a patient having bilirubin >3 mg/dL in combination with AST >20 x ULN has a 10% to 50% chance of death from fulminant hepatic failure or need for liver transplantation. According to the hypersensitivity rule, the presence of ALT >2 x ULN in combination with hypereosinophilia is the definition of hypersensitivity liver injury. Dr. Sherman cautioned, however, that these findings require individualized assessment for each patient, since the "normal" range varies among laboratories, based on the average levels found in a local population.
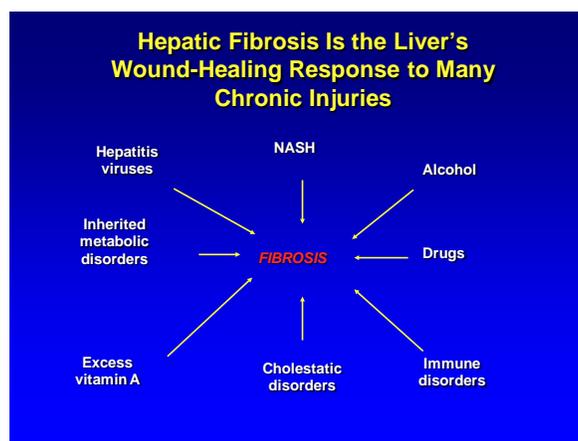

Hepatic Fibrosis Is the Liver's Wound-Healing Response to Many Chronic Injuries

Hepatitis viruses — NASH — Alcohol
Inherited metabolic disorders → FIBROSIS ← Drugs
Excess vitamin A — Cholestatic disorders — Immune disorders

Figure 1. Substances and conditions associated with hepatic injury

Injury to the liver by HCV or other causes stimulates the hepatic stellate cells that line the hepatic sinusoids to deposit collagen matrix. Accelerated cell death leads to gradual collagen deposition that eventually results in cirrhosis. That is, a liver lobule that is completely surrounded by a collagen (scar) band defines cirrhosis. Although the median time to develop cirrhosis after HCV infection is 30 to 35 years, in some people it can occur in fewer than 5 years, whereas others may never develop cirrhosis.

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At this time, determining the stage of a patient's fibrosis is a key factor in deciding whether and when to start anti-HCV treatment. Although several staging systems are available, Dr. Sherman felt that the easiest to utilize is the 5-stage Metavir system:
- F0: no excess fibrosis
- F1: mild portal fibrosis
- F2: moderate fibrosis with portal expansion and rare bridges
- F3: extensive collagen bridges between portal areas
- F4: cirrhosis (liver lobule surrounded by scar)

For years, biopsy served as the gold standard for fibrosis staging, and, when a biopsy sample is large enough (≥2.5 cm in length and ≥16G in width) and not fragmented, the findings are highly accurate. However, Dr. Sherman stressed that liver biopsy is an invasive procedure that can lead to serious complications, eg, bleeding, infection, injury to a nearby organ. For those reasons, he advised that biopsy should be reserved for evaluation of cases in which other staging approaches provide conflicting or inadequate findings.

In recent years, however, noninvasive methods of staging liver fibrosis have been increasingly utilized. These include transient elastography (acoustic and MRI-based) and assessment of serum biomarkers. Ultrasonic elastography, such as *FibroScan®,* require expensive technology and provide very accurate results in patients whose fibrosis is at the lowest and highest ends of the spectrum. Dr. Sherman explained that this technique basically works by measuring the movement of the liver when it is vibrated. MRI elastography is also highly accurate, but is not widely available and typically costs $3,000-$4,000.

Serum biomarkers, on the other hand, utilize nonspecific markers of fibrosis and are less reliable. The FIB-4 formula uses a patient's serum ALT and AST levels, platelet count, and age to give a score that can be correlated with fibrosis stage. These biomarkers measure liver injury and the sequestration of blood in the spleen and account for older patients' longer time to develop progressive fibrosis. For example, a FIB-4 score of <1.45 corresponds to Metavir F0/1, and a score of >3.25 corresponds to F3/4.

To underscore the importance of assessing fibrosis stage, Dr. Sherman said that in HCV-infected cirrhotic patients, 2 clocks are running:
- The risk of hepatic decompensation
- The risk of hepatocellular carcinoma (HCC)

Cirrhotic patients have a 5%/year risk for decompensation, or a 50% risk over 10 years.

Hepatic decompensation

Of the various physiological changes that occur when a patient develops cirrhosis, the primary one is the alteration of blood flow through the liver, as it is impeded by the collagen deposits surrounding the liver lobules. Portal blood flow is decreased, leading to increased pressure in the portal vein, ie, portal hypertension. A number of other serious complications can then ensue:

- Enlargement of the spleen, which can result in cytopenias
- Ascites (along with hepatic-renal syndrome, hepatic hydrothorax, and bacterial peritonitis)
- Encephalopathy
- Bleeding varices
- Coagulopathy

A practitioner whose patient has a MELD score ≥10 should refer the patient to a hepatologist. In many areas, however, hepatologists may be difficult to access, and practitioners may need to provide initial care of such patients.

Patients who develop ascites, bleeding varices, hepatic encephalopathy, or coagulopathy are considered to have transitioned from compensated to decompensated cirrhosis, which brings a very high near-term risk of death. A patient with decompensated cirrhosis should be immediately referred to a liver transplant center.

An important tool for assessing impending decompensation is the model for end-stage liver disease (MELD) score, which utilizes creatinine, bilirubin, and international normalized ratio (INR) in a complex regression formula. A practitioner whose patient has a MELD score ≥10 should refer the patient to a hepatologist. In many areas, however, hepatologists may be difficult to access, and practitioners may need to provide initial care of such patients.

Ascites

Ascites is the accumulation of fluid in the peritoneal cavity, causing abdominal swelling. When a practitioner first notes the presence of ascites, Dr. Sherman stressed that a diagnostic tap of abdominal fluid should be performed. The critical evaluations of the tapped fluid include the serum albumin minus ascitic albumin (SAAG) level and the cell count. A SAAG >1.1 points to portal hypertension as the cause of the ascites; a cell count with >250 neutrophils/mL indicates spontaneous bacterial peritonitis (SBP), which should be treated, even without positive ascitic fluid cultures. Initial management of ascites includes use of diuretics—eg, aldactone 50 mg and furosemide 20 mg once daily—and large-volume paracentesis (LVP) (Figure 2). Many patients require LVP for comfort. Placement of a chest tube for drainage is absolutely contraindicated, as this decreases survival dramatically.
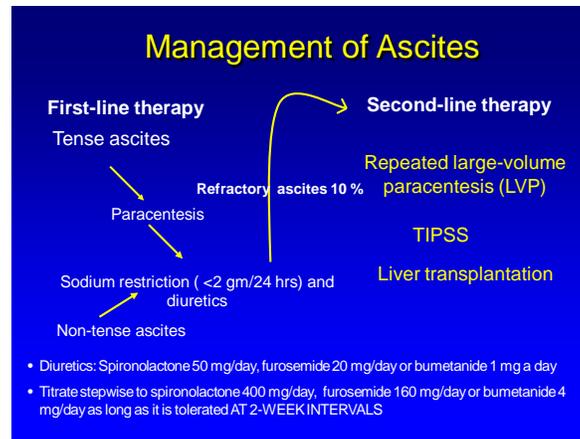
Figure 2. Management of ascites.

Varices

Clinicians should screen any cirrhotic patient for esophageal varices—dilated, twisted veins—using esophagogastroduodenoscopy (EGD). Use of nonselective beta-blockers (eg, nadolol or propranolol) can reduce splanchnic pressure and the risk of variceal bleeding. Larger varices may need ligation (banding). Bleeding varices are a medical emergency, with survival rates ranging from 50% to 70%, but approximately 70% of survivors will rebleed.

Hepatic encephalopathy

Early signs of hepatic encephalopathy (HE) include disturbed sleep patterns, episodes of confusion, and loss of concentration. HE patients may also have tremors, especially in the hands, and may be at risk of accidents when driving or operating heavy machinery. Treatments include lactulose and rifaximin.

Hepatocellular carcinoma

Dr. Sherman concluded by reviewing key issues that clinicians should be aware of regarding hepatocellular carcinoma (HCC):

- All cirrhotic patients should be screened for HCC every 6 months.
- Surveillance is best done by ultrasound, but obese patients may require CT.
- Although no longer recommended, many hepatologists use alpha-fetoprotein (AFP) levels as an adjunct.
- A lesion suspicious for HCC should immediately lead to referral to a transplant center (not a general surgeon) for resection.

Management of HIV/HCV Coinfection

Persons who are infected with both hepatitis C virus (HCV) and HIV merit particular consideration, since each virus can affect the other's disease course, and there are potential drug interactions between a number of their treatments. In fact, the treatment guidelines developed by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (www.hcvguidelines.org)

include recommendations specifically for the HIV/HCV-coinfected population. **Susanna Naggie, MD, MHS**, of the Duke University School of Medicine, reviewed some of the important issues involved in managing these patients.

Dr. Naggie began by emphasizing the guidelines' goal in treating HCV: "to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by achievement of virologic cure as evidenced by SVR [sustained virologic response]." This goal, she stressed, applies to coinfected as well as monoinfected patients, because SVR has been associated with significant improvements in liver-related morbidity and mortality. She then cited findings from the D:A:D study (a multicohort, international study that has followed thousands of HIV-positive patients for approximately 15 years) showing that liver-related complications today are the second leading cause of death, following non-AIDS-defining cancers, among HIV-infected individuals.

HIV infection itself should not be considered a risk factor in deciding to start treatment with direct-acting antivirals (DAAs): "HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications."

To underline the importance of timely treatment of HCV in coinfected patients, Dr. Naggie cited the recently reported findings of a study of deferring initiation of HCV treatment in HIV-coinfected patients. Zahnd and colleagues, who performed the study, found that HIV-infected patients can progress to end-stage liver disease even after achieving SVR if treatment is delayed until the later stages of liver disease, and that delaying treatment also increases the risk of ongoing HCV transmission. Dr. Naggie also urged clinicians to continue to monitor patients' liver function after they attain SVR; to detect fibrosis progression due to continuing risk factors.

Comparable efficacy and safety

A key message is that HIV infection itself should not be considered a risk factor in deciding to start treatment with direct-acting antivirals (DAAs): "HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications." Dr. Naggie expressed the hope that this recommendation will help to reduce the perception that HIV/HCV-coinfected patients are more difficult to treat, thereby removing a long-time barrier to treating these individuals.

Dr. Naggie then reviewed specific direct-acting antiviral (DAA)-based regimens that are now available, or soon will be, and their applicability for coinfected patients. Genotype 1 HCV infection is the predominant genotype in the United States, and both 2- and 3-drug regimens, with different mechanisms of action, are available for these patients. Figure 3 shows the regimens that have been evaluated in HIV/HCV-coinfected patients. In general, patients should receive HCV treatment for 12 weeks, although there are some caveats.

Figure 3. DAA regimens that have been evaluated in coinfected patients.

At this time, the AASLD/IDSA guidelines recommend the following regimens for noncirrhotic HIV/HCV-coinfected patients:

- Ledipasvir plus sofosbuvir
- Simeprevir plus sofosbuvir, with or without ribavirin
- Paritaprevir/ritonavir/ombitasvir plus dasabuvir plus ribavirin (genotype 1a)
- Paritaprevir/ritonavir/ombitasvir plus dasabuvir (genotype 1b)

To address the question of whether HIV/HCV-coinfected patients achieve the same SVR rates as HCV-monoinfected patients, Dr. Naggie compared the results from several clinical trials in which both monoinfected and coinfected patients received the same HCV regimens.

- In the ION trials, monoinfected and coinfected patients achieved comparable SVR12 rates (96% vs 97%, respectively) with fixed-dose ledipasvir/sofosbuvir. She pointed out that the only subgroup of coinfected patients who experienced HCV relapse were black patients; further analysis to determine the cause of this outcome is underway.
- In the TURQUOISE and SAPPHIRE trials evaluating fixed-dose paritaprevir/ritonavir/ombitasvir plus dasabuvir plus ribavirin, coinfected vs monoinfected patients achieved SVR12 of 93% vs 96% (naive patients) and 90% vs 96% (experienced patients), respectively.
- In trials of daclatasvir plus sofosbuvir overall SVR12 rates were 97% vs 98% in coinfected vs monoinfected patients.

Findings such as these, Dr. Naggie said, confirm that high rates of SVR that can be achieved with DAA regimens in HIV/HCV-coinfected patients having genotype 1 HCV.

Several studies have reported findings of treatment with sofosbuvir plus ribavirin in patients with genotypes 2 and 3 HCV, which are the second and third most common genotypes found in the United States:

- Genotype 2: treatment-naive patients, SVR12, 89%; treatment-experienced patients, SVR12-16, 90%
- Genotype 3: treatment-naive patients, SVR24, 91%; treatment-experienced patients, SVR24, 88%

Finally, recently presented findings from the C-EDGE study of the NS3/4 protease inhibitor grazoprevir plus the NS5A inhibitor elbasvir reported identical SVR12 rates (95%) in both monoinfected and coinfected participants.

Some DAA regimens that contain HCV protease inhibitors (PIs) (eg, simeprevir, paritaprevir) may need to be administered with ribavirin in patients with genotype 1a infection to decrease relapse rates. In addition, the Food and Drug Administration recommends 24 weeks of treatment for PI-containing regimens in most cirrhotic patients. With ledipasvir/sofosbuvir, cirrhotic treatment-experienced patients are more likely to relapse and therefore benefit from either the addition of ribavirin to the 12-week regimen or extending the 12-week ribavirin-free regimen to 24 weeks.

Because many clinicians and patients would like to reduce the time to achieve SVR to even fewer than 12 weeks, Dr. Naggie presented findings of ledipasvir/sofosbuvir trials in which treatment-naive patients received 8 or 12 weeks of treatment. HCV-monoinfected patients achieved SVR8 of 94% vs SVR12 of 95%. However, coinfected patients achieved SVR8 of 75.6% vs SVR12 of 96.4%—a cautionary outcome regarding further reduction in treatment duration.

Drug-drug interactions

Although a range of trial findings have demonstrated that HIV/HCV-coinfected patients can achieve SVR rates that are comparable to those achieved by HCV-monoinfected patients, Dr. Naggie concluded with a discussion of the myriad drug-drug interactions between antiretrovirals and DAAs. She explained that, in fact, interactions can occur with all ART regimens to one degree or another (Figure 4).

ARV Interaction Score Card

DDI	Simeprevir	Sofosbuvir	Ledipasvir	Daclatasvir	P/r/O + D
	Substrate of CYP3A4, OATP1B1/3	Substrate of P-gp and BCRP	Inhibitor/ Substrate of P-gp and BCRP	Inhibitor of OATP1B1/3, BCRP, Substrate of P-gp and CYP3A4	Inhibit/Sub of UGT1A1, OATP1B1/3, BCRP, CYP3A4, CYP2C8, P-gp
ATV/r	No data	No data	LDV ↑; ATV ↑	DCV ↑*	ATV ↔; ABT450 ↑
DRV/r	SIM ↑; DRV ↔	SOF ↑; DRV ↔	LDV ↑; DRV ↔	No data	DRV ↓; 3D ↓
LPV/r	No data	No data	No data	No data	LPV ↔; ABT450 ↑
TPV/r	No data	No data	No data	No data	No data
EFV	SIM ↓; EFV ↔	SOF ↔; EFV ↔	LDV ↓; EFV ↓	DCV ↓*	No PK data**
RPV	SIM ↔; RPV ↔	SOF ↔; RPV ↔	LDV ↔; RPV ↔	No data	ABT450 ↑; RPV ↑
ETV	No data	No data	No data	No data	No data
RAL	SIM ↔; RAL ↔	SOF ↔; RAL ↔	LDV ↔; RAL ↔	No data	3D ↔; ↑ RAL
ELV/cobi	No data	No data	No data	No data	No data
DLG	No data	No data	No data	No data	No data
MVC	No data	No data	No data	No data	No data
TDF	SIM ↔; TFV ↔	SOF ↔; TFV ↔	LDV ↔; ↑TFV	DCV ↔; TFV ↔	3D ↔; TFV ↔

* Decrease DCV dose to 30mg QD, Increase DCV dose to 90mg QD. ** 3D + EFV led to premature study discontinuation due to toxicities

Slide courtesy of Jennifer Kiser

Figure 4. Interactions with DAAs can occur with virtually all ARV regimens.

As the red, green, and yellow cells in Figure 4 indicate, some ARV-DAA combinations are contraindicated (red), whereas others should be administered with caution (yellow). For some combinations, this will require adjustment of components of either the ART or the DAA regimen.

Pharmacokinetics: Navigating the Drug Interactions with New HCV Regimens

In her presentation, "Pharmacokinetics: Navigating the Drug Interactions with New HCV Regimens," **Jennifer J. Kiser, Pharm D**, of the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, reviewed the main drug interaction issues involved in administering direct-acting antivirals (DAAs). She discussed the range of concerns that would need to be considered in selecting an HCV regimen in the case of a black woman who is HIV/HCV-coinfected and has other comorbidities for which she also takes medications.

The patient's HIV is suppressed on a tenofovir/emtricitabine plus darunavir/ritonavir regimen; her HCV RNA is 9,600,000 IU/mL, and she was previously diagnosed with stage 2 fibrosis. The initial decision involved which DAA regimen—sofosbuvir plus simeprevir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir plus dasabuvir plus ribavirin—would require her ART regimen to be changed. Dr. Kiser then showed why the risk of drug-drug interactions associated with each of these potential regimens would require adjustment to the patient's ART regimen.

Sofosbuvir

The nucleotide analog sofosbuvir, unlike many antiretrovirals, is not metabolized by the cytochrome (CYP) P450 enzymes, and does not inhibit or induce CYP enzymes; therefore, it is not susceptible to interactions with coadministered drugs whose metabolism is affected by these enzymes. However, sofosbuvir is a substrate for the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Therefore, compounds that induce P-gp or BCRP (eg, antiepileptic agents, the antibacterial rifampin, and the HIV protease inhibitor [PI] tipranavir) may lower sofosbuvir concentrations and should be avoided.

This, Dr. Kiser said, seems to be good news for the case patient, but the potential interactions with the coadministered DAA will also need to be considered.

Simeprevir

Sofosbuvir is often prescribed in combination with the NS3/4A PI simeprevir, which is a substrate for CYP3A. Therefore potent CYP3A inhibitors (eg, ritonavir-boosted HIV PIs) may significantly increase simeprevir concentrations, while potent CYP3A inducers (eg, the HIV non-nucleoside reverse transcriptase inhibitor efavirenz) may reduce simeprevir concentrations by as much as 71%. The case patient is currently receiving darunavir/ritonavir, which can increase simeprevir concentration by 2.6-fold, even after a significant reduction in the simeprevir dose. This means that the use of HIV PIs with simeprevir is seriously limited.

Ledipasvir

Sofosbuvir and ledipasvir are available in a fixed-dose tablet. Ledipasvir absorption requires an acidic environment, and gastric acid modifiers may reduce its exposure. Approximately 70% of a ledipasvir

dose is excreted unchanged, with the rest presumably metabolized by CYP3A. Like sofosbuvir, ledipasvir is a P-gp substrate, meaning that potent P-gp inducers may reduce exposures. Although renal or hepatic impairment does not alter ledipasvir pharmacokinetics, Dr. Kiser cautioned that ledipasvir raises concentrations of the HIV nucleotide analog tenofovir, which itself has been associated with nephrotoxicity. Moreover, the increased tenofovir exposure from ledipasvir coadministration is of particular concern in HIV-infected patients who are also taking a ritonavir-boosted PI. Ritonavir-boosted PIs increase tenofovir concentrations approximately 25% to 35%, and the additional increase of 30% to 60% from ledipasvir will lead to tenofovir concentrations above the range for which safety data have been established. She stressed that, until safety data are available, the combination of a ritonavir-boosted PI, tenofovir, and ledipasvir/sofosbuvir should be avoided. In patients who cannot be switched from a ritonavir-boosted PI—eg, if needed as part of a salvage regimen—renal function and urine protein and glucose levels should be monitored every 2 to 4 weeks. Notably, the case patient's ART regimen included tenofovir and a boosted PI.

Paritaprevir/ritonavir, ombitasvir, dasabuvir

The DAA regimen of ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir (sometimes known as "3D") contains an NS3/4A inhibitor, an NS5A inhibitor, and a non-nucleoside NS5B polymerase inhibitor. Although highly effective in HCV treatment, this regimen is associated with a large number of drug interactions, since its components are substrates and inhibitors of CYP3A and CYP2C8, uridine glucuronosyltransferase 1A1 (UGT1A1), and P-gp and OAT1B1. Fortunately, Dr. Kiser added, the regimen's manufacturer has conducted extensive drug-drug interaction studies, and the results are readily available. For example, the coadministration of 3D and darunavir has been shown to reduce the darunavir trough level by approximately half. She said that the only HIV PI that should be coadministered with the 3D regimen is unboosted atazanavir, because ritonavir is already contained in 3D. Coadministration of 3D with efavirenz is contraindicated, as patients in clinical trials experienced severe tolerability issues.

Other coadministered drugs and substances

Dr. Kiser concluded by emphasizing the great importance of conducting a systematic review of potential drug-drug interactions before prescribing DAAs, and that this must begin with a thorough interview with the patient, who should be encouraged to disclose the use of any recreational drugs, over-the-counter medications, and herbal treatments. For example, without being carefully questioned, many patients will not remember to mention nonprescription drugs such as those used to treat GERD. She presented a flow chart designed to assist clinicians in identifying and managing drug interactions in HCV patients (Figure 5).
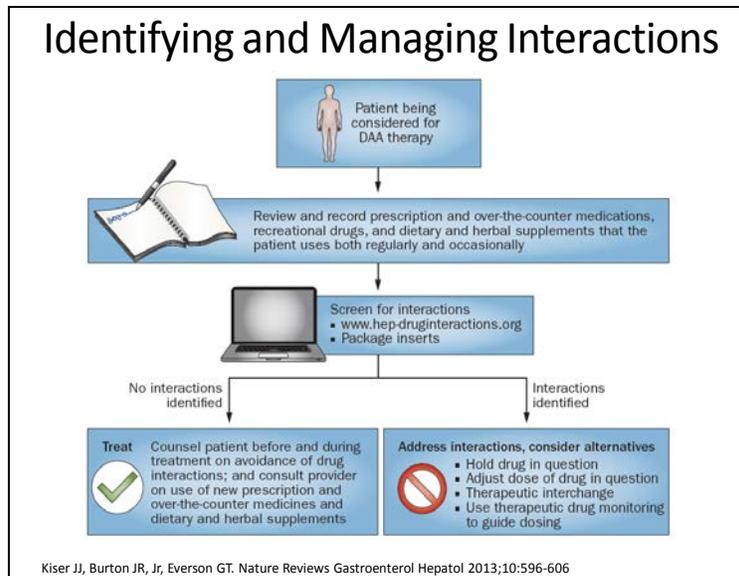
Identifying and Managing Interactions

Kiser JJ, Burton JR, Jr, Everson GT. Nature Reviews Gastroenterol Hepatol 2013;10:596-606

Figure 5. A thorough review of potential interactions with DAAs is essential.

Additional considerations

Other issues besides potential drug-drug interactions, particularly renal or hepatic impairment, can also influence the selection of a DAA regimen:

- Sofosbuvir is renally cleared, and concentrations are increased 3-fold and 6-fold in individuals with moderate and severe renal impairment, respectively. Studies are under way to determine the pharmacokinetics, safety, and dosing in individuals with renal impairment. Sofosbuvir levels are increased about 2-fold in individuals with decompensated cirrhosis, but preliminary data suggest that the combination of ledipasvir/sofosbuvir and ribavirin can result in high SVR rates in decompensated cirrhotics.

- Less than 1% of simeprevir is renally eliminated, but concentrations are increased 2-fold and 5-fold in patients with moderate and severe hepatic impairment, respectively. Therefore, simeprevir should not be prescribed for those patients.

- Although renal impairment does not significantly alter the pharmacokinetics of 3D, the addition of ribavirin is required in patients with HCV genotype 1a infection (like the case patient), and ribavirin must be dose-adjusted. Paritaprevir and dasabuvir are increased 10-fold and 4-fold, respectively, in individuals with hepatic impairment.

Drug interaction resources

Dr. Kiser emphasized the value of several online resources in assessing potential interactions with DAAs. Each is freely accessible and updated regularly:

- University of Liverpool: www.hep-druginteractions.org
- Toronto General Hospital: http://www.hcvdruginfo.ca/
- Specific to antiretroviral interactions: the drug interaction tables in the US Department of Health and Human Services HIV treatment guidelines: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

Audience Questions

Historically, HCV patients who use alcohol or marijuana would not be allowed to receive treatment until they had been abstinent for 6 months. Has that approach changed with the advent of DAAs?

Kenneth E. Sherman, MD, PhD: For alcohol use, there are not enough data to make a definitive recommendation. However, cirrhotic patients who continue to use alcohol would be at greater risk of hepatic decompensation, and in most areas they would need to have abstained for ≥6 months to be considered for transplant. Marijuana use is not likely to be a problem regarding treatment initiation or outcome.

Jennifer J. Kiser, PharmD: From a pharmacological perspective, use of recreational drugs would not be a concern. Most restrictions on such use originate with the payer.

Is there any evidence to support withholding ART in HIV/HCV-coinfected patients during the time that they are receiving HCV treatment?

Susanna Naggie, MD, MHS: If a patient is willing and able to tolerate a regimen of sofosbuvir plus pegylated interferon and ribavirin, that would be one option that would not require ART discontinuation. Another option would be daclatasvir plus sofosbuvir, for which there is no contraindication with any ART regimen. Waiting for the approval of daclatasvir would be preferable to discontinuing ART to use one of the currently approved regimens.

Kenneth E. Sherman, MD, PhD: Data from the SMART trial indicated that ART interruption is not a good idea, particularly for patients who have underlying liver disease.

Challenging Cases: HIV/HCV Coinfection

Because of shared transmission modes, HIV-infected individuals are at risk for infection with hepatitis C virus (HCV). HIV/HCV coinfection is associated with more rapid progression of hepatic fibrosis and poorer prognosis, suggesting that such patients should be prioritized for HCV therapy. In the past, however, HCV treatment rates have been lower in the HIV/HCV-coinfected population, owing to lower response rates, comorbidities, patient and practitioner perceptions, and adverse events associated with interferon-based therapy. The availability of HCV direct-acting antivirals (DAAs) should decrease such barriers to HCV treatment and cure. However, for many coinfected patients, medical comorbidities, social and behavioral issues (including access to care and cost of medications), and complex drug interactions between many DAAs and antiretroviral medications complicate clinicians' ability to provide optimal management.

With that background, Robert S. Klein, MD, moderated a discussion based on 4 illustrative cases to explain important issues regarding the treatment of HIV/HCV coinfection. Participating in the discussion were Raymond T. Chung, MD; Susanna Naggie, MD, MHS; and David L. Thomas, MD, MPH.

Case 1
The first case was a 48-year-old black man:

- Recently diagnosed with asymptomatic HIV infection
  - CD4+ cell count: 400/mm^3
  - HIV RNA: 45,000 copies/mL
- Chronic HCV infection
  - ALT 75
  - Total bilirubin 1.2
  - INR 1.1
  - Albumin 3.5
  - Platelet count 100,000
  - HCV RNA level 1.6 million
  - Genotype 1a
  - Transient elastography: 13.5 kPa
  - Serum creatinine: 1.8; creatinine clearance: 35 mL/min
  - Cryoglobulinemia type 2 and 1+ proteinuria on urinalysis

All 3 discussants agreed that this patient should start HCV treatment, as his laboratory results show evidence of advanced liver disease and some renal impairment, and Dr. Thomas pointed out that study findings have shown evidence that treating HCV infection can contribute to improved renal function. Concerning whether to start both HCV and HIV treatment simultaneously, Dr. Naggie advised that she would start HIV treatment first, as most patients will achieve virologic suppression within several weeks. Dr. Chung agreed, adding that trial data seem to indicate that HCV treatment in the context of controlled HIV infection is more likely to achieve optimal outcomes.

Dr. Klein asked which ART regimens would be more appropriate and which should be avoided for this patient. Dr. Thomas suggested that dolutegravir or another integrase inhibitor plus abacavir, assuming the man is HLA-B*5701-negative, would allow a greater number of HCV regimen choices, adding that most specialists would try to avoid the use of tenofovir, due to renal concerns and potential interactions with DAAs.

Dr. Klein then asked what dose of ribavirin should be prescribed for this patient, if the 3D HCV regimen (paritaprevir/ritonavir/ombitasvir plus dasabuvir) is used. Drs. Naggie and Chung agreed that ribavirin 200 mg and 400 mg on alternating days should be used in a patient with this creatinine clearance level, but cautioned that hemoglobin should be monitored carefully.

Case 2

The second case concerned a 53-year-old woman with AIDS:
- Remote history of *Pneumocystis jiroveci* pneumonia
- Long, complicated history of antiretroviral therapy
- Prior assays showing mixed CXCR4 and CCR5 tropism
- Prior PI mutations documented, with susceptibility only to darunavir among the PIs
- HIV RNA undetectable on darunavir/ritonavir, tenofovir/emtricitabine, raltegravir
- Chronic HCV infection
  - Genotype 1a
  - HCV RNA level of 2 million
  - Childs A cirrhosis with an elastography result of 16 kPa
  - eGFR: 38

Because she has genotype 1a HCV infection, Dr. Naggie said that ledipasvir/sofosbuvir would be a good choice but that the tenofovir should be discontinued, due to potential interaction with ledipasvir; this would still leave 2 fully active agents, darunavir and raltegravir, in her ART regimen. If the patient were prescribed the 3D regimen, her genotype 1a disease would require the addition of ribavirin, and the darunavir should probably be discontinued because of the risk of significant reduction in darunavir concentrations. If this patient had genotype 3 HCV infection, Dr. Thomas thought that a good approach would be peginterferon/ribavirin plus sofosbuvir or to wait for the approval of daclatasvir in the United States.

Case 3

The third case is a 63-year-old man with HIV/HCV coinfection:
- End-stage renal disease (ESRD) and on hemodialysis
- Compensated cirrhosis
- Hepatocellular carcinoma diagnosed in 2013 with recurrence in 2014
- ART includes atazanavir/ritonavir and lamivudine
- Long-standing HIV viral suppression; CD4+ cell count of 466 (29%)
- HCV GT1a
  - Treated in 2002 with standard interferon-α for about 6 weeks; treatment discontinued due to relapse of illicit drug use
  - No varices or gastropathy
  - Albumin, 3.6; total bilirubin, 1.3; platelet count, 290,000; INR 1.0
  - HCV RNA level, 2.5 million
  - Child Pugh A (5)
- Concomitant medications include famotidine and omeprazole

Dr. Naggie said that this patient is not a good transplant candidate, because he would need both kidney and liver transplantations and HIV-infected patients tend to have poor outcomes with dual transplants. Dr. Thomas recommended offering the patient the 3D regimen for HCV treatment, while withholding the ritonavir boosting of the atazanavir. Dr. Naggie's recommendation was to discontinue the famotidine and omeprazole due to the apparent lack of need for them and to prescribe ledipasvir/sofosbuvir off-label, with instruction to take the medication before dialysis on the days when that is scheduled. This usage is considered off-label because sofosbuvir exposure is significantly increased in patients with ESRD, although Dr. Naggie said that preliminary findings from a very small trial have suggested that ledipasvir/sofosbuvir may be used safely in some ESRD patients. She thought that the 3D regimen would not be appropriate because the patient would require the addition of ribavirin because of his 1a genotype, and that would not be suitable due to his renal disease.

STATE OF THE ART: Treatment of Hepatitis C

Mark S. Sulkowski, MD, of the Johns Hopkins University School of Medicine, began his presentation, "STATE OF THE ART: Treatment of Hepatitis C," by first reviewing the identification of HCV and the beginnings of HCV treatment. In 1986, Hoofnagle and colleagues first reported that the use of recombinant interferon alfa in patients with non-A, non-B hepatitis (as HCV was then known) improved serum ALT levels in most patients. During the next decade, HCV was identified as the cause of the great majority of non-A, non-B hepatitis, and molecular techniques were developed to test HCV RNA response during interferon therapy. These advances showed that the majority of patients treated with interferon alfa did not achieve HCV eradication, ie, sustained virologic response (SVR). Furthermore, the safety and poor tolerability of prolonged interferon treatment kept many HCV-infected patients from undertaking treatment. In 1995, several studies demonstrated that the addition of ribavirin to interferon alfa led to higher SVR rates, even though ribavirin monotherapy did not reduce HCV RNA. Dr. Sulkowski presented an illustration of the HCV lifecycle showing the identification of a growing number of potential drug targets that became available after identification of the virus itself (Figure 6).
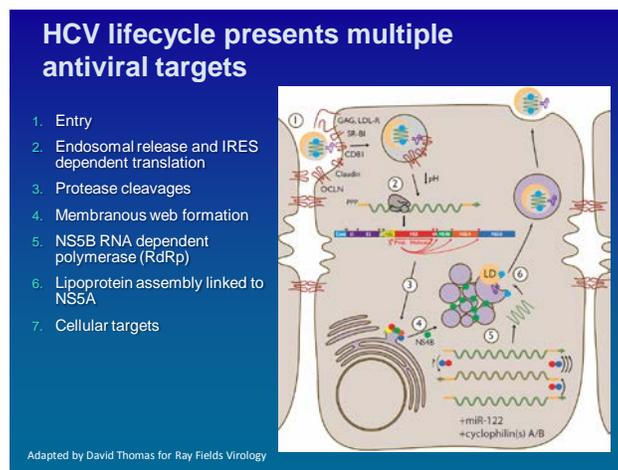

Figure 6. A range of therapeutic targets has been identified.

The DAA era

The march toward the era of direct-acting antivirals (DAAs) began in 2003 with the report of a potent inhibitor of the HCV NS3/4A protease known as BILN 2061, but it was not until 2011 that the HCV protease inhibitors (PIs), telaprevir and boceprevir, entered clinical practice, as part of triple therapy with interferon/ribavirin. However, neither could be used as monotherapy and their usefulness was limited by toxicity. Then, in 2010, a study in the journal *Nature* reported a great reduction in viral replication with a single dose of the NS5A inhibitor daclatasvir, which interfered with the assembly and release of new virions. However, the emergence of resistant variants soon became a concern with this class of drugs.

Non-nucleoside polymerase inhibitors can potentially target several regions of HCV NS5B polymerase inhibitor, although only one, dasabuvir, is currently approved for clinical use. Typically, Dr. Sulkowski said, this class of drugs offers relatively modest inhibition of viral replication, although they make an important contribution to the efficacy of DAA triple therapy. The nucleos(t)ide NS5B polymerase inhibitors, such as sofosbuvir, target a highly conserved active site of the virus. Unlike the PIs and the non-nucleoside inhibitors, these drugs offer a high barrier to resistance. First approved to treat HCV in 1998, ribavirin continues to have a role to play in the treatment of some HCV patients, largely through

its ability to prevent the emergence and selection of resistant variants. Host-targeting inhibitors, aimed at, eg, miR-122 or cyclophilin A, remain in clinical development and none have yet been licensed for clinical use. Dr. Sulkowski pointed out, however that one of them, the injectable miravirsen, was associated with significant and long-lasting viral suppression and may be useful in future one-shot treatments.

The most recent guidelines no longer recommend the use of interferon for most HCV-infected patients, particularly in the United States and many areas of Europe.

With that background, Dr. Sulkowski began the discussion of the current treatment landscape by saying that the most recent guidelines no longer recommend the use of interferon for most HCV-infected patients, particularly in the United States and many areas of Europe. Similarly to HIV treatment, an HCV regimen must be designed by selecting drugs that hit different viral targets. He then discussed the differing treatment approaches for each of the HCV genotypes. Because most North American patients have genotype 1a or 1b HCV infection, most of the presentation dealt with treatment of those patients.

DAA regimens for genotype 1a or 1b that do not include a nucleos(t)ide polymerase inhibitor

The first example of this type of regimen is the NS5A inhibitor daclatasvir plus the PI asunaprevir, which is approved for use in Japan, where the epidemic largely involves genotype 1b infection (resistance developed quickly in genotype 1a patients). Dr. Sulkowski said that this particular regimen is unlikely to be used in the United States. Another regimen in this category is the PI paritaprevir/ritonavir plus the non-nucleoside NS5B inhibitor dasabuvir plus ribavirin. A small trial showed that this regimen worked well in relatively easy to treat patients—eg, treatment-naive noncirrhotics—but it was significantly less effective in patients who had previously received interferon therapy. These results, Dr. Sulkowski stated, confirmed the idea that host factors can be an important determinant in the success of a DAA regimen. In the AVIATOR trial of paritaprevir/ritonavir plus the NS5A inhibitor ombitasvir plus dasabuvir plus ribavirin, 96% of patients achieved SVR, with relapse in only 1.2%. Removing 1 drug from the regimen significantly increased relapse rates: 12.2% without ombitasvir, 10.1% without dasabuvir, 7.6% without ribavirin, thereby underlining the important contribution of each drug class to the success of the regimen. Further investigation of this regimen found that 99% of genotype 1b patients achieved SVR without the inclusion of ribavirin, whereas in genotype 1a patients only 90% of patients who did not receive ribavirin achieved SVR (vs 97% of those who got ribavirin). Dr. Sulkowski said that this further supports ribavirin's role in minimizing resistance-related virologic failure. In the TURQUOISE study of this regimen in cirrhotic patients, significantly higher percentages of patients achieved SVR with 24 weeks vs 12 weeks of treatment.

Another investigational regimen evaluated agents in the same drug classes: the NS5A inhibitor daclatasvir, the PI asunaprevir, and the non-nucleoside inhibitor beclabuvir in both treatment-naive and -experienced patients. Similar to the paritaprevir/ritonavir plus ombitasvir plus dasabuvir regimen, patients with genotype 1a infection achieved significantly higher SVR12 rates with the addition of ribavirin.

The investigational single-tablet regimen of the PI grazoprevir plus the NS5A inhibitor elabasvir has also shown very high SVR rates in both treatment-naive and treatment-experienced patients. Here again, Dr. Sulkowski explained, the addition of ribavirin or an additional 6 weeks of therapy appeared to yield

higher SVR rates in cirrhotic and prior null-responder patients. This regimen is likely to be submitted for Food and Drug Administration review in 2015.

DAA regimens for genotype 1a or 1b that include a nucleos(t)ide polymerase inhibitor

Dr. Sulkowski stated that the development of NS5B nucleoside polymerase inhibitors has been challenging, with the first agent in the class, BILN 2061, being discontinued due to cardiac toxicity. More recently, however, the combination of an NS5A inhibitor, daclatasvir, or a PI, simeprevir, with the nucleotide inhibitor sofosbuvir has been shown to lead to rapid and profound declines in HCV viral load, particularly when ribavirin is added.

In current clinical practice, the fixed-dose combination of the NS5A inhibitor ledipasvir and the nucleotide inhibitor sofosbuvir has been shown to result in ≥93% SVR rates with 8, 12, or 24 weeks of treatment in naive genotype 1 patients. He added that, in trials of this regimen, the addition of ribavirin did not confer significant additional benefit. However, he advised that definitive data on which patients should receive shorter therapy are not yet available. In cirrhotic patients who had previously failed interferon-based therapy, 90% achieved SVR12 with ledipasvir/sofosbuvir, but the addition of ribavirin resulted in SVR12 rates of 96%.

With such high rates of treatment success in genotype 1 patients, Dr. Sulkowski explained that investigators have now begun to explore the possibility of shorter treatment durations, a goal of great interest to clinicians and patients alike. However, he expressed his belief that the results of durations as short as 4 weeks thus far indicate that treatment durations of fewer than 8 weeks do not appear to be likely in the near future.

Treatment of persons with HCV genotype 2, 3, 4 , 5, or 6 infection

In lower-middle and low income countries, genotypes 3 and 4 HCV infection are the most common and a major global focus of treatment development. The PI simeprevir is not effective in genotype 3 infection, although the investigational PI grazoprevir is effective, but not at the dose at which it has been developed. Dr. Sulkowski explained that this situation illustrates that the first DAAs that became available have proved to be less suitable for treatment of genotype 3 patients. In patients with genotype 2 infection, sofosbuvir plus ribavirin has shown SVR12 rates of 97%, but only 56% in genotype 3 patients. He added, however, that sofosbuvir plus ribavirin for 24 weeks led to SVR rates of 92% and 95% in treatment-naive cirrhotic and noncirrhotic genotype 3 patients, respectively, compared with 62% and 87% in treatment-experienced patients. Daclatasvir plus sofosbuvir has been shown to result in SVR12 rates of 100% in both treatment-naive and -experienced genotype 3 patients who were HIV-coinfected. However, in cirrhotic monoinfected genotype 3 patients, SVR 12 rates were only 63% with sofosbuvir plus ribavirin. While evaluations of other multiclass combinations continue, Dr. Sulkowski said that for now, the combination of interferon/ribavirin plus sofosbuvir remains significantly more effective vs sofosbuvir plus ribavirin for genotype 3 patients.

For patients with genotype 4 HCV infection, a number of different regimens can be very effective:
- Ledipasvir/sofosbuvir
- Daclatasvir plus asunaprevir plus beclabuvir
- Ombitasvir plus paritaprevir/ritonavir

Dr. Sulkowski then explained that, although it appears that patients with genotype 4 infection can readily achieve SVR, the real challenge will be access to the medications, since genotype 4 infection is prevalent in lower-income areas.

In concluding, Dr. Sulkowski said that the hope for the future lies in the development of regimens that are active against all HCV genotypes. One investigational regimen that has shown great promise is sofosbuvir plus the investigational NS5A inhibitor velpatasvir with or without the investigational PI GS-9857. This regimen has demonstrated SVR12 rates >90% in patients with all genotypes of HCV infection. He added that other pangenotypic strategies are also currently being evaluated.

HCV Treatment: The Unanswered Questions

Speaking on "HCV Treatment: The Unanswered Questions," **Andrew J. Muir, MD, MHS** of the Duke Clinical Research Institute observed that, from the vantage point of his clinic, the HCV treatment glass appears to be half-full. His optimism arises from the fact that highly effective, tolerable, interferon-free HCV treatments today are available for patients with all HCV genotypes. The greatest challenge in his own situation is the frequent need to secure prior authorization from third-party payers. He acknowledged, however, that outside his clinic the glass can often look more like half-empty:

- Treatment can be long and complicated.
- Care typically needs to be managed by a specialist.
- Access to treatment is not available to everyone who needs it.
- HCV treatment in developing countries is a huge challenge.

Illustrating with a flow chart of HCV treatment provision (Figure 7), Dr. Muir said that some patients are lost to care at each stage of diagnosis and treatment, which is a time-consuming process that involves a variety of clinical encounters.
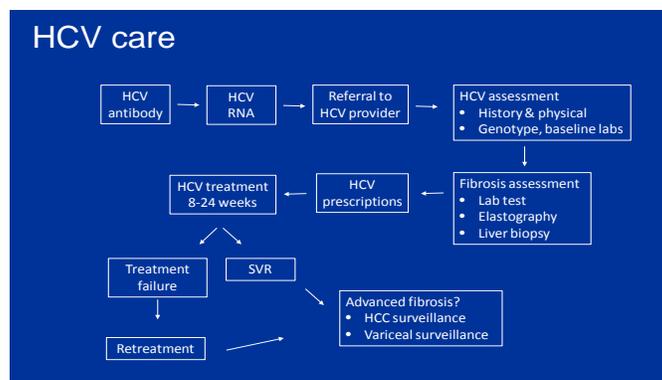

Figure 7. HCV diagnosis and treatment flow chart.

Dr. Muir said that he thought of the topic of his presentation as an effort to depict what the HCV treatment cascade could and should look like, and he did so by addressing 4 questions:

- What should future regimens look like?
- Which populations should receive treatment?
- What should treatment models be?
- What does SVR (sustained virologic response) mean?

What should future regimens look like?

To suggest the possible shape of future regimens, Dr. Muir first discussed a trial in which 60 treatment-naive genotype 1 patients received ledipasvir/sofosbuvir (a current standard regimen) for 12 weeks, ledipasvir/sofosbuvir plus an investigational non-nucleoside inhibitor for 6 weeks, or ledipasvir/sofosbuvir plus an investigational protease inhibitor for 6 weeks. The investigators reported SVR rates of 100%, 95%, and 95%, respectively. The C-SWIFT trial also aimed to compare different treatment regimens: 102 treatment-naive genotype 1 patients received grazoprevir/elbasvir plus sofosbuvir for 4 vs 6 weeks for noncirrhotic patients or 6 vs 8 weeks for cirrhotic patients. SVR rates were 38.7%, 86.7%, 80%, and 94.7%, respectively. Four weeks of treatment, Dr. Muir said, unfortunately did not come anywhere close to an acceptable outcome, since a widely accepted goal currently is SVR rates of >90%.

His hopes for the shape of future regimens is informed significantly by the needs of patients in less-developed regions, where care is often managed by nurses. Key regimen features that would be suitable for these demographics include:
- More pangenotypic agents
- SVR >90% (including compensated cirrhotics)
- Improved tolerability
- Once-daily dosing
- Treatment duration of 4 weeks
- Algorithms to allow easy determination of who should get treatment

Which populations should get treatment?

Current treatment priorities, Dr. Muir said, are determined by guidelines and the requirements of third-party payers and focus on patients with the greatest need, eg, those at risk for complications of HCV infection, those with advanced fibrosis, HIV/HCV-coinfected persons, and post-transplant patients. Answering the question of who should receive treatment in the future, he continued, will mean addressing important questions like:
- Is eradication of HCV going to be a goal?
- Should individuals at all stages of HCV infection be targeted?
- How can injection drug users best be managed?
- How can the needs of the developing world be addressed?

He cited a French study as an exploration of some of these issues. That study's goal was to assess the impact of interventions at different levels of the HCV care cascade on the prevalence and incidence of infection among the IDU population. The researchers assumed an average of 1.25 years from HCV infection to diagnosis and 2.1 years from diagnosis to linkage to care, an annual 14% of patients lost to follow-up, and a Metavir score of ≥F2 in 81.3% of patients. He said that, unfortunately, the investigators found that there was no benefit to earlier diagnosis, improved linkage to care, or improved adherence to treatment. The one measure that was associated with reducing HCV prevalence was early treatment with highly effective regimens.

What should treatment models be?

To suggest the kinds of decisions that will need to be made, Dr. Muir compared quotations by Voltaire ("The perfect is the enemy of the good") and Confucius ("Better a diamond with a flaw than a pebble without"). In the HCV context, this reflects the dilemma of needing to decide whether the highest quality of care that is now available to some can be extended to all or whether less than perfect regimens should be rolled out for as many patients as possible. A basic question to be decided is who should manage the care of HCV patients: Hepatologists? Infectious disease specialists? Gastroenterologists? Primary care providers? Advanced practice providers? He explained that, for example, in some less-developed regions, systems that provide HIV care via nurse clinicians are already in place and could serve as a base or model for increasing access to HCV care.

There was no benefit to earlier diagnosis, improved linkage to care, or improved adherence to treatment. The one measure that was associated with reducing HCV prevalence was early treatment with highly effective regimens.

Even in the United States today, HCV patients often need to travel considerable distances to access appropriate care. Dr. Muir added that, when gasoline prices spiked the last time, his clinic noted a clear decline in the number of patient visits for HCV care. This underlines the importance of making care as close to patients' own communities as possible.

Dr. Muir said that inspiration could be taken from programs that provide care to persons who inject drugs (PWID), which have developed several types of clinical models:

- Specialized hospital-based clinics
- Drug detoxification program centers
- Opioid substitution therapy centers
- Community-based clinics

Experience has shown that a core component of models that have seen success in PWID populations is the pursuit of a multidisciplinary approach that incorporates:

- Clinicians
- Nursing staff
- Drug and alcohol support services
- Psychiatric services
- Social work services
- Peer support

What does SVR mean?

As DAAs have allowed increasing numbers of HCV-infected individuals to be cured, Dr. Muir said that the need for a clear definition of what SVR means has also increased. To shed light on this issue, he first cited a hopeful study that followed, for a median 8.4 years, 530 HCV patients with either advanced fibrosis or cirrhosis who had received treatment. Key findings were all-cause mortality, liver-related mortality or transplant, or hepatocellular carcinoma (HCC) in patients who achieved SVR vs those who did not achieve SVR. Figure 8 shows the dramatic reductions in all these outcomes that were experienced by patients who attained SVR.
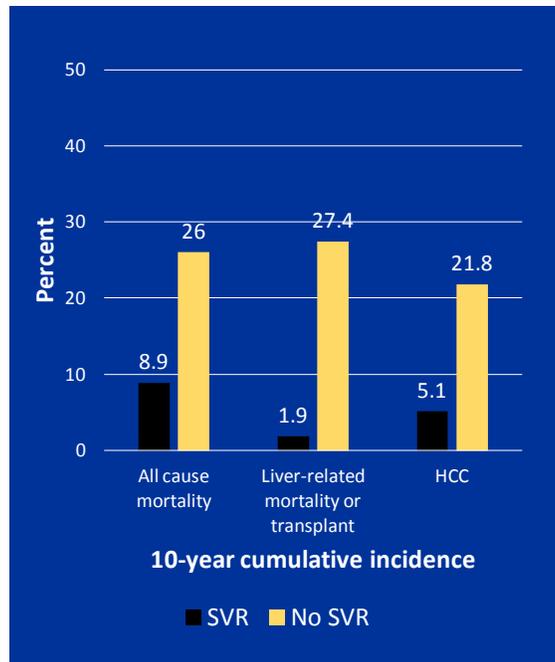
Figure 8. Posttreatment outcomes in patients who either did or did not achieve SVR.

In contrast, Dr. Muir said that another study may temper clinicians' optimism: 351 patients with Child Pugh class A cirrhosis, no prior decompensation, some with SVR and some without SVR were followed for a mean 5.3 years, assessing them for HCC, any liver complication, and all-cause mortality. A worrisome finding was the number of HCC cases that began to appear after 7 years, raising concerns about whether surveillance of such patients should ever be discontinued and how the risk of complications might be identified after 2, 5, or 10 years.

Dr. Muir said that an urgent need is to reduce the number of clinical encounters involved in HCV care so as to broaden treatment availability and access to care.

He further explained that ongoing concerns include whether a patient with Child Pugh B/C cirrhosis will improve, remain stable, or progress and require transplantation. For patients with earlier-stage liver disease, the impact of HCV eradication on their health-related quality of life—fatigue, brain fog, and other symptoms—is also unclear. Clinicians need to better understand how HCV infection contributes to these symptoms and whether treatment will alleviate them.

Dr. Muir concluded by referring to the flow chart in Figure 7 showing the number of steps involved in HCV diagnosis and treatment, and the patient attrition that results from the complexities of the process. He said that an urgent need is to reduce the number of clinical encounters involved in HCV care (Figure 9) so as to broaden treatment availability and access to care.
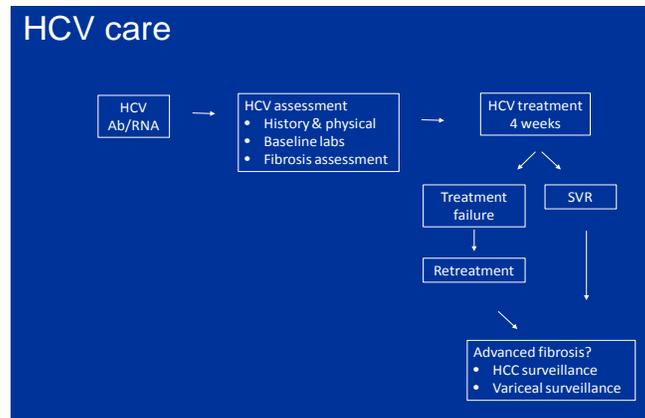
Figure 9. Simplified flow chart for HCV diagnosis and treatment.

Remaining (and Dwindling) Unmet Needs in the DAA Era

Raymond T. Chung, MD, of Harvard Medical School and the Massachusetts General Hospital, began his presentation by stating that the direct-acting antiviral (DAA) therapy revolution has lifted nearly all boats among HCV-infected persons, including those with genotype 1, 2, 4, 5, and 6 infection and even HIV/HCV-coinfected patients. Nevertheless, some groups have experienced lesser degrees of treatment benefit, including patients with genotype 3 infection, those with cirrhosis (particularly decompensated), those with profound renal impairment, and those with prior failure on regimens of pegylated interferon/ribavirin and either telaprevir or boceprevir or other DAA failures, eg, sofosbuvir. Dr. Chung presented a great variety of data illustrating the possibilities for lifting these patients' boats also.

Genotype 3 patients

The VALENCE study assessed sofosbuvir 400 mg daily plus weight-based RBV for 24 weeks in patients with genotype 2 or 3 HCV infection (250 genotype 3 treatment-naive and -experienced patients). The genotype 3 patients achieved SVR12 rates of 91% and 68% (noncirrhotics vs cirrhotics) with 24 weeks of treatment, suggesting, Dr. Chung said, that higher response rates in genotype 3 patients can be achieved with longer treatment, compared with the 30% to 63% rates achieved in earlier trials of 12 or 16 weeks in this population. A subanalysis found comparably high rates among all patients with and without cirrhosis (92% and 93%, respectively), although rates were only 68% in cirrhotic genotype 3 patients.

The phase III ALLY 3 trial evaluated the investigational once-daily NS5A inhibitor daclatasvir 60 mg plus sofosbuvir 400 mg for 12 weeks only in patients with genotype 3 infection. In treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12, whereas in those with cirrhosis (Metavir F4), 58% achieved SVR12. In experienced patients, 86% of cirrhotics achieved SVR. Dr. Chung explained that these findings show that treatment success in patients with advanced fibrosis or cirrhosis continues to lag.

One cohort of the ELECTRON-II study examined ledipasvir/sofosbuvir with or without ribavirin for 12 weeks in 51 treatment-naive patients with HCV genotype 3 infection. All patients in the ribavirin-containing arm achieved SVR12 compared with 64% of those in the ribavirin-free arm. Although these data raise the possibility that adding ledipasvir to sofosbuvir and ribavirin may shorten treatment

duration for genotype 3 patients, the high EC_{50} (half maximal effective concentration) of ledipasvir for genotype 3 and the homogenous patient population limit the study's generalizability. Nevertheless, Dr. Chung said that the findings indicate that SVR rates can still be improved for these patients.

A dose-finding trial of sofosbuvir plus the investigational pangenotypic NS5A inhibitor GS-5816, with or without ribavirin, was evaluated in patients with all 6 HCV genotypes. Genotype 3 patients receiving either 25 mg or 100 mg of GS-5816 achieved SVR rates of 93%; however, all participants were treatment-naive and noncirrhotic. Dr. Chung explained that GS-5816 represents one effort to make this class of drugs more pangenotypic.

The BOSON study evaluated sofosbuvir plus ribavirin (for either 16 or 24 weeks) vs sofosbuvir plus pegylated interferon/ribavirin (for 12 weeks) in persons with genotypes 2 and 3 infection. The investigators reported that the now "older" regimen of 12 weeks of sofosbuvir plus pegylated interferon/ribavirin resulted in SVR in 93% of genotype 3 patients, one-third of them with compensated cirrhosis. Dr. Chung noted that the addition of interferon was associated with increased SVR rates across all patient groups (91%-96%), including cirrhotics (86% SVR in treatment-experienced cirrhotics) (Figure 10). He added that, although interferon-free treatment is a universal goal, at this time there remain some groups for whom it continues to be an important option.
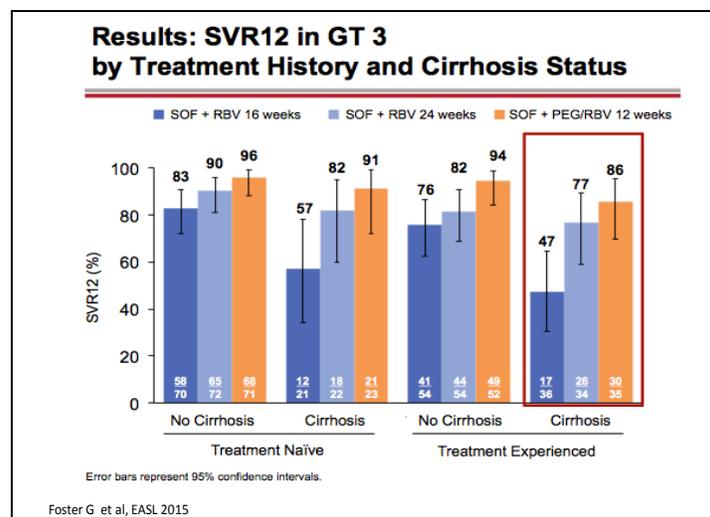

Figure 10. Favorable SVR12 rates with the addition of interferon.

Compensated cirrhosis

Achieving SVR remains a challenge for cirrhotic patients. Dr. Chung explained that reasons for this may include limited drug delivery due to portal hypertension and nodules or impaired immune function. Nevertheless, several strategies that can increase SVR rates for these patients may be available now or in the near future. For compensated cirrhotics, Dr. Chung presented findings from 3 trials, highlighting the benefit of extended treatment:

- In cohort 2 of the COSMOS trial comparing simeprevir plus sofosbuvir vs simeprevir plus sofosbuvir plus ribavirin, 100% of patients with Metavir scores of F3-F4 were able to achieve SVR with 24 weeks of dual therapy, compared with 93% of patients receiving triple therapy for either 12 or 24 weeks. A key lesson of this study, Dr. Chung said, was that treatment-experienced

cirrhotics appear to benefit from longer treatment duration.

- In the ION-1 trial, treatment-naive compensated cirrhotic patients achieved 100% SVR with either 12 or 24 weeks of treatment with ledipasvir/sofosbuvir plus ribavirin. In the ION-2 trial of the same regimen in treatment-experienced patients, 100% of patients achieved SVR with 24 weeks of either ledipasvir/sofosbuvir or ledipasvir/sofosbuvir plus ribavirin (vs 86% and 82%, respectively, with 12 weeks).

- In the TURQUOISE-II study of paritaprevir/ritonavir plus ombitasvir plus dasabuvir plus ribavirin, 95.9% of patients with compensated cirrhosis achieved SVR with 24 weeks of treatment vs 91.8% of those receiving 12 weeks of treatment. The benefit of longer treatment applied across subgroups (relapsers, partial responders, null responders).

Decompensated cirrhosis and posttransplant patients

Patients with decompensated cirrhosis, however, present greater challenges in achieving SVR, and a range of efforts is ongoing to determine optimal approaches for this population. For patients with decompensated cirrhosis, use of interferon is contraindicated. Dr. Chung said that lessons may be found in the experience of using lamivudine to stabilize hepatic decompensation in patients with chronic HBV infection; many such patients experienced gradual but marked improvement in liver function.

Preliminary findings from the SOLAR-2 trial of ledipasvir/sofosbuvir plus ribavirin 600 mg dose escalated for either 12 or 24 weeks in 99 patients with genotype 1 or 4 infection and decompensated cirrhosis showed SVR rates of 87% and 89% for 12 and 24 weeks, respectively. Those with Child Pugh class C cirrhosis achieved SVR 90%. Dr. Chung drew attention to the finding that total bilirubin and serum albumin levels improved substantially at Week 4 post-therapy in both groups. Model for end-stage liver disease (MELD) scores improved in >50% of treated patients, although some experienced worsening hepatic function. These results indicate that 12 weeks of ledipasvir/sofosbuvir plus ribavirin for genotype 1 or 4 patients may lead to improved hepatic function and reduce the likelihood of recurrent HCV infection after transplantation. He cautioned, however, that those already on the liver transplantation list should carefully weigh treating HCV against lowering their priority on the transplantation list if successful HCV treatment improves their MELD score.

The C-SALT study evaluated 12 weeks of grazoprevir/elbasvir in 30 patients with Child B cirrhosis vs 10 noncirrhotic patients. Researchers found that 90% of cirrhotic patients achieved SVR, vs 100% of noncirrhotics.

The CORAL-1 trial assessing 24 weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir plus ribavirin in 34 liver transplant recipients with recurrent genotype 1 HCV found that 100% of participants achieved SVR12. However, Dr. Chung added that careful dose reductions of coadministered tacrolimus and cyclosporine A were required.

The SOLAR-1 study included 223 liver transplant recipients with recurrent genotype 1 or 4 HCV infection and various degrees of fibrosis or cirrhosis; they received ledipasvir/sofosbuvir plus ribavirin for 12 or 24 weeks. Among patients with F0-F3 fibrosis, 98% achieved SVR12 with 24 weeks of treatment, vs 96% of those in the 12-week arm. SVR12 rates among cirrhotic patients ranged from 67% to 96% with 24 weeks of treatment, vs 60% to 96% with 12 weeks. Since all patients received ribavirin, its importance cannot be ascertained, but ribavirin likely contributed to the high SVR12 rates. However, he added, an option

for patients who cannot tolerate ribavirin is 24 weeks of ledipasvir/sofosbuvir, based on the findings of the SIRIUS study.

Limited data are available for treatment of patients with HCV genotype 2 or 3 infection in the post-transplant setting; recommendations largely reflect those in the nontransplant population.

Renal impairment

Dr. Chung stated that HCV-infected patients with renal impairment may represent the greatest remaining population with unmet needs, mainly because both sofosbuvir and ribavirin are cleared renally. He said that one study of reduced doses of sofosbuvir (200 mg) and ribavirin (200 mg) for 24 weeks in patients with eGFR <30 reported SVR12 rates of only 40%, despite the presence of high levels of sofosbuvir's active metabolite, GS-331007. Studies evaluating sofosbuvir 400 mg plus ribavirin; ledipasvir/sofosbuvir; and paritaprevir/ritonavir/ombitasvir plus dasabuvir in patients with renal impairment are ongoing.

The observational HCV-TARGET study is assessing the use of various sofosbuvir-containing regimens (with pegylated interferon/ribavirin, with only ribavirin, with simeprevir, with simeprevir plus ribavirin) in patients with varying degrees of renal impairment in real clinical practice. Reported SVR12 rates range from 100% with all regimens in patients with eGFR ≤30 to as low as 33% in those with eGFR 30-45 receiving sofosbuvir plus pegylated interferon/ribavirin (Figure 11). Dr. Chung indicated that, on the whole, the results are favorable for treatment of renally impaired patients.
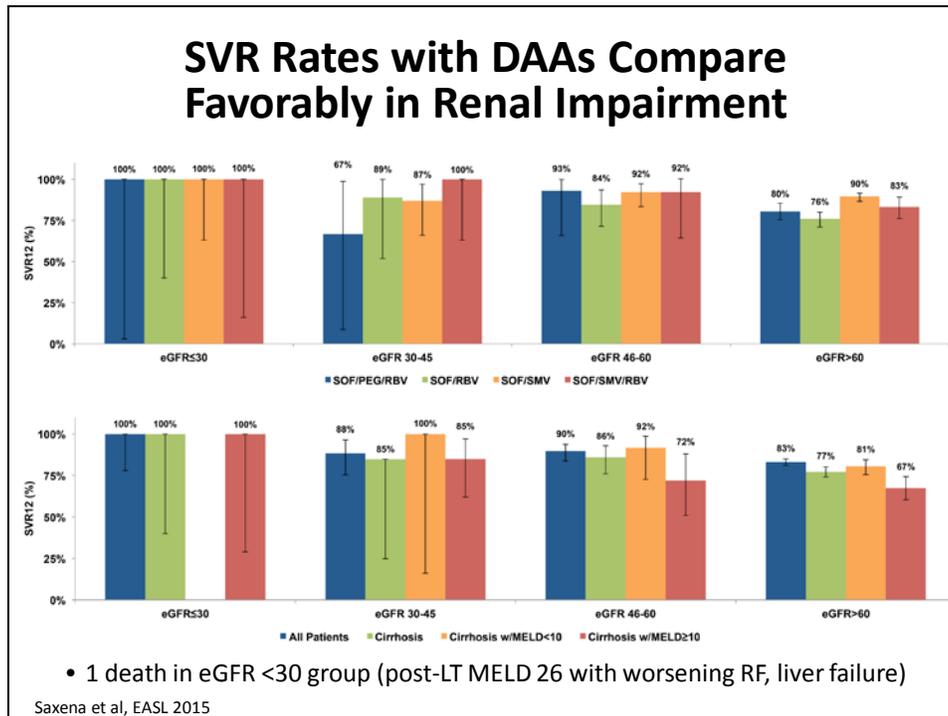

Figure 11. Favorable SVR rates achieved in renal impairment.

The C-SURFER study evaluated grazoprevir/elbasvir for 12 weeks in 122 genotype 1 patients with stage 4/5 kidney disease. The researchers reported an SVR rate of 99% in the modified analysis group and

94% in the full analysis group. Dr. Chung stated that these findings are very promising for these patients with seriously unmet HCV treatment needs.

He summarized: Currently approved DAAs can be used safely in patients with mild to moderate renal impairment, but there are currently no approved all-oral, DAA-based regimens for those with severe renal impairment or end-stage renal disease. Until the findings of ongoing studies are available, the current treatment for these patients remains pegylated interferon-2a 135 mcg/week and ribavirin 200 mg daily.

Triple-therapy and sofosbuvir failures

Dr. Chung said that the most recently emerged unmet need is in patients who have failed treatment with triple therapy containing a first-generation PI (telaprevir or boceprevir) or a sofosbuvir-based regimen. Although the PI resistance-associated variants (RAVs) typically recede, whether retreatment with newer PIs is feasible remains unclear.

As discussed earlier, the SIRIUS study demonstrated equally high SVR12 rates with either sofosbuvir/ledipasvir plus RBV for 12 weeks or sofosbuvir/ledipasvir for 24 weeks in a group of cirrhotic patients who had failed prior triple therapy. Dr. Chung said that results like these clearly indicate that treatment of failures of one class of DAAs can be successfully salvaged with the use of 2 DAA classes, particularly when one of them (sofosbuvir) has a high barrier to resistance.

Furthermore, the AI44040 Study assessed daclatasvir plus sofosbuvir with or without ribavirin in both naive and experienced patients, including 41 who had previously failed either telaprevir or boceprevir plus pegylated interferon/ribavirin. The investigators reported that 100% of these patients achieved SVR4 and that 100% achieved SVR12 in the dual-therapy group vs 95% in the triple-therapy group, providing proof-of-concept that the combination of 2 potent DAAs having different viral targets can be effective in patients who have failed pegylated interferon/ribavirin plus a PI.

In a study of ledipasvir/sofosbuvir plus ribavirin in 51 patients who had failed sofosbuvir-containing therapy, researchers reported that 98% of participants achieved both SVR12 and SVR24. Dr. Chung said that these findings are encouraging for the retreatment of patients who have experienced failure of a DAA regimen.

Summary

Dr. Chung concluded by summarizing the present outlook for those HCV-infected groups who have benefited to a lesser extent from the advent of DAA regimens: The remaining populations who continue to need more effective treatments include persons with genotype 3 HCV infection, cirrhotic patients, post-liver-transplant patients, persons with renal impairment, and those who have failed treatment containing either a first-generation PI or sofosbuvir. A range of completed and ongoing studies indicate that most of these patients can be treated successfully, either now or very soon, and that, in even the most challenged patients, hepatic and renal functions may improve when SVR is attained. A leading challenge in the future will be how to manage patients who experience treatment failure with multiple DAA classes.

Audience Questions

Concerning the onset of HCC several years after a patient has achieved SVR, should primary care physicians perform any particular monitoring for early detection?

Andrew J. Muir, MD, MHS: The level of resources that should be committed to ongoing monitoring of patients whose HCV infection is cured remains a topic of discussion. In patients with early-stage fibrosis, continued viral load monitoring is not needed, although liver function testing should continue. If liver function becomes abnormal, checking viral load may then be merited.

Raymond T. Chung, MD: Patients with F4, possibly even F3, fibrosis merit continued post-SVR screening for complications. The HCC risk reduction with SVR is now thought to be approximately 75%, so risk remains for some patients. Additional concerns for increased surveillance could be patients with other ongoing conditions, such as fatty liver disease, metabolic syndrome, or continued alcohol use.

Dr. Sulkowski said that it is important to emphasize to post-SVR patients that SVR is not the equivalent of a vaccine and that they can be reinfected with HCV.

Mark S. Sulkowski, MD: It's also important to emphasize to post-SVR patients that SVR is not the equivalent of a vaccine and that they can be reinfected with HCV. For cirrhotic patients, abstaining from alcohol consumption and achieving and maintaining ideal weight are critical, and consumption of coffee may be helpful.

How should paritaprevir/ritonavir/ombitasvir plus dasabuvir be used in patients with severe renal dysfunction?

Raymond T. Chung, MD: This regimen is not subject to significant renal clearance, so this could be a viable approach for patients with severe renal impairment. The greater challenge would be its use in genotype 1a patients, who require the addition of ribavirin, which can be dose-reduced, but such patients may already be anemic. This issue is being examined in clinical trials, but at least in theory, this regimen could be used in this patient group.

Mark S. Sulkowski, MD: For patients with severe renal impairment, it may be appropriate to consider whether they would be candidates for renal transplant before proceeding with HCV treatment.

Treat Everyone Now? YES

In a debate over whether all HCV-infected persons should begin treatment now or at some later time, **Marion G. Peters, MD**, of the University of California, San Francisco, presented the case to "Treat Everyone Now." As her presentation, and the next, made clear, this is a topic of keen interest to clinicians, patients, insurers, and policy makers. She began by reviewing some of the demonstrated benefits of successfully treating HCV infection with the use of DAA regimens, which can result in cure in >95% of patients in most groups:

- End disease progression and possibly reverse fibrosis
- Ameliorate the frequent extrahepatic manifestations of HCV infection
- Decrease the risk of further infection in drug-using populations
- Decrease disease-related morbidity and all-cause mortality

Benefits of HCV treatment

Dr. Peters then showed a graph comparing hospitalization rates due to HIV, HCV, and HBV infection between 2004 and 2011. Strikingly, HBV hospitalization rates have been stable and HIV rates have declined significantly—both while HCV hospitalization rates have continued to rise, particularly in more recent years. She continued, saying that society is only at the beginning of the increased economic, health, and societal burdens that will be associated with HCV infection if treatment rates are not substantially increased. The arrow in Figure 12 indicates the current situation, and, following present trends, Dr. Peters stated that society will not be able to return to this point for approximately 45 years. She added that cure of HCV infection, ie, SVR, is associated with:

- 70% reduction in hepatocellular carcinoma
- 50% reduction in all-cause mortality
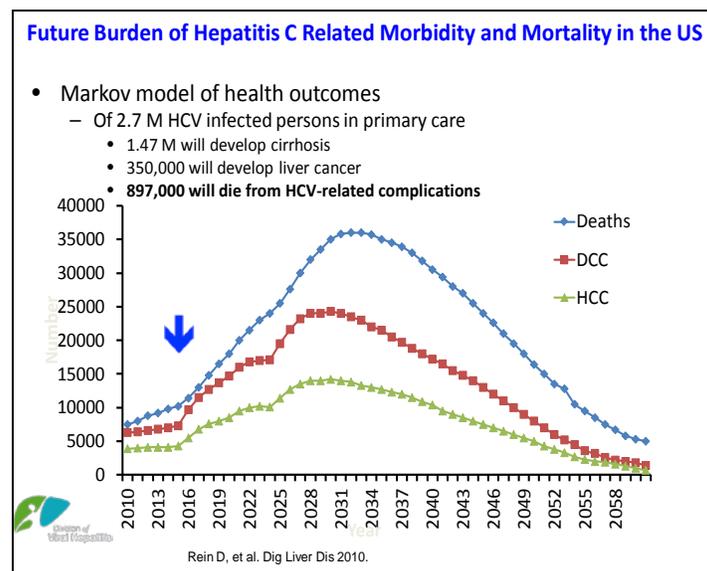
Figure 12. Projected growth in HCV-related mortality, decompensated cirrhosis, and hepatocellular carcinoma.

Moreover, SVR has been associated with objective improvements, such as improved measures of liver transient elastography and reduced portal hypertension. She added that, although the exact number of

patients who will have reduced risk of cirrhosis cannot be determined, some will undoubtedly experience that benefit, along with the benefit of not having to be screened for cirrhosis for life.

Cost-effectiveness

Issues of cost-effectiveness are unavoidably linked to any discussion of when to initiate HCV treatment. Dr. Peters cited one study that concluded that oral DAA regimens, at a cost of $70,000, had an incremental cost-effectiveness ratio (ICER) of $15,709/QALY (quality-adjusted life year), which she said is significantly below the normally accepted amount of $50,000/QALY in the United States. She further explained that this study concluded that providing DAA therapy without staging may be the most cost-effective approach for treating HCV genotype 1 patients. She went on to explain that, although the cost-effectiveness of HCV treatment varies among different studies, it appears that treatment of patients with moderate or advanced fibrosis—ie, those with scores of >F1—is cost-effective and that immediate treatment of patients with minimal or no fibrosis likely can also be cost-effective at lower treatment cost.

Dr. Peters then discussed the major part that insurers, both private and public, play in decisions about which HCV-infected patients can receive treatment when. Medicaid and related programs in 30 states require that patients have some degree of fibrosis before they will cover the cost of HCV treatment and most of those will cover only those with scores of F3-F4—ie, the more advanced stages of liver disease. Other requirements can include:

The problem is that so many HCV-infected persons are now eligible to receive treatment (with millions more undiagnosed), that many lack access to care, and that fiscal constraints play such a large role in treatment decision making.

- Limiting treatment for those with a history of drug use and alcohol use
- Requesting data on abstinence, adherence, drug and alcohol use, psychiatric state
- In rehab for ≥6 months
- Limits on the types of practitioners who can prescribe DAAs

Other issues, she said, arise from the policies of private insurers. Dr. Peters cited a study contending that some private insurers make HCV coverage decisions with the expectation that many HCV-infected persons will age out of private insurance and into Medicare coverage, thereby shifting costs to the public sector. In 2009, there were an estimated >400,000 HCV patients, but by 2024 1 million HCV-infected Americans are projected to age into Medicare. With current treatment rates, more than one-third of those would die from HCV or related causes like HCC, diabetes, or end-stage liver disease. This same study concluded that providing oral DAA therapy could substantially reduce HCV-related morbidity and mortality within Medicare and that treatment prior to Medicare entry would likely be more effective in reducing the health consequences of HCV, since many Medicare patients enter the program in advanced stages of disease.

The heart of the when-to-treat dilemma, Dr. Peters stated, is not that attaining SVR improves quality of life and reduces all-cause mortality, along with liver morbidity and mortality, or that DAAs are too expensive compared with, eg, cancer or HIV treatment. Rather, the problem is that so many HCV-infected persons are now eligible to receive treatment (with millions more undiagnosed), that many lack access to care, and that fiscal constraints play such a large role in treatment decision making.

Treat Everyone Now? NO

In contrast to Marion G. Peters' presentation, **Stuart C. Ray, MD, FIDSA**, of the Johns Hopkins University School of Medicine, discussed the reasons <u>not</u> to "Treat Everyone Now." He started by stating that practitioners who manage HCV-infected patients may wear different hats in different situations—eg, advocating for their patients vs advocating for the public good. He explained that on one hand, they have a "sacred trust" to support their patients' well-being while, on the other hand, adhering to laws and regulations, and sometimes helping to shape those laws and regulations. The latter can mean making the most judicious use of available resources, because, Dr. Ray, cautioned, if clinicians do not do so, others will make such decisions.

Determining patient need

He acknowledged that a large proportion of HCV-infected individuals, especially those with fibrosis scores of >F1 should receive treatment, as the benefit of reducing end-stage liver disease (ESLD), hepatocellular carcinoma, and extrahepatic manifestations is clear. However, most HCV patients will not progress to ESLD. Moreover, there is not a good history of controlling infectious diseases through treatment, with a very small number of exceptions, such as guinea worm, and at this time there is no evidence that wider treatment of HCV will substantially reduce the incidence.

He then pointed out that there are in fact individual patients who may not benefit from HCV treatment: acutely infected persons who have a high likelihood of spontaneously clearing the infection, recently infected persons who lack the risk factors associated with rapid disease progression, or those who are asymptomatic and have no evidence of disease. For patients in these groups who want to begin treatment anyway, Dr. Ray said that that is where laws and regulations are important, adding that he's happy that HCV specialists are helping to formulate them.

Dr. Ray added that there are other groups of patients for whom HCV treatment may not be appropriate:
- Persons with competing conditions likely to lead to mortality
- Persons with decompensated cirrhosis and renal impairment, who can be successfully treated post-transplant
- Persons like injection drug users who continue to engage in risky behaviors and therefore are at high risk of reinfection

The public sphere

Referring to the public sphere, Dr. Ray felt that as part of systems-based practices, physicians should participate in public discourse concerning which patients should receive treatment and when and how resources can best be allocated, while avoiding conflicts of interest. He also said that at times it may be suitable to discuss these issues with patients when considering whether to undertake HCV treatment—eg, by explaining that the cost of treatment is likely to decrease more rapidly than their liver disease is likely to progress.

Citing a French study (Figure 13), Dr. Ray said that the incremental cost-effectiveness ratio (ICER) for persons with minimal fibrosis is significantly lower than it is for persons with significant fibrosis. He further noted that a number of analyses have shown that there are wide variations in cost-effectiveness related to a patient's gender and age.

Stage	ICER
F0	40 653 € ($43,999) / QALY
F1	31 348 € ($33,928) / QALY
F2	17 651 € ($19,104) / QALY
F3	11 359 € ($12,294) / QALY
F4	12 080 € ($13,074) / QALY

*Assumes total drug cost of € 67 291 ($72,830) per course of treatment

Figure 13. Cost-effectiveness of sofosbuvir-based treatment in France.

Dr. Ray then said that DAAs, although much more tolerable than pegylated interferon or ribavirin, are not without risks themselves. Some have serious interactions with some of the coadministered medications that many HCV patients take, and this can be especially the case in ritonavir-containing regimens, which are associated with a large number of drug-drug interactions. He explained that this is just one more of the important issues that must be weighed when considering the risks and benefits of HCV treatment.

The United States does not have sufficient resources (eg, trained HCV treaters and finances) to treat every HCV-infected American, which would require an estimated $100 billion.

Dr. Ray summarized the key points that favor offering HCV treatment primarily to members of groups who meet certain criteria of medical need:

- There is a substantial minority of HCV-infected persons for whom treatment is not now urgent.
- The cost-effectiveness of HCV treatments is increasing rapidly.
- Clinicians are still learning what the determinants of safe and effective HCV treatment are.
- The United States does not have sufficient resources (eg, trained HCV treaters and finances) to treat every HCV-infected American, which would require an estimated $100 billion.

He concluded by stating that it is likely that society is approaching a time when it will be cost-effective, feasible, and clearly safe to treat all persons who have HCV infection—but that time has not yet arrived.

Acute HCV Infection

Most discussions of HCV management concern chronic infection and its complications, but in his presentation on "Acute HCV Infection, "**Arthur Y. Kim, MD, FIDSA**, of the Harvard Medical School and Massachusetts General Hospital, reviewed the issues involved in the earliest phase of HCV disease. The need to enhance case finding, diagnosis, and potential early treatment initiation ran as themes throughout his presentation.

Defining acute HCV infection

Dr. Kim explained that acute HCV infection has a working definition as the first 6 months following acquisition of the virus, although there is considerable variation in how patients present. During this time, individuals have the greatest likelihood of spontaneously clearing the virus and the virus is most likely to respond to treatment with interferon. Clearance of the virus, he said, is associated with protection from the consequences of reinfection, likely because clearance is associated with the relevant T-cell responses that can help to clear a reinfection. However, this phenomenon is not associated with viral clearance that occurs with HCV treatment.

Individuals are less likely to engage in risky behaviors—eg, opioid or heroin injection or sharing needles—when they become aware that they are HCV-positive.

Defining and identifying acute infection offers practical individual and public health benefits, including educating the patient about HCV and offering HAV and HBV vaccinations, as well as the potential to disrupt ongoing infection by treating the acutely infected person. One important reason for early diagnosis of HCV infection, Dr. Kim continued, is that studies have shown that individuals are less likely to engage in risky behaviors—eg, opioid or heroin injection or sharing needles—when they become aware that they are HCV-positive.

Dr. Kim offered several suggestions that can point to acute HCV infection:
- Acute illness that is typically associated with HCV infection, such as jaundice or dark urine
- Having tested HCV-antibody-negative within the past year
- Recent start of injection drug use or changes in injection practices
- ALT >5-10 x ULN (but can fluctuate significantly)

He stressed, however, that many individuals will be asymptomatic during acute infection, so clinicians should not rely on symptom presentation for suspicion of acute infection.

Transmission

In some situations, sexual transmission of HCV can occur. An early study of HCV prevalence in female partners of hemophiliacs found an HCV prevalence of 2.6%. A more recent study of monogamous HCV-serodiscordant heterosexual couples found that the risk of HCV transmission was approximately 1 in 190,000 sexual contacts, and guidelines do not recommend barriers for discordant monogamous heterosexual couples. Sexual transmission among men who have sex with men (MSM) has also been reported and is primarily associated with sexual activities that can involve tissue abrasion or blood exposure. Dr. Kim said that the risk of viruses being transmitted by needlestick injuries is sometimes characterized by a "rule of 3s"—ie, the risk of transmission with HBV is 30%, with HCV it is 3%, and with HIV it is 0.3%. He further explained that HCV has been found to persist in syringes for several days.

Paraphernalia employed in injection drug use also poses risks for users, he explained. Heating of "cookers" for drug preparation destroys HIV in 7 to 10 seconds, but HCV requires 80 to 95 seconds to be destroyed. In addition, 80% of the cotton swabs used during injection have been found to be positive for HCV RNA.

Dr. Kim cautioned, however, that the large increase in illegal use of opiates in recent years is fueling the epidemic of ongoing HCV transmission, particularly among young adults, who are at risk of transitioning from use or abuse of oral opioids to injection of heroin.

The large increase in illegal use of opiates in recent years is fueling the epidemic of ongoing HCV transmission, particularly among young adults, who are at risk of transitioning from use or abuse of oral opioids to injection of heroin.

Epidemiology

For 2010, the Centers for Disease Control and Prevention (CDC) reported an estimated 17,000 incidents of acute HCV infection in the United States. Although only 850 actual cases were reported, the CDC calculated that, for each reported case, there were 3.3 symptomatic persons and 16.7 asymptomatic persons. These estimates were developed using criteria to confirm a positive HCV diagnosis that were somewhat stringent:

- An acute illness with any sign or symptom consistent with acute viral hepatitis (eg, anorexia, abdominal discomfort, nausea, vomiting), and either jaundice/dark urine or serum (ALT) level >400 IU/L.
- Laboratory criteria for diagnosis to include ≥ 1 of the following:
  - Antibodies to HCV (anti-HCV) screening-test-positive
  - HCV recombinant immunoblot assay positive
  - Nucleic acid test for HCV RNA positive (including genotype)
- Both of the following: immunoglobulin M antibody to HAV negative and IgM antibody to HBV core antigen negative

Dr. Kim said that some state and local health departments have more rigorous HCV screening and reporting procedures than others and some of their findings are discrepant with the data reported by the CDC. In Massachusetts, for example, a rigorous program (BAHSTION: Boston Acute HCV Study: Transmission, Immunity, and Outcomes Network) linking hospitals, practitioners, prisons, laboratories, and the state health department recently reported that only 1 of 183 clinical cases of acute HCV infection were actually reported to the CDC, when the CDC's strict definition was used. The investigators concluded that national statistics may significantly underestimate the burden of acute HCV infection in this country. The CDC has subsequently relaxed its definitional criteria and has begun to see increased numbers of cases reported. Findings like these, Dr. Kim said, suggest that the number of acute HCV cases that are identified clinically likely represent only the tip of the epidemic's iceberg (Figure 14).
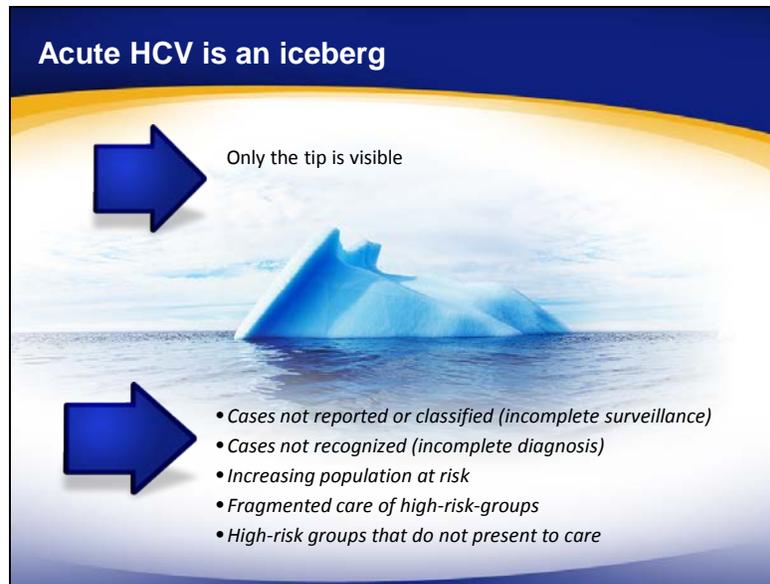
Acute HCV is an iceberg

Only the tip is visible

- *Cases not reported or classified (incomplete surveillance)*
- *Cases not recognized (incomplete diagnosis)*
- *Increasing population at risk*
- *Fragmented care of high-risk-groups*
- *High-risk groups that do not present to care*

Figure 14. Large numbers of acute HCV cases likely remain undetected.

Increasing diagnosis and treatment of acute HCV

Dr. Kim concluded by providing some pointers for improving screening and diagnosis of HCV infection. For example, targeted screening programs, such as in correctional facilities, can lead to significantly increased rates of diagnosis. Clinicians should exercise high clinical suspicion, along with careful consideration of laboratory findings (eg, acute infections are more likely among younger individuals). Practitioners should ask injection drug users about sharing of drug paraphernalia and ask MSM about potentially risky sexual practices. He added that individuals engaging in high-risk behaviors should receive HCV antibody screening annually. Changes in liver test results should prompt further investigation.

Dr. Kim said that, when acute HCV is diagnosed, delaying treatment initiation for 3 to 6 months may be advisable to allow for spontaneous clearance to minimize overtreatment of patients. Earlier treatment initiation may be advisable in persons with the IL28B genotype, as these individuals tend to respond less well to later treatment. Treatment guidelines suggest that persons who are at heightened risk for further transmission (eg, a surgeon who is viremic after a needlestick injury or a person who recently injected drugs) are candidates for immediate treatment, whereas others at lower risk (such as those who are not actively injecting drugs) may be able to defer therapy until the chronic phase of infection. The guidelines recommend that, if a clinician and patient agree to start treatment during the acute infection period, the same regimens recommended for use in chronic infection should be used.

Hepatocellular Carcinoma

At the start of his presentation, "Hepatocellular Carcinoma," **Jorge A. Marrero, MD** of the University of Texas Southwestern Medical Center said that although HBV is the driving force behind hepatocellular carcinoma (HCC) globally, in the United States, HCV is the driving force. Both new cases and deaths due to HCC have increased during the last 2 decades (Figure 15), although new cases have increased at a faster rate than deaths, largely due to improved diagnosis and treatment. The 5-year survival rate during 2003-2009 was 16.1%, but Dr. Marrero pointed out that in the preceding decade, that rate was in single digits.
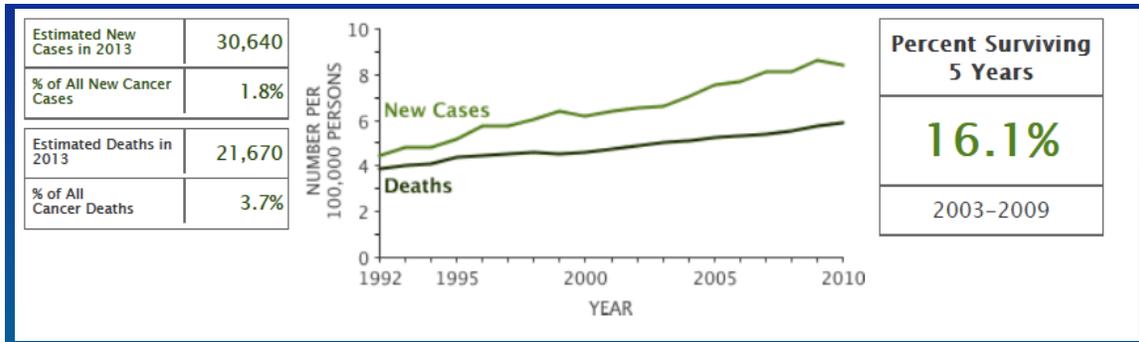

Figure 15. Incidence of HCC in the United States.

A feature distinguishing HCC from other cancers is that it occurs only in a diseased organ—ie, an injured liver (due to HCV, HBV, alcohol, nonalcoholic steatohepatitis [NASH]) in which fibrosis and cirrhosis have developed, accompanied by mutations occurring in ≥1 oncogenic or tumor suppressor genes. A recently published analysis has shown overwhelming evidence that HCV-infected patients who achieve SVR have a considerably reduced risk for HCC vs untreated patients or those who fail to achieve SVR. Dr. Marrero, cautioned, however, the magnitude of this effect varied significantly and that patients who achieve SVR should continue to be followed closely.

Surveillance

Groups for whom the American Association for the Study of Liver Diseases (AASLD) recommends HCC surveillance include:

- HBV carriers
- Persons with HCV-related cirrhosis
- Persons with:
    - Stage 4 primary biliary cirrhosis
    - Genetic hemachromatosis and cirrhosis
    - Alpha 1-antitrypsis deficiency and cirrhosis
    - Other cirrhosis

A study employing HBV data reported significantly lower mortality among patients who were screened for HCC vs a control group. Although no randomized trial data for HCV-related mortality reductions are available, Dr. Marrero said that a cohort analysis has shown that surveillance with alpha-fetoprotein (AFP) and ultrasound for HCC in HCV-infected persons was associated with a nearly 2-fold reduction in mortality.

Dr. Marrero said that a key concern in HCC surveillance is its low utilization, which a variety of studies have found to be approximately 17%. Current screening techniques have a sensitivity of 60% to 70%, and increased screening rates using current techniques would substantially increase HCC detection and survival rates.

Staging and treatment

Although a variety of HCC staging systems have been developed and used around the world, Dr. Marrero said that the system that has been most widely validated is the Barcelona Clinic Liver Cancer (BCLC) system. BCLC employs measures of tumor burden, performance status, and Child Pugh score and assigns the following stages:

- Very early
- Early
- Intermediate
- Advanced

BCLC or very early HCC. Dr. Marrero explained that patients with very early stage HCC have tumors <2 cm, no metastasis, no significant portal hypertension, and Child class A. In a recent meta-analysis of resection for very early HCC, the 5-year overall survival rate ranged from 27% to 81% (median 67%), and there was a trend toward improved overall survival in recent years. The operative mortality rate ranged from 0% to 5% (median 0.7%). A problem with resection, he continued, is that it leaves the patient with a liver that may still be HCV-positive and cirrhotic, and therefore the recurrence rate is significant. However, the risk recurrence can be significantly reduced by treating HCV and achieving SVR.

BCLC stage A or early HCC. Patients at this stage have a single lesion <5 cm or ≤3 lesions (each <3 cm in diameter) without metastasis, which are the Milan criteria for transplant. One early study reported a 4-year survival of 75% in transplant patients. A central problem with liver transplantation is the finite number of organs available, which Dr. Marrero said had plateaued at approximately 6,200 transplants per year in the United States, of which approximately 1,200 were in HCC patients. He added that these numbers are dwarfed by the 33,604 HCC cased reported in 2014. Therefore, clinicians must rely more on the use of either resection or ablation. Radiofrequency ablation (RFA) has been successfully used as primary treatment or as a bridge to transplant, and in several randomized trials, RFA has led to better survival vs percutaneous ethanol injection. Outcomes of RFA and resection have been comparable, although Dr. Marrero added that in patients with portal hypertension, RFA is preferable. The strengths of the institution where a patient is receiving treatment also play a key role in outcomes.

BCLC stage B or intermediate HCC. Patients at this stage can present with large (>5 cm) single tumors or with multifocal disease, and the degree of hepatic function can vary significantly. At this stage, Dr. Marrero said, transarterial chemoembolization (TACE) has been shown to improve overall survival in randomized trials and is the treatment of choice. However, TACE is associated with a response rate of only approximately 40% and 2-year survival vs controls, who received conservative management. TACE via drug-eluting beads (100 microns in size) that are loaded, most often, with doxorubicin has shown less comorbidity and equal efficacy compared with conventional TACE, due to the low plasma concentration and high tumor concentration. Radioembolization with yttrium 90 with microspheres has been studied in phase 2 trials. The role and efficacy of yttrium 90 has not been well-defined. In addition, some patients at this stage of HCC may be candidates for transplantation.

BCLC stage C or advanced HCC. The difference between patients at this stage and the intermediate stage is the presence of portal vein involvement and/or metastasis. Dr. Marrero said that sorafenib is the only drug that has been proven to improve overall survival (by 3 months) compared with placebo and is the treatment of choice for patients at this stage. Sorafenib is a multikinase inhibitor that works by delaying HCC progression, but it does not improve quality of life, since it is associated with significant adverse effects, eg, diarrhea, anorexia, alopecia. Some specialists believe that dose escalation may result in less severe adverse events. A large number of other agents are being evaluated for treatment of HCC at this stage, but Dr. Marrero said that results thus far have largely been negative.

He concluded by expressing the hope that wider use of DAAs will help reduce the incidence of HCC and the risk of tumor recurrence in patients already diagnosed with HCC.

Staging Liver Disease in Clinical Practice 2015

To review the issues involved in staging of liver disease, **David L. Thomas, MD**, MPH, of the Johns Hopkins University School of Medicine, first presented clinical findings and key questions for 2 patients:
- A 35-year-old woman who is HCV-antibody and RNA-positive for an unknown time, with normal examination findings and laboratory findings showing ALT of 100 U/L, AST of 75 U/L, and platelet count of 263 x 10^9/L.
- A 45-year-old man who is HCV-antibody and RNA-positive for an unknown time, with normal examination findings and laboratory findings showing ALT of 100 U/L, AST of 110 U/L, and platelet count of 99 x 10^9/L.

Important questions for both patients that staging can help to answer include:
- Do they need treatment? If so, for how long?
- Do they need a biopsy?
- Could they die of liver disease?
- Do they need an ultrasound?
- Do they need an upper gastrointestinal (GI) exam?

Dr. Thomas explained that liver staging is basically a histopathologic question—ie, how much scarring is there in a patient's liver? Before the advent of DAAs, a main use for staging was to decide which patients could benefit from starting treatment with pegylated interferon and ribavirin. Typically, this meant those with a fibrosis score of F3-F4 would be recommended for treatment, and in some cases patients with F2. Other patients would be monitored, since the pre-DAA treatments involved such challenging adverse events. With DAAs, that situation has evolved with the recognition that nearly all HCV-infected patients could benefit from treatment. Today, Dr. Thomas said, one purpose of staging can be so that third-party payers can determine whether they will cover the cost of DAA therapy.

He continued by saying that another important use of staging today is to identify cirrhosis and F3-F4 fibrosis, so that these patients can be monitored for the development of hepatocellular carcinoma (HCC). Other purposes for staging include determining the duration of DAA therapy and management of portal hypertension.

Acceptable methods of staging are:
1. Liver biopsy
2. Serum markers
3. Elastography
4. Combinations of 1, 2, and 3

Dr. Thomas noted that measuring a patient's viral load; determining HCV genotype; and ultrasound, CT, or MRI are not methods of staging.

Staging methods

Biopsy. Liver biopsy, said Dr. Thomas, remains the most definitive staging method and may identify other causes of liver disease, such as alcohol use or hemochromatosis. The validity of biopsy findings, he explained, are highly dependent on the size and location of the tissue sample that is taken from a patient. Tissue samples <15-20 mm long are especially likely to miss significant disease. However, even in carefully controlled trials, the average size of a biopsy is often <20 mm. However, he said, in general practice, it is much worse. One study of laparoscopically obtained biopsies of >15 mm found that the left lobe differed from the right by ≥1 on a 4-point scale 33% of the time. In addition, biopsy is an invasive procedure and can lead to complications such as bleeding or infection.

Tissue samples <15-20 mm long are especially likely to miss significant disease. Even in carefully controlled trials, the average size of a biopsy is often <20 mm. In general practice, it is much worse.

Serum markers. Serum fibrosis markers also can stage disease. One test (*FibroSURE™*) applies levels of $\alpha2$-macroglobulin, apolipoprotein A_1, γ-glutamyl transferase (GGT), haptoglobin, and total bilirubin in a complex algorithm to determine relatively high negative and positive predictive values for significant liver fibrosis or cirrhosis. One advantage to this test, Dr. Thomas said, is that because insurers pay for it, they are more likely to agree that findings of F2-F3 merit HCV treatment. Other approaches employ standard laboratory findings to predict fibrosis score. The APRI (AST-platelet ratio index) makes use of a simple calculation using the quotient of the AST/upper limit of normal divided by the platelet count x 100. Dr. Thomas said that he finds the similar FIB4 calculation—which is the quotient of age*AST/platelet count*sq root of ALT—somewhat more informative, as it also takes the patient's age into consideration. In one systematic review, investigators reported average areas under the receiver operating curves of 0.82 to 0.9 for detection of cirrhosis using these algorithms compared with biopsy.

The 35-year-old patient mentioned previously would have a FIB4 score of 1.0, corresponding to probabilities of advanced, moderate, and mild fibrosis of 12%, 45%, and 43%, respectively. The male patient, on the other hand would have a FIB4 index of 5, indicating an 80% probability of advanced fibrosis; he would need to be monitored for cirrhosis and possibly referred for an upper GI exam.

Elastography. Liver stiffness measurement (LSM) by elastography was approved in 2013 in the United States as a noninvasive method of staging liver disease. Elastography has good negative predictive value for ruling out cirrhosis, said Dr. Thomas, and it appears to provide good correlation with hepatic venous pressure gradient, which is the gold standard indicator for portal hypertension. One limitation of the test: For approximately 20% of patients the test does not yield a valid result. He added that there are other radiographic tests like magnetic resonance elastography that can be used to stage fibrosis, but high cost may limit their use.

Selecting a method

As for which test should be used for any given patient, Dr. Thomas said that, to some extent, that depends on the resources and capabilities of the institution and that use of any one of them can be defended. The serum marker calculations are highly correlated with each other, and therefore he advised that there is little to be gained from ordering multiple tests. Tests can also be combined to stage liver fibrosis. He said that concordant noninvasive test results can be especially useful. When both elastography and serum tests are consistent with low-stage disease, a clinician can be as confident as possible that the risk of cirrhosis is low and that the patient can safely be managed without screening for HCC or varices. He suggested that sequential testing can also be valuable to monitor trends in a particular patient.

Dr. Thomas further explained that HIV coinfection does not appear to substantially alter the performance of staging tests. In general, the pretest probability of cirrhosis is higher in coinfected patients, and therefore the negative predictive values of tests used to rule out cirrhosis can be lower.

> *HIV coinfection does not appear to substantially alter the performance of staging tests. In general, the pretest probability of cirrhosis is higher in coinfected patients, and therefore the negative predictive values of tests used to rule out cirrhosis can be lower.*

Returning to the case of the woman patient, Dr. Thomas said that she clearly should be offered HCV treatment. With her FIB4 index, the likelihood of cirrhosis is low, and she probably does not need to have a biopsy, since she is going to be treated and is very unlikely to die of liver failure. He did recommend that, if available, elastography would be useful, although not an upper GI exam. Once she has achieved SVR, she can then be sent back to her primary care physician for ongoing care.

The male patient, on the other hand, probably has cirrhosis. He requires treatment urgently and could be the type of patient, with advanced disease, for whom longer treatment duration would be beneficial. Dr. Thomas thought that he did not need a biopsy. If not treated, he could certainly die of his liver disease. Ultrasound and upper GI exam would also be merited.

Dr. Thomas concluded with a reminder that the noninvasive testing methods were validated in patients who had not achieved SVR using DAAs and suggested that patients receiving treatment with DAAs will likely benefit from continued monitoring after cure.

Audience Questions

How does the validity of the staging methods differ in HIV/HCV-coinfected patients?

David L. Thomas, MD, MPH: The noninvasive methods generally have comparable validity. However, since coinfected patients have a higher pretest risk for cirrhosis, it is preferable to assume that the stage is more likely to be higher. Multiple studies, however, have shown that elastography's validity in HIV-positive patients is high.

Do you treat patients with F3 and F4 differently, considering that there is overlap in the findings of the noninvasive tests?

David L. Thomas, MD, MPH: As much as possible, I prefer to treat them for the same duration. Patients with F3 still have a measurable incidence of HCC and end-stage liver disease, and approximately 15% of them in fact should be F4.

In what circumstances should a patient with acute HCV infection be treated?

Arthur Y. Kim, MD, FIDSA: I use the time while waiting for spontaneous clearance of the virus to try to stabilize other areas of the patient's health, such as getting them into substance abuse treatment. These are often young people who have other causes of instability in their lives, and addressing these other conditions while weighing the decision to start DAA therapy can enhance their chances of not becoming reinfected.

Is use of DAAs as postexposure prophylaxis in cases of HCV exposure appropriate?

Arthur Y. Kim, MD, FIDSA: On the analogy of HIV postexposure prophylaxis, such a use of DAAs may seem attractive. However, with a likely transmission risk of approximately 2%, a large number of persons would have to be treated to prevent one case of infection, and anyone who does seroconvert can be treated with a high probability of success if and when HCV infection is confirmed. Even more important is the high cost involved in the use of DAAs.

Panel Discussion: Barriers to Management of HCV [Moderated by David Thomas, MD, MPH]

Treating Substance Abusers

In his presentation, "Treating Substance Abusers," **Alain H. Litwin, MD, MPH**, of the Montefiore Medical Center and Albert Einstein College of Medicine, reviewed the host of experiences and challenges in providing HCV treatment to injection drug users. He began with some sobering statistics: People who inject drugs (PWID) are at the core of the HCV epidemic, and in many areas 80% of new infections are among PWID and 60% of existing infections are among current and former PWID. Worldwide, he said, there are approximately 10 million PWID who are HCV-positive. In some methadone clinics, as many as 90% of PWID are HCV-positive, as are up to 17% of people who use but do not inject drugs. However, at 1%-6%, HCV treatment rates among PWID are low.

Barriers to care

Patient level. Barriers to increasing HCV care rates in this population occur at the patient, provider, and system levels, he continued. Patient-level barriers include limited knowledge of the natural history of HCV; asymptomatic disease, leading to a misperception of the longer-term risks; low social support; competing priorities in part due to high poverty rates, homelessness, and incarceration; mistrust of providers and healthcare institutions; fears about treatment that date back to the interferon era; comorbidities; cognitive impairment; and patterns of frequent drug use, which may lead to suboptimal adherence to visits and antiviral medications.

Provider level. Physician barriers include limited knowledge of HCV screening, care, and treatment; limited knowledge of the disease of addiction and its treatment; concerns regarding poor adherence and risk of reinfection; mistrust of PWID; concerns about concomitant alcohol use, relapse, or reinfection; limited capacity to address psychosocial issues; and reluctance to treat PWID. Primary care and addiction providers also may not believe that HCV care is within their core roles.

Structural level. Structural barriers include inadequate screening venues, limited HCV workforce (providers and care coordinators); fragmented healthcare system with few treatment settings suitable for this population's needs; poor access to staging of liver disease; poor access to substance abuse treatment; high cost; and systematic exclusion of PWID from antiviral treatment due to payer restrictions based on stage of liver disease or ongoing drug and alcohol use.

Improving access to care

Despite the availability of highly efficacious regimens, PWIDs face more barriers to treatment than ever. Dr. Litwin said that many models for increasing access to HCV care for PWID have been developed:

- Directly observed therapy
- Peer navigation
- Case management
- Incentives to access and remain in care

Potential structural improvements include:

- Education at all levels (specialists, infectious disease physicians, HIV providers, primary care providers)

- Sensitization to substance use and its related comorbidities

With the growing spread of heroin use into less populated areas and the accompanying growth in HCV infections, Dr. Litwin urged that everyone to some degree needs to become an addiction specialist. Improvements needed at the structural level include standard HCV testing and referral guidelines; integrated care teams; telemedicine, whereby specialists mentor others in remote locations; and expansion of HCV care in correctional facilities.

One model approach

Dr. Litwin then discussed a program of integrated HCV and opiate agonist treatment that has been developed by Albert Einstein College of Medicine/Montefiore Medical Center. Located in the Bronx, New York City, the program is a network of community-sited facilities that also offer comprehensive primary care. Dr. Litwin stressed the broad inclusiveness of the program, in which healthcare providers work closely with patients, who in turn are supported by friends, family, and other community members. Outreach events include, for example, "Love Your Liver" day.

He said that a small study (N = 73) of providing HCV treatment to program participants (with high rates of mental illness and HIV infection) found that 45% achieved SVR; he stressed that this occurred when the standard treatment was pegylated interferon/ribavirin, which was administered onsite.

Dr. Litwin discussed the value of directly observed therapy (DOT) in enhancing health outcomes among PWID. To investigate the impact of DOT on HCV, his program conducted a randomized trial in their facilities. Eighty HCV-infected adults began care with pegylated interferon/ribavirin, randomized to DOT (directly observed daily ribavirin plus provider-administered weekly interferon) or treatment as usual (TAU, ie, self-administered ribavirin plus provider-administered weekly interferon). The researchers observed significant differences in pill count adherence between the treatment arms (88% in the DOT arm vs 77% in the TAU arm). There were no differences in adherence to interferon between treatment arms and no differences in virologic outcomes between treatment arms: 55% SVR in the DOT arm vs 50% SVR in the TAU arm. He stressed again that these findings were from the interferon era and that DOT therapy with once-daily DAAs will likely lead to higher rates of adherence and SVR.

Dr. Litwin continued, saying that, although DOT clearly can be beneficial in enhancing treatment, it does not provide significant social support. The Bronx program developed a set of support groups that included medical providers. This helped participants address their barriers to remaining in care and helped to build a community of support for them. Figure 16 indicates more of this program's benefits.
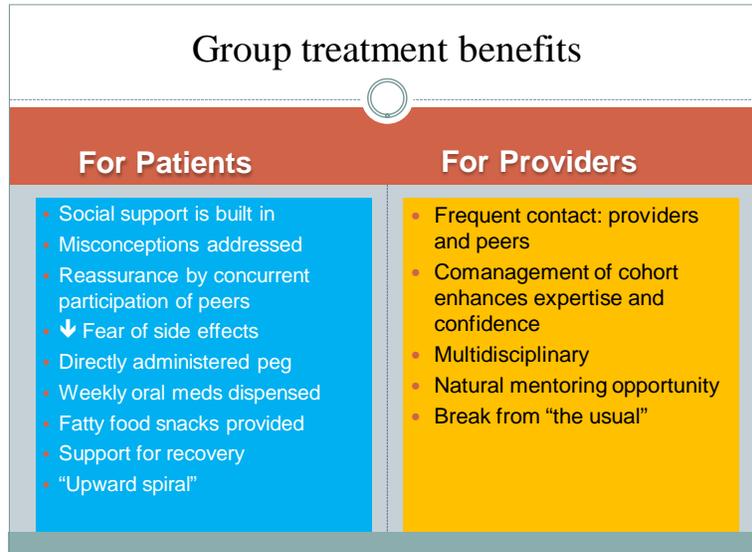
Figure 16. Wide-ranging benefits of HCV support groups.

A retrospective chart review of support group participants who were taking a variety of drugs (opiates, cocaine, benzodiazepines) and receiving HCV triple therapy, which included either telaprevir or boceprevir, found that 62% achieved SVR.

Dr. Litwin mentioned that ongoing studies of the use of DAAs in opiate agonist treatment patients, that are being done by the manufacturers of fixed-dose ledipasvir/sofosbuvir and the 3D regimen (paritaprevir/ritonavir/ombitasvir plus dasabuvir), have reported SVR12 rates of 94% and 97%, respectively. He added that an important initial finding is that there do not appear to be any significant drug-drug interactions between opiate agonists and DAAs.

The Bronx program has also launched a tele-mentoring program to support diverse healthcare providers in treating HCV care, as well as to educate and support treatment navigators and other support persons. He stressed that this program is not unique to the Bronx and that others are at work around the United States, as well as in Canada, Europe, and Australia. A meta-analysis of such efforts reported that 83% of participants had completed their HCV treatment, supporting the idea that addiction treatment enhances completion of HCV therapy. The same analysis also reported SVR rates of 56% (with pegylated interferon/ribavirin treatment).

A study from 10 years ago found that only 30% of addiction treatment physicians believed that current drug users would be eligible for HCV treatment, although that percentage increased with an increasing number of months since patients had stopped using. Another more recent study found that only 48% of HIV providers would be likely to prescribe ART for active drug users. Moreover, many Medicaid programs place a variety of restrictions—eg, months of abstinence, enrollment in treatment programs, urine or serum screening—on which patients can receive DAA therapy. Dr. Litwin expressed his belief that all drug-using patients should be eligible for treatment and a patient should be excluded from treatment only on the basis of evidence-based reasons.

In an effort to improve HCV treatment access for substance users, Dr. Litwin discussed the International Network on Hepatitis in Substance Users (INHSU)'s 2013 "Recommendations for Management of HCV Infection Among People Who Inject Drugs":

- HCV treatment can be considered for PWID, provided they wish to receive treatment and are able and willing to maintain regular appointments.
- A history of IDU and recent drug use at treatment initiation are not associated with reduced SVR, and decisions to treat must be made on a case-by-case basis.
- HCV treatment for PWID should be considered on an individualized basis and delivered within a multidisciplinary team setting.
- Access to harm reduction programs, social work, and social support services should be a component of HCV clinical management.
- OST (opioid substitution treatment) is not a contraindication for liver transplantation, and individuals on OST should not be advised to reduce or stop therapy.

Dr. Litwin commented that the first recommendation is the most important, adding that updated recommendations are now in development.

Summary
He concluded with a summary of the key points of his presentation:
- Barriers to effective HCV care for PWID can be overcome by onsite treatment, addiction treatment, multidisciplinary teams, and intensive models of care—eg, peers, DOT, and group treatment.
- Barriers to HCV care are greater than ever and will limit scaling up of treatment.
- Advocacy is urgently needed to increase access to care and promote social justice.

Panel Discussion: Barriers to Management of HCV
Adherence to Treatment of HCV

Mark S. Sulkowski, MD, of the Johns Hopkins University School of Medicine, introduced his presentation, "Adherence to Treatment of HCV," by explaining that it would not be a strictly didactic talk. Instead, he discussed the issues that would arise in developing adherence efforts for several different patients. He said that today there is a common theme that HCV treatment is now easy—with once daily dosing for most regimens. However, he continued, the much discussed SVR rates of >95% occurred in clinical trials, whereas clinicians need to consider what could happen in translation to actual practice. DAAs will only work as well as the patients are able to take them. The 84 consecutive days in a typical 12-week DAA regimen is a critical point to remember. With some diseases, such as hypertension or HIV, a patient can miss a dose or even several days of dosing, resume treatment, and continue to enjoy the same treatment benefits. At this time, Dr. Sulkowski said, it is not yet known what would happen to an HCV patient's SVR if a dose is missed for whatever reason.

Patient 1

Jim, a 65-year-old man with HCV genotype 1b and stage 1-2 fibrosis, has long been eager to start HCV treatment, and he's demonstrated adherence to treatments for hypertension and lipid elevations. He is married with grown children, is a business owner, does not use alcohol, and has a remote (40 years ago) history of IDU. Dr. Sulkowski stressed that this man is highly motivated, and his potential adherence challenges are likely to involve prompt access to treatment, timely monthly refills, and the need for routine lab and office visits.

Jim gets his first DAA prescription filled at a pharmacy, but his insurer then requires that a mail order pharmacy fill it thereafter, which will require a new prescription to be written. Dr. Sulkowski pointed out at this point there could be the challenge of whether he will have the refill when the current supply nears its end. Very few insurers will release the entire DAA treatment course at once. So, there are potential roadblocks to uninterrupted access to drugs, raising the issue of who will be responsible for making sure this patient will have his medications. Moreover, some payers want an HCV RNA test done at week 4 to prove that the patient is taking the medication. If the lab's sample or its report become lost or delayed, the patient may find himself several weeks into treatment with no more medication. Jim does not appear to need much adherence support, but the healthcare delivery system contains potential barriers that may threaten his adherence. If his treatment is interrupted, Dr. Sulkowski stressed that no one knows at this time how forgiving DAA regimens may be.

> *The much discussed SVR rates of >95% occurred in clinical trials, whereas clinicians need to consider what could happen in translation to actual practice. DAAs will only work as well as the patients are able to take them.*

Patient 2

Kim, a 43-year-old woman, is triple-infected with HIV, HCV, and HBV. She has been on ART with suppressed HIV RNA for approximately 5 years. But her HBV DNA is not suppressed, and she admits that she does not take her ART on some days. A biopsy has identified early cirrhosis, and she is not actively using drugs. However, she lives 2 hours from Dr. Sulkowski's clinic and depends on medical transport. Her local primary care provider is not comfortable managing any of her 3 viral infections. In addition, she depends on medical assistance.

Dr. Sulkowski said that distance is the first challenge to her adherence, and her adherence to ART is known to be questionable. This patient's antiretrovirals are sent to her HIV nurse at the Johns Hopkins clinic, not to the patient, who must meet with the nurse and work out an individualized treatment plan. When she begins DAA therapy, her medication is mistakenly sent to her home during the holiday period. At her next clinic visit, 18 tablets of ledipasvir/sofosbuvir were missing, and her HCV viral load was found to be unchanged from baseline. Now Kim comes in weekly and has a pillbox filled with the next week's DAAs. Although Kim has finished 12 weeks of DAA therapy, Dr. Sulkowski now wonders whether any harm could have been caused by the uneven dosing at the start of treatment. He stressed that distance is clearly an adherence challenge in situations like this, which are not uncommon. In this case, tele-medicine likely was not feasible, because no healthcare professional in her own community was willing to manage HCV infection. He stressed that many other patients who live at such a distance from an HCV treatment facility may not be able to access a program that could provide as much as the one at Hopkins did.

Patient 3

Ned is a 58-year-old with schizoaffective disorder who is an active alcohol user; he is also illiterate and cognitively impaired. A biopsy has identified cirrhosis. He lives with his parents and cannot be reached by telephone. Nevertheless, he has not missed any of his visits to the hepatitis clinic in 10 years. He is also in a day program, but it does not provide active alcohol treatment. Dr. Sulkowski explained that Ned's potential adherence challenges are clear, with his active alcohol use being the main one.

Successful HCV treatment requires a major commitment involving a large number of healthcare providers and other support staff—case managers, pharmacists, insurance coordinators—along with a committed patient. Reducing the burdens of HCV disease will be a decades-long effort.

As a hopeful sign, the patient stopped drinking during his DAA therapy, during which he made weekly clinic visits, and his HCV viral load is undetectable. Nevertheless, Dr. Sulkowski said that the future for a patient like this will continue to present challenges, especially if he does not become engaged in alcohol treatment; otherwise, he could be at increased risk for hepatocellular carcinoma several years in the future, even in the context of his cured HCV infection.

Patient 4

Amy, a 19-year-old woman, has had HCV infection for 3 years. She is an active user of injected heroin and was previously in an opioid substitution treatment (OST) program but is no longer engaged in that. In addition, she has bipolar disorder but is also not engaged in care for that. She says that she is anxious to start HCV treatment. However, over the preceding 2 years, she has missed 4 of 6 scheduled clinic visits.

This history of missed visits, Dr. Sulkowski explained, is crucial. Studies in HIV patients have found that one of the best predictors of adherence to HIV treatment is missed clinic visits. Missing important medical appointments is a surrogate measure of competing priorities and other barriers to adherence, eg, limited access to housing or transportation. Therefore, programs that focus on visit attendance are key to both accessing and adhering to subsequent treatment. In the care of HIV-infected patients, successful strategies have included nursing interventions, peer navigators, pharmacotherapy clinics, and outreach efforts. Although HCV reinfection must be prevented after HCV cure, finite treatment duration is a major advantage to HCV care. For successful HCV treatment, clinicians will need to assess barriers to access and adherence and implement strategies to overcome the barriers that are identified.

As for Amy, Dr. Sulkowski said that she clearly needs treatment but without engaging again in an OST program and bipolar treatment, her risk of nonadherence is great. In this patient's case, deferring HCV treatment until these issue are addressed is probably appropriate.

Dr. Sulkowski concluded by stressing that successful HCV treatment requires a major commitment involving a large number of healthcare providers and other support staff—case managers, pharmacists, insurance coordinators—along with a committed patient. He said that it is important to realize that reducing the burdens of HCV disease will be a decades-long effort.

Panel Discussion: Barriers to Management of HCV

Treatment Access and Cost-Effectiveness

At the start of his presentation, "Treatment Access and Cost-Effectiveness," **John B. Wong, MD**, of the Tufts University School of Medicine and Tufts Medical Center, posed a rhetorical question: If a treatment purchases added years at a price of $250,000 per added life-year, which option would you recommend?

- American society should purchase that added life-year for all, and taxpayers should be compelled to pay extra taxes.
- Americans with the means to purchase or with private health insurance should be afforded the opportunity to purchase those added life-years for themselves or their families.

The remainder of his presentation suggested some of the issues to be considered in answering such a question and the possible implications of the answers. He then presented a series of graphs comparing the prevalence of various stages of HCV disease and the costs of providing treatment at each stage, projected out to the year 2030. These set the background against which cost-effectiveness analyses would need to be developed. A core concern is a report from last year showing that the cost of providing HCV treatment for every American who needs it would equal the cost of the entire drug budget for 1 year.

ICER

Dr. Wong then explained that answering the question of whether the DAAs provide value is essentially a question of whether their price is fair and whether the clinical benefit justifies the price. The accepted way of answering that is to perform an incremental cost-effectiveness ratio (ICER) analysis. An ICER analysis takes these considerations into account:

- Costs of drugs, drug monitoring, adverse effects, tests, and costs of the disease
- Savings from prevention or alleviation of disease complications

This calculation accounts for the "5Ds": death, disability, discomfort, drug toxicity, and dollars. Figure 17 shows the factors that are weighed in an ICER analysis.

$$\text{Value} = \text{additional cost} \div \text{additional benefit}$$

$$\frac{\text{Cost with new drug} - \text{cost with standard care}}{\text{Effectiveness with new drug} - \text{effectiveness with std care}}$$

Figure 17. Incremental cost-effectiveness ratio (ICER): How much additional benefit is associated with the additional expenditure.

Dr. Wong offered an analogy of offering a person $100 now or $100 1 year from now; most people would choose to get the $100 now. A comparable question might be whether a person would prefer to live a year in good health or to live a year with hepatocellular carcinoma (HCC); of course, most people would choose the former. ICER, he explained, tries to quantify the cost of a year of perfect health and the cost of HCC to determine what a good value is.

The cost-effectiveness of HCV treatment is considered within the context of the ICERs of other medical procedures, eg, colon cancer screening, ART for HIV infection, or hemodialysis. As an illustration, a public health official who has $1 million to spend would purchase approximately 60 life-years by spending that amount on colon cancer screening, approximately 40 life-years by spending it on HIV treatment, or approximately 18 life-years by spending it on hemodialysis. This suggests that colon cancer screening is more cost-effective than a number of other procedures.

Dr. Wong said that costs vary according to a patient's HCV genotype, with genotype 1 infection typically being the most cost-effective. Other factors to be considered include:
- Age and gender, with younger patients more cost-effective than older and women more cost-effective than men
- Treatment-naive more cost-effective than experienced, with cirrhotics more cost-effective than noncirrhotics
- Treatment-experienced, with noncirrhotics usually more cost-effective than cirrhotics

Treat now vs stage-based treatment

Whether all HCV-infected persons should be offered treatment when diagnosed or whether treatment should be based on an individual's HCV disease stage has become a topic of considerable discussion and controversy. When patients are treated earlier, he explained, the likelihood of achieving SVR is greater and the longer-term risk of HCC is reduced; however, this approach involves greater costs now and risk of drug adverse effects. Some HCV patients will not progress to F3-F4 fibrosis and may never need treatment, but the risks of developing HCC after achieving SVR with F3-F4 fibrosis are much greater, and there will be additional costs for liver disease staging.

Medicare spent $4.5 billion on new HCV drugs in 2014. Dr. Wong said that the US government can address this problem to some extent by increasing the money supply. State governments, however, have increasingly been employing exclusion criteria for HCV therapy in their Medicaid programs; states' other option would be to increase taxes.

Affordability

Dr. Wong underscored the importance of DAAs' affordability by referring to a 2014 *Lancet* article, which said that a 12-week course of therapy is "unaffordable for most of the 3.2 million people infected with HCV in the USA." In 2013, US healthcare expenditures were $2.9 trillion, or 17.4% of the gross domestic product (GDP). The key issue, he said, is the value obtained by the spending, ie, the opportunity costs. Federal budget projections indicate that spending exceeds revenues and that the trend is toward a federal debt of 100% of GDP. The budget categories in which spending is increasing are healthcare, Social Security, and interest on the national debt; this suggests, said Dr. Wong, that all other expenses (defense, education, infrastructure) must be reduced.

A recent analysis found that Medicare spent $4.5 billion on new HCV drugs in 2014. Dr. Wong said that the US government can address this problem to some extent by increasing the money supply. State governments, however, do not have that option and have increasingly been employing exclusion criteria for HCV therapy in their Medicaid programs; states' other option would be to increase taxes.

Summary

Dr. Wong concluded by recapping the key considerations regarding the cost-effectiveness of DAA therapies:

- All-oral DAA-based regimens may or may not be cost-effective.
- Liver staging and stratified therapy may improve cost-effectiveness.
- The budget impact of DAA regimens at all levels has been substantial.

Audience Questions

Considering the risk of reinfection in drug-using populations, are there patients that you choose not to treat?

Alain H. Litwin, MD, MPH: I look closely at their living situations to see if there's some kind of structure, because of the importance of support for IDUs. Some treaters use pilots to help patients keep appointments and maintain adherence. Another approach is to offer a modest stipend to patients who keep appointments. It has to be a highly individualized decision. There are not much data about how to reach young drug users living in relatively isolated locations. There's a need for pilot programs to determine better ways to reach out to such populations.

With the growing number of DAAs, why is competition among drug companies not helping to reduce the costs of the drugs?

John B. Wong, MD: In fact, there has been some decrease due to competition. For example, Medicaid has a mandated 23% reduction, based on a set price. A group of 25 states has formed a consortium to negotiate with drug companies, and they are receiving an approximately 30%-40% price reduction. Pharmacy benefits companies have also negotiated deals with DAA manufacturers, although the details of the arrangements are not public.

As an HIV practitioner, I treat active drug users, but alcoholics have always seemed to present a special challenge regarding adherence. Although the data show that most DAAs do not significantly interact with opioid substitutes, are there data about alcohol use?

Mark S. Sulkowski, MD: Data clearly show that HCV-infected persons who are actively using alcohol have a much higher risk of dying of liver-related disease. In effect, they are pouring gasoline on a fire. However, there are essentially no data showing that DAAs are less effective in active users of alcohol. My view is that patients who continue to drink should be a priority. That is, if it's possible to cure their HCV, that removes at least one health risk, although it's also important to encourage them to seek treatment for alcohol use.

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