Volume 1, Issue 1

ERx Essential Reading in Hepatitis

PRESCRIBED EXPERT ANALYSIS

Ledipasvir–Sofosbuvir Once Daily Shows High SVR In Patients Unresponsive to Interferon-Based Therapy

Source: *New England Journal of Medicine*
Commentary by Robert S. Brown, Jr., MD, MPH

Stigmatization is Common in Patients With Liver Cirrhosis, Linked to Worse Outcomes

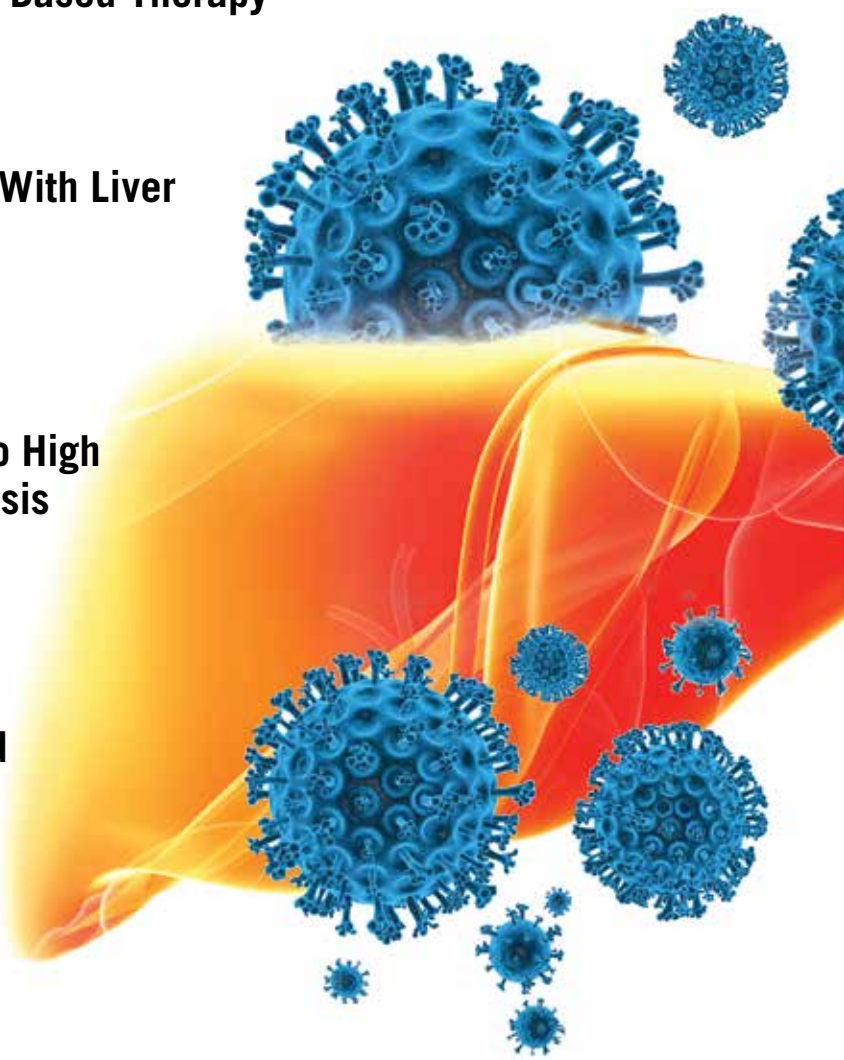
Source: *Digestive Diseases and Sciences*
Commentary by William D. Carey, MD

ABT-450 Triple-Drug Regimen Linked to High Cure Rates in HCV Patients With Cirrhosis

Source: *New England Journal of Medicine*
Commentary by Robert S. Brown, Jr., MD, MPH

Sofosbuvir plus Ribavirin Shows High Response Rates in Patients Coinfected With HCV and HIV

Source: *Hepatology*
Commentary by Paul Kwo, MD



By Meg Block, MPH

Welcome to *Essential Reading in Hepatitis*. This is an unprecedented time in the development of novel therapies to treat hepatitis C virus (HCV) infection, offering hope to the 3.2 million Americans with chronic HCV infection.[1] In fact, a cursory literature search reveals that 11 original research papers on the treatment of HCV were published in *The New England Journal of Medicine* in 2014 alone—a figure that far surpasses the number of annual HCV articles published in previous years. Although the new all-oral therapies offer patients few side effects and a cure, the high cost of treatment remains a barrier to care for many individuals.

In this inaugural issue of *Essential Reading in Hepatitis*, we are thrilled to present a compilation of some of the most important studies recently published in the world of hepatitis. To put the research into perspective, we sought out several key opinion leaders to comment on how the findings will affect treating hepatologists, gastroenterologists, infectious disease specialists, and internal medicine physicians.

Our panel of experts—including Willian D. Carey, MD, hepatologist, Past-President of the American College of Gastroenterology, and an invaluable resource as the Chair of this inaugural issue, Robert S. Brown Jr., MD, MPH, a leader in transplantation for hepatitis-related liver disease, and Paul Kwo, MD, an established voice for gastroenterologists and hepatologists—scoured the literature to select articles that reflect the current hepatitis C landscape in the United States.

As such, the article selections chosen by our experts focus on the advent of all-oral and interferon-free therapies, the cost-effectiveness of treatment, HCV-related comorbid conditions, and the role of stigma in obtaining care. Next, our writers succinctly summarized study findings and our thought leaders remarked on the findings, paying special attention to how the influx of newly available HCV therapies will affect day-to-day practice.

Meg Block, MPH

This unique format allows the busy, practicing hepatologist, gastroenterologist, infectious disease specialist, and internal medicine physician to stay up-to-date with important hepatitis-related news, while placing findings neatly into context. We hope that readers will find this and future issues of *Essential Reading in Hepatitis* an important resource in this historical time in the crusade to eradicate HCV infection.

Reference

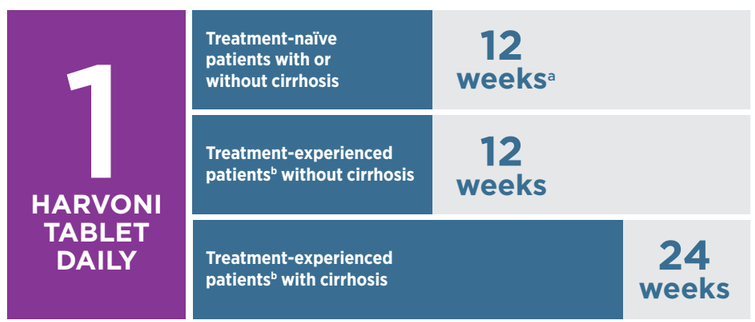
1. Hepatitis C Information for Health Professionals: Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#section1. Accessed December 6, 2014

HARVONI is a once-daily single-tablet regimen for HCV GT 1 patients[1]

NOW APPROVED

ONE IS HERE

Recommended treatment duration for HARVONI[1]



[a]HARVONI for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.[1]

[b]Treatment-experienced patients who failed treatment with either peginterferon (Peg-IFN) alfa + ribavirin (RBV) or an HCV protease inhibitor + Peg-IFN + RBV.[1]

HCV = hepatitis C virus

HARVONI is the first and only IFN- and RBV-free regimen available in one tablet taken once a day[1]

- HARVONI is IFN- and RBV-free for GT 1 treatment-naïve and treatment-experienced patients with or without cirrhosis, regardless of GT 1a or 1b subtype[1]
- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir[1]
- HARVONI can be taken with or without food[1]
- Relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups[1]
- No dose adjustments are required based on advanced age, mild or moderate renal impairment, or mild, moderate, or severe hepatic impairment. The safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis[1]
- No dose recommendation can be given for patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Risk of Reduced Therapeutic Effect of HARVONI Due to P-gp Inducers:** Rifampin and St. John's wort are not recommended for use with HARVONI as they may significantly decrease ledipasvir and sofosbuvir plasma concentrations.
- **Related Products Not Recommended:** HARVONI is not recommended for use with other products containing sofosbuvir (SOVALDI®).

ADVERSE REACTIONS

Most common (≥10%, all grades) adverse reactions were fatigue and headache.

DRUG INTERACTIONS

- In addition to rifampin and St. John's wort, coadministration of HARVONI is also not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of ledipasvir and sofosbuvir, reducing the therapeutic effect of HARVONI.
- Coadministration of HARVONI is not recommended with simeprevir due to increased concentrations of ledipasvir and simeprevir. Coadministration is also not recommended with rosuvastatin or co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of rosuvastatin and tenofovir, respectively.

Consult the full Prescribing Information for HARVONI for more information on potentially significant drug interactions, including clinical comments.

Please see Brief Summary of full Prescribing Information on the following pages.

harvoni.com/hcp

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

HARVONI® (ledipasvir 90 mg and sofosbuvir 400 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

INDICATIONS AND USAGE: HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS:

Risk of Reduced Therapeutic Effect Due to P-gp Inducers: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.

Related Products Not Recommended: Use of HARVONI with products containing sofosbuvir (SOVALDI®) is not recommended.

ADVERSE REACTIONS:

The safety assessment of HARVONI was based on pooled data from three Phase 3 clinical trials in subjects with genotype 1 CHC with compensated liver disease (with and without cirrhosis) who received HARVONI for 8 (N=215), 12 (N=539) and 24 (N=326) weeks. Adverse events led to permanent treatment discontinuation in 0%, <1% and 1% of subjects receiving HARVONI for 8, 12 and 24 weeks, respectively.

Adverse Reactions (adverse events assessed as causally related by the investigator): The most common adverse reactions (≥10%; all grades) were fatigue and headache. Adverse reactions (all grades; majority Grade 1) observed in ≥5% of subjects by treatment duration were:

- *HARVONI for 8 weeks:* fatigue (16%); headache (11%); nausea (6%); diarrhea (4%); and insomnia (3%)
- *HARVONI for 12 weeks:* fatigue (13%); headache (14%); nausea (7%); diarrhea (3%); and insomnia (5%)
- *HARVONI for 24 weeks:* fatigue (18%); headache (17%); nausea (9%); diarrhea (7%); and insomnia (6%)

Direct comparison across trials should not be made due to differing trial designs.

Laboratory Abnormalities: *Bilirubin Elevations:* Bilirubin elevations of greater than 1.5x ULN were observed in 3%, <1% and 2% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. ***Lipase Elevations:*** Transient, asymptomatic lipase elevations of greater than 3x ULN were observed in <1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. ***Creatine Kinase:*** Creatine kinase was not assessed in Phase 3 trials of HARVONI. Isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

DRUG INTERACTIONS:

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir and sofosbuvir are substrates of P-gp and BCRP while the inactive sofosbuvir metabolite GS-331007 is not. P-gp inducers (e.g. rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect; use of HARVONI with P-gp inducers is not recommended.

Established and Potentially Significant Drug Interactions: The drug interactions described are based on studies conducted in healthy adults with either HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. This list includes potentially significant interactions but is not all inclusive. **An alteration in dose or regimen may be recommended for the following drugs when coadministered with HARVONI:**

- **Acid Reducing Agents:** Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentration.
  - *Antacids:* Separate HARVONI and antacid administration by 4 hours.
  - *H_2-receptor antagonists:* Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from HARVONI.
  - *Proton-pump inhibitors:* Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.
- **Antiarrhythmics (digoxin):** Increased digoxin concentration. Monitor digoxin therapeutic concentration during coadministration with HARVONI.
- **Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **Antimycobacterials (rifabutin; rifampin; rifapentine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **HIV Antiretrovirals**
  - *Regimens containing tenofovir disoproxil fumarate (DF) and an HIV protease inhibitor/ritonavir (emtricitabine/tenofovir DF plus atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir):* The safety of increased tenofovir concentrations has not been established.

Brief Summary (cont.)

Consider alternative HCV or antiretroviral therapy. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

- *Efavirenz/emtricitabine/tenofovir DF:* Monitor for tenofovir-associated adverse reactions. Refer to VIREAD, TRUVADA or ATRIPLA prescribing information for renal monitoring recommendations.
- *Elvitegravir/cobicistat/emtricitabine/tenofovir DF:* The safety of increased tenofovir concentrations has not been established. Coadministration is not recommended.
- *Tipranavir/ritonavir:* Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

- **HCV Products (simeprevir):** Increased ledipasvir and simeprevir concentrations. Coadministration is not recommended.
- **Herbal Supplements (St. John's wort):** Decreased ledipasvir and sofosbuvir concentrations. Coadministration is not recommended.
- **HMG-CoA Reductase Inhibitors (rosuvastatin):** Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended.

Drugs without Clinically Significant Interactions with HARVONI: Based on drug interaction studies conducted with HARVONI or its components, no clinically significant drug interactions have been observed or are expected when used with the following drugs individually: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, tenofovir DF or verapamil.

Consult the full Prescribing Information prior to and during treatment with HARVONI for potential drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS:

Pregnancy: HARVONI is Pregnancy Category B; there are no adequate and well-controlled studies in pregnant women. HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Studies in rats have demonstrated that ledipasvir and GS-331007 are secreted in milk but had no effect on nursing pups. It is not known if HARVONI and its metabolites are secreted in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HARVONI and any potential adverse effects on the nursing child from the drug or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of HARVONI have not been established in pediatric patients.

Geriatric Use: Clinical trials of HARVONI included 117 subjects aged 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients.

Renal Impairment: No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

Hepatic Impairment: No dosage adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.

Reference: 1. HARVONI US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. October 2014.

FEATURES

COLUMNS

By William D. Carey, MD

Dr. Carey a is Senior Hepatologist in the Department of Gastroenterology at the Cleveland Clinic in Cleveland, Ohio.

William D. Carey, MD

Out with the old, in with the new.

Disruptions destroy or greatly modify existing patterns, thinking, and ways of doing things. Disruptive technologies include the invention of metallurgy, movable typesetting, gunpowder, electricity, radio, and television. The internet and smartphones have fundamentally changed how we communicate, take pictures, find our direction on highways and byways, and acquire information.

The first effective drugs to treat hepatitis C virus (HCV) infection were interferons—weak agents of limited efficacy, high cost, and myriad of side effects. A whole generation of hepatologists attained their distinctive HCV skill set by becoming "interferonologists." We knew the arcane (and now largely useless) interluken-28B–effect of previously-failed therapy, degree of hepatic fibrosis, HIV-coinfection status, racial differences in response, etc. Armed with this arcania, we had limited ability to eradicate infection. Only the brave non-specialist would consider treatment of HCV infection.

The introduction of direct-acting antiviral (DDA) therapy for viral hepatitis represents a pharmacologic disruption of the first order. At first, it seemed that little had changed: Telaprevir and boceprevir still required interferon and ribavirin. As rapidly as these vanguard DAAs appeared, they were replaced by better agents. All at once, we are treating nearly all cases of HCV without interferon. Indeed, a single pill or 2 nearly devoid of significant side effects are now prescribed.

Short of a preventive vaccine, all that prevents the widespread elimination of HCV infection is the development of a more effective therapeutic superhighway upon which the DAA can be delivered. Better identification of infected individuals, lower costs, and, importantly, migration of management out of the offices of specialists are needed.

It gives me a great deal of satisfaction to serve as Chair Editor in the first iteration of *Essential Reading in Hepatitis.* Filtering the robust literature on hepatitis C provides a valuable service to the existing and emerging base of health care providers. My co-commentators, Paul Kwo, MD, and Robert S. Brown Jr., MD, MPH, and I have been participants throughout the entire evolution of the hepatitis C story, from it's certain identification 20 years ago.

Dr. Kwo is Medical Director of Liver Transplantation and Professor of Medicine in the Division of Gastroenterology/Hepatology at Indiana University School of Medicine in Indianapolis; Dr. Brown is Director of the Transplantation Initiative and Director of the Center for Liver Disease and Transplantation at NewYork-Presbyterian Hospital/Columbia University Medical Center, and Frank Cardile Professor of Medicine at Columbia University College of Physicians and Surgeons in New York City. We have all participated in hepatitis C clinical trials, and between the 3 of us have managed thousands of HCV-infected patients.

We hope that you will agree that the studies selected for this inaugural issue represent important 2014 milestones in hepatitis C management. We have barely scratched the surface in important contemporary research in hepatitis C. We, like you, look forward to future issues of *Essential Reading in Hepatitis* that will add to a better fabric of understanding of contemporary HCV management.

ERx Essential Reading in Hepatitis
PRESCRIBED EXPERT ANALYSIS

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Updated HCV Guidelines Target Baby Boomers, Advocate One-Time Screening, Use of Interferon-Free Therapies

Sources: U.S. Preventative Services Task Force and American Association for the Study of Liver Diseases

Recommendations for screening, diagnosing, and treating hepatitis C virus (HCV) infection call for targeted screening methods and use of new interferon-free therapies. The updated guidelines were released by the U.S. Preventive Services Task Force (USPSTF) and the American Association for the Study of Liver Diseases (AASLD), in collaboration with other organizations.[1,2] All recommendations are subject to further updated medication recommendations in 2015.

Task Force Recommends Screening for All Baby Boomers

In June 2013, the USPSTF issued its Recommendation Statement on screening for HCV in adults. The following 2 major screening recommendations were made:

- All adults at risk of infection (Table).[1]
- Use of the one-time, anti-HCV antibody test, followed by polymerase chain reaction testing for viremia, to screen all adults born between 1945 and 1965.

People with continued risk for HCV infection (eg, injection drugs users) should be screened regularly; however, it is unclear from current evidence how often this screening should be conducted, according to the Task Force.

People born between 1945 and 1965 and those without on-going risk factors for HCV only need to be screened once using the anti-HCV antibody test followed by polymerase chain reaction testing. This recommendation applies to all asymptomatic adults without known liver disease or functional abnormalities. People in this age group are considered at risk because they may have received a blood transfusion before the institution of universal blood screening in 1992, or may have other generation-related risk factors for HCV. In fact, data evaluated by the USPSTF indicate that this age group accounts for as many as three-fourths of cases of HCV infection in the United States.

AASLD/IDSA/IAS-USA Guidelines

In September 2014, the AASLD and Infectious Diseases Society of America (IDSA), in collaboration with the International Antiviral Society–USA (IAS–USA), released a continually updated guidance on the screening, management, and treatment of HCV. At the time of publication of *Essential Reading in Hepatitis*, the latest updates included the following:

Chronic HCV Treatment: Treatment is recommended for all patients with chronic HCV infection (except those with <12 months to live due to non-liver related comorbid conditions), and should be prioritized based upon patients who will derive the most benefit, or will have the greatest impact on limiting further HCV transmission. For example, the highest priority should be given to patients with advanced fibrosis, compensated cirrhosis, liver transplant recipients, patients with severe extrahepatic hepatitis C, and those at high risk for complications related to these conditions.

Combine or replace interferon-based therapies with interferon-free regimens to treat the vast majority of HCV patients. Evidence-based studies now demonstrate the high efficacy of interferon-free medications for the treatment of HCV of all genotypes, including treatment-naïve and nonresponding patients, those with cirrhosis, and those with comorbid conditions, such as HIV. Treatment length and drug combinations will vary. The treatment guidelines are being continually updated based on new therapies and other developments. To view the latest treatment recommendations for chronic HCV infection, please visit www.hcvguidelines.org.

Monotherapy with peginterferon, ribavirin, or direct-acting antivirals should not be given to treatment-naïve patients of all gentoypes. Peginterferon-based combination therapy for 24 weeks or more should NOT be given to treatment-naïve patients with genotypes 1, 2 or 3. See guidelines for further detail on treatments that should not be given.

Acute HCV treatment: During acute HCV infection (ie, within 6 months of the exposure) there is a 20% to 50% chance of spontaneous resolution of infection. If the practitioner and patient decide to delay treatment, monitoring for spontaneous clearance is recommended for a minimum of 6 months. If clearance occurs during this time, treatment is not recommended. If the decision is made to initiate treatment during acute infection or after 6 months of monitoring, please visit the latest treatment recommendations at www.hcvguidelines.org. When initiating treatment during acute infection, it is recommended to monitor HCV RNS for 12 to 16 weeks to allow for spontaneous clearance before treatment initiation.

Table. Risk Factors for HCV Infection

- Current or past use of injection drugs
- Sex with an with an injection drug user
- Received a blood transfusion before 1992
- Long-term hemodialysis
- Born to an HCV-infected mother
- Incarceration
- Intranasal drug use
- Obtained an unregulated tattoo
- Other percutaneous exposures

Data derived from U.S. Preventive Services Task Force.[1]

References

1. U.S. Preventive Services Task Force. *Screening for Hepatitis C Virus Infection in Adults: U.S. Preventive Services Task Force Recommendation Statement.* Available at: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-c-screening. Accessed November 24, 2014.
2. American Association for the Study of Liver Diseases and Infectious Diseases Society of America. *Recommendations for Testing, Managing, and Treating Hepatitis C.* Available at: http://www.hcvguidelines.org/full-report-view. Accessed November 24, 2014.

Robert S. Brown, Jr., MD, MPH

Dr. Brown is Director of the Transplantation Initiative and Director of the Center for Liver Disease and Transplantation at NewYork-Presbyterian Hospital/Columbia University Medical Center, and Frank Cardile Professor of Medicine at Columbia University College of Physicians and Surgeons in New York City.

Robert S. Brown, Jr., MD, MPH

New HCV screening and treatment guidelines are paving the way for more comprehensive detection and care of patients that, if implemented, will lead to far-reaching improvements in the quality of life and lifespan of patients with HCV infection. The USPSTF Final Recommendation Statement on screening recommends, for the first time, that all adults born between 1945 and 1965 be screened for HCV using a one-time anti–HCV antibody test, followed by polymerase chain reaction testing to confirm positive antibody tests. Approximately three-fourths (75%) of HCV-infected patients in the United States were born during this time period, and the majority of these individuals remain undiagnosed.

The rationale behind the updated guidelines is two-fold. First, the new guidelines recognize that the prior risk-factor based screening approach failed to identify the majority of cases because most patients do not have current risk factors, and/or do not perceive themselves at risk.[1] The change in our screening methods from standard, risk factor-based screening to birth cohort screening is expected to be more successful.

> *"The change in our screening methods from standard, risk factor-based screening to birth cohort screening is expected to be more successful."*
>
> —Robert S. Brown, Jr., MD, MPH

Second, adoption of the one-time antibody test will identify more than 75% of HCV-infected individuals because most HCV patients were born between 1945 and 1965. The one-time antibody test is inexpensive, highly sensitive, and very specific, allowing doctors to detect patients who test positive for HCV while minimizing the chance of false negatives. Applying the test only once and solely in the group with the highest prevalence, will be a more cost-effective method than screening the entire population, while also minimizing missed cases that occurred with the risk-factor based screening method.

The AASLD Recommendations for Testing, Managing, and Treating Hepatitis C have been updated to include treatment using the newer, interferon-free regimens. Interferon-free therapy using combinations of potent, direct-acting oral agents is expected to yield sustained virologic response (SVR) rates of more than 90% to 95%. The majority of patients will be treated for 12 weeks duration, with a smaller portion of patients treated for 8 weeks (those easy-to-treat) and 24 weeks (those hard-to-treat).

It has been shown in population-based studies of patients with HCV that achieving SVR after 12 or 24 weeks of therapy is equivalent to a durable cure and is associated with decreased liver-related, and all-cause mortality. These survival advantages are seen in patients with both mild and advanced liver disease, which is the rationale for treating all HCV patients with effective and tolerable anti-viral therapy. Although therapy should be prioritized for patients with advanced liver disease, it should not be denied to patients with milder forms of liver disease who will also benefit from a cure.

Concern about the cost of the newer therapies is evolving. Fear over the ability to pay for universal HCV therapy remains at the forefront. However, this concern is likely overstated as we have not identified the majority of patients with HCV or linked them to care. Treatment of patients with mild liver disease is cost effective relative to the expense of patients who experience treatment failure.[2]

Additionally, it is not ethically correct to force patients to wait until they have cirrhosis to treat them. Cirrhosis increases patients' risk of liver cancer and mortality even if they are cured at that point. If patients are treated early in their disease progression, the new medications can cure both HCV and liver disease, preventing any risk of liver cancer or cirrhosis. The hope is that, as more agents come out and competition increases in the marketplace, costs will come down. We can be encouraged that, down the road, interferon-free therapy and near universal cure of HCV will be accessible to all patients.

References

1. Chou R, Cottrell EB, Wasson N, Rahman B, Guise JM. Screening for hepatitis C virus infection in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2013;158(2):101-108.
2. Backx, MA, Lewszuk A, White JR, et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. *J Viral Hepat.* 2014;21(3):208-215.

Dr. Brown disclosed financial relationships with Abbvie, Gilead Sciences, Janssen Pharmaceuticals, and Merck.

Large Gaps in HCV Care Identified in Meta-Analysis

Source: *PLoS One*

Substantial gaps exist in the care of patients with chronic hepatitis C virus (HCV) infection, including lack of prescribing HCV therapy in 84% of patients and lack of achieving sustained virologic response (SVR) in 91% of patients, according to a meta-analysis by Yehia et al.[1]

The authors conducted a systematic review of 9,581 articles published between January 2003 and July 2013, identifying 10 citations that met study criteria and addressed steps along the treatment cascade for patients with chronic HCV infection in the United States. The investigators developed a 7-step treatment cascade for optimal care, and used the study data to estimate the number of people who completed each step of this cascade (Figure).[1]

Data from one of the examined studies—the National Health and Nutrition Examination Survey (NHANES)—suggests that 3.2 million people in the United States have chronic HCV infection. Given that this survey did not include such high-risk groups as homeless, incarcerated, or institutionalized people, Yehia et al estimated the actual prevalence to be 3.5 million.

Half of Infected Adults Are Unaware of Their HCV Status

Half of people with HCV infection have been diagnosed and are aware of their HCV status, according to the NHANES data. Further analysis showed that less than half of patients (43%) diagnosed with HCV have outpatient health care coverage.

Liver biopsy to stage hepatic fibrosis, while not required by current clinical guidelines, is useful for guiding HCV treatment decisions, noted the authors. However, studies included in the analysis suggest that only 17% of patients diagnosed with HCV who have health insurance have undergone a liver biopsy to accurately stage their liver disease.

In addition, the analysis showed that only 16% of patients were prescribed HCV therapy. Specifically, the authors found that less than half of diagnosed HCV patients (37%) who have commercial health insurance were prescribed interferon-based HCV therapy. Comparable analysis from the Veterans Administration (VA)—the largest provider of HCV care in the country—is more dire, suggesting that a mere 8% of patients meet the same criteria. Studies of interferon-free therapies were not included in the meta-analysis.

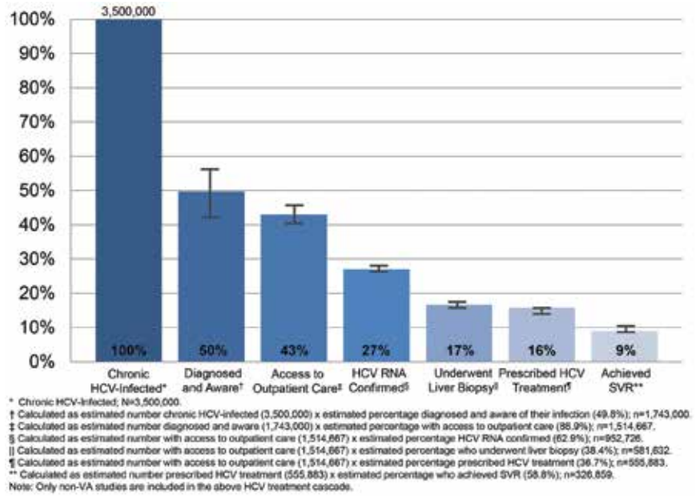
Less than 10% of HCV Patients Are Cured

Among treated patients, between 47% and 75% of patients achieved SVR, depending on genotype. In the overall pooled population, only 9% of patients with health insurance achieved SVR with antiviral treatment. This estimate is even lower—7%—in studies of HCV-infected Veterans.

The authors concluded that improved screening methods combined with new, emerging antiviral medications that have a shorter treatment duration and higher efficacy may increase the number of people given treatments and improve cure rates. Educating providers and the public about prevention and treatment, improving access to treatment providers, and addressing the expense of treatment are crucial to obtaining the most benefit from these new therapies, the authors noted.

Screening Baby Boomers May Improve Diagnosis Rates

The authors added that the 2012 Centers for Disease Control and Prevention recommendation for one-time HCV testing for people born between 1945 and 1965 (a group that encompasses an estimated three-fourths of all HCV infections) may improve the proportion of patients diagnosed and referred for HCV treatment.



* Chronic HCV-Infected; N=3,500,000.
† Calculated as estimated number chronic HCV-infected (3,500,000) x estimated percentage diagnosed and aware of their infection (49.8%); n=1,743,000.
‡ Calculated as estimated number diagnosed and aware (1,743,000) x estimated percentage with access to outpatient care (88.9%); n=1,514,667.
§ Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage HCV RNA confirmed (62.9%); n=952,726.
‖ Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage who underwent liver biopsy (38.4%); n=581,632.
¶ Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage prescribed HCV treatment (36.7%); n=555,883.
** Calculated as estimated number prescribed HCV treatment (555,883) x estimated percentage who achieved SVR (58.8%); n=326,859.
Note: Only non-VA studies are included in the above HCV treatment cascade.

Figure. Treatment Cascade for People with Chronic Hepatitis C Virus (HCV) Infection, Prevalence Estimates with 95% Confidence Intervals.

Reprinted with permission from Yehia BR, Schranz AJ, Umscheid CA, Lo Re V 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. *PLoS One*. 2014 Jul 2;9(7):e101554.

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Practitioners in the community manage patients individually using the best available tools of diagnosis and treatment. Health care planners, on the other hand, examine the overall impact of a given action or expenditure of resources on disease control. This timely systematic review by Yehia et al shows how primitive outcomes have been in reducing HCV disease burden to date and serves as a blueprint for measuring success in eradication of HCV throughout the next decade.

There are many distinguishable intersecting domains, referred to as a cascade, involved in optimal management of any disease. Key steps in this cascade for HCV include awareness of infection, access to health care, and being prescribed an effective antiviral therapy. Finally, real-world measurement of the success of therapy (absence of virus 12-24 weeks after treatment is ended [sustained virologic response]) is required. The review identifies and quantifies large gaps in all of these domains.

According to the authors, approximately 3.5 million people in the United States are infected with HCV. Only half of these people are aware that they are infected, most of whom have access to outpatient care. Only 16% of infected people have been offered treatment and, of these, 59% are estimated to have achieved durable viral elimination. Overall, only 9% of those with HCV were cured during the decade ending July 2013.

The study authors argue (unconvincingly in my view) that among the steps in the cascade is the need for liver biopsy for disease staging. Reliance on liver biopsy for staging constitutes a significant barrier to HCV eradication. It restricts management to a small group of specialists, carries with it some patient risk, and the importance of advanced fibrosis or cirrhosis for the individual is increasingly distinct from likelihood of HCV cure. Fortunately, as the authors point out, surrogate non-invasive means for estimating fibrosis are increasingly available and are rapidly replacing liver biopsy in HCV screening.

Age-cohort screening (one time testing of those born between 1945-1965 regardless of admitted risk behavior) is an important advance, as is highly effective all-oral therapy. Younossi et al recently demonstrated through an elegant Markov modeling analysis that birth cohort screening followed by treating all infected individuals (instead of restricting treatment to those with significant fibrosis) with all-oral regimens provides the maximum reduction in development of cirrhosis, hepatocellular carcinoma, and need for liver transplantation, as well as an increase in life expectancy compared to strategies that restrict treatment to those with advanced fibrosis.[1] Younossi et al concluded: "Availability of highly efficacious and well tolerated oral agents makes birth cohort screening of baby boomers highly cost-effective with great health and economic benefit at the population level."

Age-cohort screening is a necessary but clearly insufficient step when used alone in the HCV treatment cascade, as only 70% of those infected will be detected through this strategy. Over time, this age-cohort approach will miss an ever-higher proportion of those infected, especially nearly all of those newly infected. Health care providers must be educated to inquire about risk behavior and continue to test for HCV outside of the age cohort.

A key step in improved HCV eradication requires simplified assessment and treatment such that the bulk of infected patients do not need to see a gastroenterologist, hepatologist, or infectious disease specialist. Education programs directed to the non-specialist are needed to help them identify patients who can be safely treated without referral (eg, a 28-year-old former drug user with genotype 1 HCV and a viral load < 6 million IU/ml on no medications).

Great strides were made in 2014 in simplification of treatment (non-toxic all-oral therapy, some requiring a single pill daily for as little as 8 weeks). Unfortunately, prices for such treatment stretch the ability of individuals, insurers, and the community to pay, resulting in arbitrary non-evidence based rationing of care. Hopefully, the introduction of additional all-oral therapies in the months and years to come will lower the price barrier.

In summary, we should not be blinded by the startling improvement in cure rates afforded by current and pending all-oral therapies. Addressing gaps in all steps in the HCV eradication cascade needs to be accomplished before we can reach the goal of maximum reduction in disease burden in the United States.

"We should not be blinded by the startling improvement in cure rates afforded by current and pending all-oral therapies. Addressing gaps in all steps in the HCV eradication cascade needs to be accomplished before we can reach the goal of maximum reduction in disease burden in the United States."

—William D. Carey, MD

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Dr. Carey has no financial disclosures to report.

ABT-450 Triple-Drug Regimen Shows High Response Rates, Tolerability for HCV Genotype 1b Infection

Source: *Gastroenterology*

An interferon-free, investigational regimen containing 3 direct-acting antiviral treatments—ABT-450 plus ritonavir, ombitasvir, and dasabuvir—given with or without ribavirin showed high rates of sustained virologic response rates at 12 weeks post-treatment (SVR_{12}), as well as tolerability. Findings from this open-label, phase 3 clinical trial involving patients with hepatitis C virus (HCV) genotype 1b infection were reported by Andreone et al.[1]

In the international, multicenter study—known as PEARL-II, 179 patients with HCV genotype 1b from 43 sites in 10 countries were randomized to 12 weeks of treatment with coformulated ABT-450/ritonavir/ombitasvir/dasabuvir with (n=91) or without ribavirin (n=88). None of the patients had liver cirrhosis, and all previously failed treatment with peginterferon and ribavirin.

ABT-450 Regimens Not Inferior To Interferon Regimen

The SVR12 was 100% in the triple-therapy group without ribavirin and 96.6% in the triple-therapy group with ribavirin. No virologic failures were reported. Three patients in the ribavirin group did not achieve an SVR12; of those, 2 patients discontinued because of adverse events, and 1 patient was lost to follow-up. The rates of response in these groups were not inferior to those in a previously reported study involving a similar patient population treated with telaprevir, peginterferon, and ribavirin (SVR12, 64%).[2]

In a subgroup of difficult-to-treat patients who previously did not respond to peginterferon/ribavirin treatment, SVR12 rates were 93.5% and 100% in the groups treated with or without ribavirin, respectively.

Low Rates of Treatment Discontinuation Found

The most commonlyz reported adverse events in both regimen groups were fatigue (31.9% with ribavirin and 15.8% without ribavirin, respectively) and headache (24.2% and 23.2%, respectively). Two patients in the ribavirin-containing arm discontinued treatment because of adverse events, while none of the patients in the ribavirin-free arm did so.

Both groups showed a high rate of treatment-emergent adverse events (Table).[1] The triple-therapy regimen plus ribavirin group was significantly more likely to experience decreases in hemoglobin levels of less than the lower limit of normal compared to the triple-therapy group without ribavirin (42.0% vs. 5.5% in the regimen without ribavirin group; $P<0.001$). Two patients who had hemoglobin levels of <10 g/dL received ribavirin.

In addition, the patients treated with ribavirin were significantly more likely to experience significant increases in total bilirubin of greater than 2 times the upper limit of normal (15.4% vs 1.1% in patients treated without ribavirin; $P<0.001$).

New Drug Application Granted Priority Review

A New Drug Application for the triple antiviral regimen was submitted to the U.S. Food and Drug Administration (FDA) in April 2014 and granted priority review.[3] The regimen was given a Breakthrough Therapy designation by the FDA for treatment of HVC genotype 1. This study investigated patients with HVC genotype 1b only.

Table. Safety Data From Pearl-II[1]

Adverse Event	ABT-450 Regimen[a] Plus Ribavirin (n=91)	ABT-450 Regimen[a] Without Ribavirin (n=95)
Any treatment-related adverse event	72 (79.1%)	74 (77.9%)
Serious treatment-related adverse event	2 (2.2%)	2 (2.1%)
Adverse event-related discontinuation	2 (2.2%)	0
Hemaglobin level < lower limit of normal	37 (42.0)	5 (5.5%)
Total bilirubin level > 3 times upper limit of normal	8 (8.8%)	0

[a] Regimen involved ABT-450, ritonavir, ombitasvir, and dasabuvir

[b] N value without ribavirin reflects intent-to-treat population (95) rather than treatment group (88). Adverse events listed in table do not reflect all events and thus do not add up to 100%.

Data derived from Andreone P et al.[1]

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As 2014 comes to an end, it is apparent that we have the pharmaceutical tools to eradicate HCV infection. Introduction into the therapeutic armamentarium of highly effective direct-acting antiviral agents has been rapid, stunning, and breathtaking. On the cusp of approval by the U.S. Food and Drug Administration is a new therapy described in this important report. The HCV treatment cornucopia will soon provide an abundance of all-oral, low-side effect treatment options for HCV.

Hepatitis C virus is composed of 6 major genotypes, only 4 of which are seen with any degree of frequency in the United States (genotypes 1, 2, 3, 4). Genotype 1 HCV is further divided into 1a and 1b. Approximately 75% of HCV-infected individuals in the United States are infected with genotype 1 (two-thirds genotype 1a, one-third genotype 1b). Genotype 1b is the most commonly encountered genotype in Europe and Eastern Asia.[1] The current study was conducted outside of the United States and reports stunning treatment efficacy of an oral drug combination in a group of difficult-to-treat HCV-infected individuals who failed to respond, or relapsed, during or after previous therapy.

In the era of interferon-based therapy for HCV, many virus and host features were identified as resulting in a lower likelihood of a cure. Determinants portending treatment failure included genotype 1 HCV; non-response, partial-response, or relapse to a previous course of interferon-based therapy; African American race; interleukin 28B (IL28B) CT or TT genotypes; and the presence of cirrhosis. Patients co-infected with genotype 1 or 4 HCV and HIV also have been harder to treat successfully.[2]

> *"The HCV treatment cornucopia will soon provide an abundance of all-oral, low-side effect treatment options for HCV."*
>
> —William D. Carey, MD

Although the drug regimen described in this study sounds complicated, it is not. Patients were required to take 2 pills in the morning and one pill in the evening for 12 weeks. The first pill is a combination of 3 compounds—a nonstructural (NS) protein 3/4A (NS3/4A) protease inhibitor, ritonavir in order to increase peak and trough ABT-450 blood levels, and the NS5A inhibitor ombitasvir. A second pill, dasabuvir, is administered twice daily. This combination is sometimes referred to as the 3D regimen. The study compared this 2-pill combination with or without ribavirin pills in a 12-week trial and a 48-week follow-up period.

Key findings of the trial included a cure rate of 97% to 100%. There was no advantage to receiving ribavirin. Indeed, the distinguishing features of the group receiving ribavirin included a moderate increase in cost and an increase in side effects, especially a reduction in hemoglobin levels and an increase in serum indirect-reacting bilirubin levels. The remainder of this commentary will address the implications of the results in the group who received the 2-pill (3D) regimen.

The 3D treatment success rate of 100% in a group of individuals who had failed previous therapy is remarkable. Moreover, the uniform success in blacks, those with unfavorable IL28B genotypes, and in genotype 1b suggests the transcendent power of this regimen. A major unfavorable risk factor excluded from this study was cirrhosis. However, other studies reveal that cirrhosis is only a minor barrier to the success of a 12- or 24-week course of 3D together with ribavirin for genotype 1b HCV.[3]

Overall, 99% of cirrhotics were cured after 12 weeks of treatment, and 100% were virus-free after 24 weeks. The success rate was slightly lower for those with genotype 1a (89% cure rate for 12 weeks of treatment and 94% for 24 weeks). The 3D regimen with ribavirin also has shown a greater than 90% HCV cure rate in those co-infected with HIV.[4]

We welcome the growing number of easy treatment options for HCV. Given alone for genotype 1b or with ribavirin for those with genotype 1a, cirrhosis, or HIV co-infection, 3D treatment will quickly become a pillar of treatment.

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Dr. Carey has no financial disclosures to report.

Ledipasvir–Sofosbuvir Once Daily Shows High SVR In Patients Unresponsive to Interferon-Based Therapy

Source: *New England Journal of Medicine*

Treatment with the once-daily, fixed-dose combination of ledipasvir-sofosbuvir with and without ribavirin resulted in high rates of sustained virologic response (SVR; 94% to 99%) in patients with genotype 1 chronic hepatitis C virus (HCV) infection who had not achieved an SVR to previous interferon-based treatment.

Findings from this phase 3 trial, conducted by Afdhal et al[1] and the ION-2 investigators, contributed to approval of this treatment by the U.S. Food and Drug Administration in October 2014.

Difficult-to-Treat Population

The study involved 440 patients from 64 sites in the United States with HCV genotype 1 infection who had no response or experienced a relapse or virologic breakthrough after prior treatment with peginterferon and ribavirin with or without a protease inhibitor—a population that historically has been difficult to treat. Most of the patients (79%) had genotype 1a infection, and 20% had liver cirrhosis.

The patients were randomized to 1 of 4 treatment arms:

- ledipasvir-sofosbuvir for 12 weeks
- ledipasvir-sofosbuvir plus ribavirin for 12 weeks
- ledipasvir-sofosbuvir for 24 weeks
- ledipasvir-sofosbuvir plus ribavirin for 24 weeks

All patients received the single-tablet, once-daily oral combination containing 90 mg of the nonstructural protein 5A (NS5A) inhibitor ledipasvir and 400 mg of the nucleotide analogue polymerase inhibitor sofosbuvir. Patients who received ribavirin took the additional medication twice daily, with doses determined by body weight. The primary outcome was SVR at 12 weeks post-treatment (SVR_{12}).

High Response Rate Found

The 12-week treatment groups showed an SVR_{12} of 94% to 96%, while the 24-week treatment groups showed an SVR_{12} of 99% (Table).[1] The response rates were similar among patients with genotype 1a and 1b infection, those previously treated with peginterferon plus ribavirin with or without a protease inhibitor, patients with no response to prior treatment, and among patients with relapse or virologic breakthrough on previous therapy. All of the patients who achieved an SVR_{12} maintained treatment response at 24 weeks follow-up.

> *The 12-week treatment groups showed an SVR_{12} of 94% to 96%, while the 24-week treatment groups showed an SVR_{12} of 99%.*

In the 12-week treatment groups only, patients with cirrhosis had lower rates of treatment response (82%-86%) than patients without cirrhosis (95%-100%). The researchers examined this preliminary finding further and found that cirrhosis status was unrelated to early treatment and outcome. The authors were unable to identify baseline predictive factors among cirrhosis patients that might indicate relapse after 12 weeks of treatment.

Table. Treatment Response Rates at 12 Weeks

Treatment Arm	SVR_{12} Rate
Ledipasvir-sofosbuvir for 12 weeks (n=109)	94%
Ledipasvir-sofosbuvir plus ribavirin for 12 weeks (n=111)	96%
Ledipasvir-sofosbuvir for 24 weeks (n=109)	99%
Ledipasvir-sofosbuvir plus ribavirin for 24 weeks (n=111)	99%

SVR_{12}, sustained virologic response at 12 weeks post-treatment

Data derived from Afdhal et al.[1]

Ribavirin Linked to High Rates Of Adverse Events

Adverse events were common in all of the groups (67%-90%), although only patients in the 24-week arms experienced serious events. The most common adverse events included fatigue, headache, and nausea. None of the patients discontinued treatment because of an adverse event.

As expected, patients who received the regimens containing ribavirin had higher rates of adverse events known to be associated with ribavirin—including fatigue, nausea, insomnia, arthralgia, cough, rash, irritability, dyspnea, and anemia—than patients who received ledipasvir-sofosbuvir alone.

Serious treatment-emergent adverse events occurred in 9 patients (2% of the overall group)—6 patients (6%) who received ledipasvir-sofosbuvir for 24 weeks and 3 patients (3%) who received ledipasvir-sofosbuvir plus ribavirin for 24 weeks. These events included one case each of acute cholecystitis, convulsions, hepatic encephalopathy, intervertebral disk protrusion, noncardiac chest pain, spondylolisthesis, upper gastrointestinal hemorrhage, unstable angina, and wound infection.

One patient experienced on-treatment virologic failure, and 5% of patients taking ledipasvir-sofosbuvir plus ribavirin had decreases in hemoglobin of <10 g/dL.

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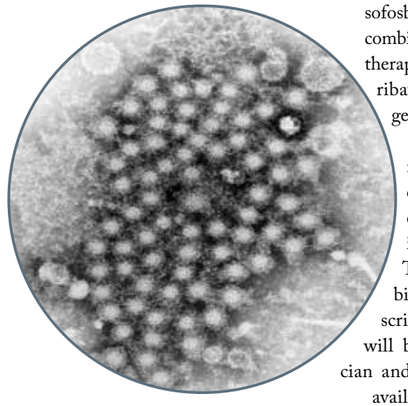
This study by Afdhal and colleagues adds to the body of data showing that the single-tablet combination of ledipasvir and sofosbuvir offers an excellent treatment option for a wide variety of patients with HCV infection. This is the only study of ledipasvir-sofosbuvir that includes patients who failed interferon-based triple therapy with a protease inhibitor, which was the previous standard of care.

> *"Clinicians will now have numerous interferon-free combination regimens to choose from when treating patients with HCV."*
>
> —Robert S. Brown, Jr., MD, MPH

These findings also reveal that the majority of previously treated patients only need to take the regimen for 12 weeks, and could be treated without using ribavirin. Overall, the differences in SVR rates between genotype subgroups and treatment length were not statistically significant.

At the current time, ledipasvir in combination with sofosbuvir is the only available, FDA-approved single tablet. Sofosbuvir is available separately, or can be combined with simeprevir. Simeprevir was approved by the U.S. FDA in November 2014 to be taken in combination with sofosbuvir as an interferon-free combination (or in combination therapy with peginterferon and ribavirin) for patients with genotype 1 HCV.



Transmission electron micrograph shows numerous hepatitis virions.

Image courtesy of CDC/ E.H. Cook, Jr.

Clinicians will now have numerous interferon-free combination regimens to choose from when treating patients with HCV. The choice of which combination regimen to prescribe may not be simple; it will be determined by clinician and patient preference, the available data relevant to the patient being treated, and, obviously, insurance coverage and pricing.

Specifically, clinicians may choose different regimens based on the presence or absence of cirrhosis, prior treatment regimens, and, possibly, genotype subtype. For example, HCV genotype 1b responds better to protease inhibitors, while genotype 1a may respond better to NS5A inhibitors.

One subgroup that benefited from 24 weeks of treatment in this study was cirrhosis patients who failed prior therapy. However, for several reasons, it is better to treat patients with 12 weeks of therapy, if possible. Taking therapy for 24 weeks increases cost, the chance of adverse events, the possibility that therapy may be interrupted, and lowers the chance of compliance.

> *"Regardless of which interferon-free regimen and length of treatment is prescribed, it is a significant advantage for clinicians to have more rather than fewer choices when treating patients with HCV."*
>
> —Robert S. Brown, Jr., MD, MPH

Regardless of which interferon-free regimen and length of treatment is prescribed, it is a significant advantage for clinicians to have more rather than fewer choices when treating patients with HCV. In all studies of the new, interferon-free therapies reviewed in this issue of *Essential Reading in Hepatitis*, it is clear that the efficacy bar is now set very high, with SVR rates of greater than 90% to 95% in virtually all subgroups studied.

Dr. Brown disclosed financial relationships with Abbvie, Gilead Sciences, Janssen Pharmaceuticals, and Merck.

Stigmatization is Common in Patients With Liver Cirrhosis, Linked to Worse Outcomes

Source: *Digestive Diseases and Sciences*

Physicians should be aware of how commonly patients with cirrhosis feel stigmatized, and should address stigma when discussing the disease and treatment course with patients.

The vast majority of patients with cirrhosis feel stigmatized, a perception that is linked to numerous negative consequences including depression, decreased tendency to seek medical care and worsened quality of life, according to a study conducted by Vaughn-Sandler et al.[1]

Study findings are based on survey responses from 149 patients with cirrhosis from a variety of causes: hepatitis C/hepatitis B infection (34.2%), fatty liver disease (28.2%), alcoholism (12.1%), and other causes (25.5%). Participants were enrolled in the Cirrhosis Program at the University of Michigan and had a mean age of 58 years. The majority of respondents were white (92%) and nearly half were male (49%).

Participants were surveyed on 4 domains of stigmatization: stereotypes, discrimination, shame, and social isolation. The questions were taken from previously validated surveys as well as one statement created by the authors that asked, "Some people assume that because I have liver disease, I must have been a drinker." Respondents were asked to select the most appropriate answer on a 4-point Likert scale.

Nearly 90% of Patients Feel Stigmatized

Overall, 89% of respondents agreed or strongly agreed with at least one of the stigma-related statements. The most commonly reported perceived stigmas are shown in the Table.[1] The mean stigma score based on the 4-point scale was 2.04.

The following factors were significantly associated with greater perceived stigma: younger age (P=0.008), hepatitis C (P=0.001) or alcohol (P=0.01) as the etiology of liver disease, and less social support (P<0.001). While only 12.1% of respondents were diagnosed with alcoholic cirrhosis, 59.9% of patients reported that they had been assumed to be alcoholics because of their cirrhosis.

Greater Stigma Linked To Avoiding Medical Care

Higher levels of perceived stigma also were associated with negative consequences and poorer outcomes, including being less likely to seek medical care (P<0.001) and depression (P<0.001), which, in turn, was associated with worse quality of life (P<0.001). A trend toward being less adherent to medication also was found among patients with greater perceived stigma (P=0.06). In fact, 22% of patients said they avoided seeking medical care for fear of being judged.

The authors concluded that physicians should be aware of how commonly patients with cirrhosis feel stigmatized, and should address this stigma when discussing the disease and treatment course with patients. Furthermore, the authors speculated that stigma in the general public could influence the amount of money given to fund research for cirrhosis and support for public programs.

Table. Most Common Stigmas Reported by Patients With Cirrhosis (N=149)

Perceived Stigma	Percentage
Some people assume that because I have liver disease, I must have been a drinker	82%
I avoid telling other people about my liver disease	75%
Other people think I am partially to blame for my liver disease	72%
I feel like I am partially to blame for my liver disease	72%
I feel less competent that I did before I was diagnosed with liver disease	72%

Data derived from Vaughn-Sandler et al.[1]

Reference

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A patient recently told me that her daughter would not let her have contact with her grandchildren for fear that her HCV might be transmitted. Most of the people I have talked to who have undergone treatment feel this way.

The consequences of disease go beyond the effects of perturbations of disordered physiology. Diseases and their manifestations occur in a social context including family, workplace, and the community. Social isolation, shame, and discrimination may be a consequence of disease, some more than others.

Diminished quality of life in patients with liver disease and cirrhosis has been previously demonstrated.[1] In addition, liver-specific quality of life measurement tools have been described and validated.[2] However, the literature is impoverished on the impact of perceived social stigmatization in patients with cirrhosis. Liver disease is amongst the least understood diseases by the community and one of the more stigmatizing. This may derive from the notion that only socially proscribed behavior (alcohol abuse, use of "dirty" needles, and/or sexual promiscuity leading to hepatitis B or HCV infection) results in cirrhosis. Social isolation can be a particularly demoralizing aspect of chronic liver disease and cirrhosis.

The study by Vaughn-Sandler et al explores the degree to which individuals with cirrhosis perceive themselves to be stigmatized by their condition by employing adaptations of standardized questions from other validated question sets. While these questionnaires seem plausible, they need to be externally validated. Perhaps as important, no comparator is used in this study (eg, what might the differences be in responses in individuals with heart disease, etc).

With these caveats, interesting observations are made. Most important, nearly 9 out of 10 cirrhotics responding to the survey felt stigmatized in one or more domains. Those who developed cirrhosis from alcohol or viral hepatitis felt most stigmatized. The impact of stigmatization goes beyond the individual decrement of self-worth. It may lead, as well, to decreased interaction with the health profession and delay in diagnosis and/or application of effective therapy. Indeed, 22% of patients stated that they avoided seeking medical care for fear of being judged.

It is incumbent upon health care providers to avoid attitudes, behaviors, and body language that may be interpreted as opprobrium. How best to accomplish this depends on the circumstances. I try to be forward-looking and focus on management of existing medical problems rather than delving on their origins. This can be challenging in the event that risky behavior continues and its modification is required as part of medical management. Judicious use of humor sometimes helps.

Providing a patient with the opportunity to discuss feelings of stigmatization are easy to accomplish and may go a long way to ameliorating loss of self-esteem. At the very least, it identifies the health care provider as an empathetic therapeutic partner. Open-ended questions such as "Do you worry about what others think of your condition?" may serve to get the conversation going.

Better public information will likely decrease stigmatization. For example, a generation ago, public discussion about breast cancer, colon cancer, and erectile dysfunction was taboo. Conversations between those affected by these disorders and their health care providers are considerably easier now than in years past. As advertising ramps up for highly effective HCV therapy, expect a similar lowering of barriers. Hopefully, this will be accompanied by less perceived stigmatization.

The authors wonder if biases against certain diseases may have a harmful effect on research funding. Evidence to support this is hard to find. Cumulative National Institutes of Health research categorical spending projected for 2015 is nearly the same for liver diseases ($1.4 billion) as for heart diseases ($1.6 billion).[3]

Finally, the current study suggests topics for additional research. I would like to know the answers to the following questions: Is the sense of stigmatization a feature of the conditions that led to cirrhosis (eg, alcohol abuse, at-risk behavior) rather than cirrhosis? Has society's hierarchy of disease prestige changed in the 3 decades since publication of the Album et al study cited by Vaughn-Sandler?[4] Are there racial, gender, religious, and cultural differences in perceived stigmatization (95% in the current study were white)?

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Dr. Carey has no financial disclosures to report.

Interferon-Free Regimens Found More Cost Effective Than Standard Treatment for HCV Infection

Source: *Journal of Hepatology*

Interferon (IFN)-free regimens to treat hepatitis C virus (HCV) infection were found to be more cost effective, increase life expectancy, and reduce the risk for developing advanced liver disease when compared with IFN-based treatment, according to Younossi et al.[1] The data, derived from a decision analytic Markov model developed by the authors, suggest that treating all patients with IFN-free regimens is more effective than making treatment decisions based on stage of liver disease.

Treating all HCV genotype 1 patients with an interferon-free regimen was determined to be the most cost-effective strategy.

The model simulated patients from time of treatment decision until death and compared the following 12-week treatment strategies in patients with HCV genotype 1:

- Triple therapy (pegylated-IFN-α, ribavirin, and a direct-acting antiviral agent) with staging guidance
- Triple therapy for all patients
- IFN-free regimen with staging guidance
- IFN-free regimen for all patients

The IFN-free regimen was based on pooled results of clinical trials involving the following 12-week oral regimens: 1) ABT-450 plus ritonavir, ombitasvir, dasabuvir, and ribavirin; 2) daclatasvir, asunaprevir, and BMS-791325; and 3) sofosbuvir plus ribavirin. The cost of the IFN-free regimen was unavailable when this study was published because the treatments were not yet approved by the U.S. Food and Drug Administration. Thus, the authors set the average total treatment cost for IFN-free regimens to be equal to the average total treatment cost of triple therapy ($5,800 per week).

The staging-driven treatment strategies initiated treatment at fibrosis stages F2 to F4, with staging repeated every 5 years for patients less than 70 years of age. A treatment-naïve patient aged 50 years was used as the reference case.

Interferon-Free Regimen For All Patients Deemed Most Effective

Treating all HCV genotype 1 patients with an IFN-free regimen was determined to be the most cost-effective strategy, with an incremental cost-effectiveness ratio of $15,709 per quality-adjusted life years (Table).[1] Both of the triple therapy strategies had higher costs, lower effectiveness, and poorer outcomes (ie, lower life expectancy and greater progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma, and liver transplantation) than the IFN-free regimens (Table). [1]

When the authors considered a scenario in which the baseline costs were increased by 50% (to $8,700 per week), triple therapy with staging-guidance was the least costly option, but the IFN-free regimens remained more cost-effective because of superior outcomes. Furthermore, a sensitivity analysis showed that treating all HCV genotype 1 patients with an IFN-free regimen remained the most cost-effective strategy, even after eliminating the cost of liver disease.

The authors noted that the efficacy and safety of these regimens must be confirmed in randomized, clinical trials.

Reference

1. Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. *J Hepatol*. 2014;60(3):530-537.

Table. Cost and Efficacy of Interferon-Based Versus Interferon-Free Regimens for Treatment of Hepatitis C Virus Genotype 1 Infection

Treatment Regimen	Cost	Effectiveness (QALY)	Life Expectancy (years)	Cirrhosis (%)	Decompensated Liver Disease or HCC (%)	Liver Transplant (%)
IFN-free regimen for all patients	$90,681	18.391	29.978	6.5	10.9	2.7
IFN-free regimen with staging guidance	$77,133	17.529	29.827	10.6	12.7	3.1
Triple therapy with staging guidance	$93,981	16.386	28.324	29.4	24.2	5.2
Triple therapy for all patients	$106,554	17.201	28.520	23.6	21.3	4.6

HCC, hepatocellular carcinoma; **IFN,** interferon; **QALY,** quality-adjusted life years

Data derived from Younossi et al.[1]

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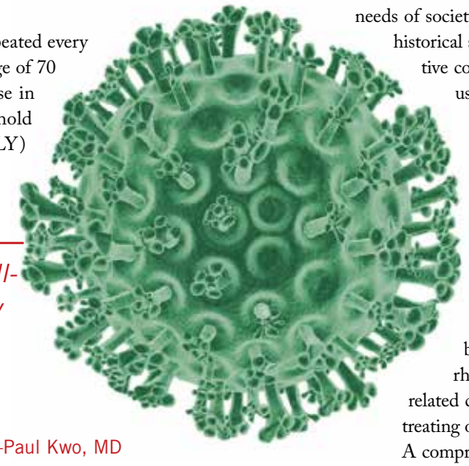
This paper by Younossi and colleagues used a decision analytic Markov model to assess the efficacy and cost of a variety of strategies for treating HCV in genotype 1 individuals. The authors compared the cost of IFN-based and IFN-free therapy, either with staging, or treating everyone with IFN-free medications regardless of their stage of disease.

"Treating mild disease will reduce the pool of hepatitis C-infected individuals in the United States and worldwide, which can potentially lead to eradication of this blood-born disease."

—Paul Kwo, MD

In the staging groups, patients with mild fibrosis were not treated; only those with moderate to advanced fibrosis (F2-4) received treatment. The analysis was repeated every 5 years until the patients reached the age of 70 years. Analysis included a 50% decrease in the cost of all-oral therapy. The threshold used in quality-adjusted life years (QALY) studies typically has been $50,000 per QALY, based on the cost of dialysis.



"These data suggest that all-oral, interferon-free therapy regardless of fibrosis stage may be the most effective treatment strategy."

—Paul Kwo, MD

The cost of all-oral therapy without staging ($90,681) was lower than IFN-based therapy with staging ($93,981) and without ($106,554), but higher than an all-oral staging strategy where only advanced fibrosis individuals were treated. The most effective treatment strategy as determined by the decision analytic Markov model turned out to be treating all genotype 1 patients with IFN-free therapy, with a value of 18.391 QALYs. The other treatment groups had lower QALY values. The incremental cost analysis demonstrated that the strategy of treating all patients had the highest incremental cost-effectiveness ratio. These data suggest that all-oral, IFN-free therapy regardless of fibrosis stage may be the most effective treatment strategy.

As we replace IFN-based treatments with the new all-oral, IFN-free therapies, we need to make every effort to achieve sustained virologic response rates in the real world that are comparable to what we have seen in clinical trials.

As we move to eradicate HCV worldwide, we have to look at the needs of society as a whole. These therapies are costly but, by historical standards, are less expensive and far more effective compared with the IFN-based therapies we have used previously.

A strategic and successful approach to HCV treatment should lead to markedly reduced deaths by preventing HCV-related cirrhosis and cancer, as well as reducing the number of liver transplants required for hepatitis C-related cirrhosis. Treating mild disease will reduce the pool of hepatitis C-infected individuals in the United States and worldwide, which can potentially lead to eradication of this blood-born disease. If we have fewer cases of cirrhosis and cancer, we will spend less on HCV-related complications, and can allocate our resources to treating other diseases.

A comprehensive treatment strategy is the only way are going to eradiate chronic hepatitis C in the United States and other countries. By using more effective screening strategies, including screening those born between 1945 and 1965, we can identify new cases of HCV infection and offer therapy to these individuals.

Dr. Kwo has received consulting fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen, and Merck; he has received funds for research support from Abbvie, Bristol-Myers Squibb, Conatus, Gilead Sciences, Janssen, Merck, and Roche.w

ABT-450 Triple-Drug Regimen Linked to High Cure Rates In HCV Patients With Cirrhosis

Source: *New England Journal of Medicine*

Twelve-week treatment with the interferon-free regimen of ABT-450/ritonavir, ombitasvir, and dasabuvir plus ribavirin was linked to sustained virologic response (SVR) rates of more than 90% in patients with hepatitis C virus (HCV) genotype 1 infection and compensated cirrhosis, according to an open-label, phase 3 trial by Poordad et al.[1]

A total of 380 patients with Child–Pugh class A cirrhosis were randomized to either 12 or 24 weeks of treatment with ABT-450/r–ombitasvir (ABT-450 150 mg, ritonavir 100 mg, and ombitasvir 25 mg once daily), dasabuvir (250 mg twice daily), and ribavirin administered according to body weight. The primary efficacy endpoint was SVR at 12 weeks following treatment cessation.

The study included patients with thrombocytopenia, hypoalbuminemia, or major depression—conditions that historically are part of exclusion criteria for clinical trials, according to the study authors. Patients previously treated with peginterferon–ribavirin also were included.

At 12 weeks after the last treatment dose, SVR rates were 91.8% among patients treated for 12 weeks, and 95.9% among patients treated for 24 weeks. The between-group difference in SVR rate was not statistically significant.

In subgroup analysis, a clinically meaningful difference in SVR rate was found among patients with HCV genotype 1a infection, cirrhosis, and a null response to prior peginterferon–ribavirin treatment who were treated for 24 weeks compared to those treated for 12 weeks (92.9% vs. 80.0%; Figure).[1] While this difference was not statistically significant, the authors noted that the numeric difference in SVR suggests that longer treatment duration may be more effective in this subgroup of patients.

The relapse rate following treatment was significantly greater in the 12-week group than in the 24-week group (5.9% vs. 0.6%; $P<0.05$). More than half of the relapsers in the 12-week group (58.3%) had HCV genotype 1a infection, cirrhosis, and a null response to previous peginterferon-ribavirin treatment.

Triple-Drug Regimen Was Superior and Noninferior

The SVR rates at 12 and 24 weeks after treatment met prespecified criteria for noninferiority and superiority compared to a previously reported SVR rate of 47% with telaprevir plus peginterferon–ribavirin treatment in patients with HCV genotype 1 infection and cirrhosis. Treatment superiority with the regimens was found among subgroups defined by HCV genotype, prior treatment status, and type of treatment failure (ie, relapse, partial response, null response) among previously treated patients.

Low Rate of Treatment Discontinuation Found

The 3 most common adverse events were fatigue (32.7% in the 12-week group and 46.5% in the 24-week group; $P<0.01$), headache (27.9% and 30.8%, respectively), and nausea (17.8% and 20.3%, respectively). Serious adverse events occurred in 6.2% and 4.7% of the respective groups, which led 8 patients (2.1%; 4 in each treatment group) to discontinue treatment.

Decline in hemoglobin levels to <10 g/dL occurred in 7.2% and 11.0% of the 12-week and 24-week groups, respectively. These declines were managed by reducing the ribavirin dose, with no alteration in SVR rate found.

Grade 3 or 4 increases in total bilirubin level occurred in 13.5% and 5.2% of the 12- and 24-week groups, respectively ($P<0.01$). These elevations peaked at week 2 of treatment, were not linked to treatment discontinuation, and were not linked to alterations in aminotransferase levels. In addition, grade 3 or 4 increases in alanine aminotransferase level occurred in 6 patients in the 12-week group (2.9%) compared with none of the patients in the 24-week group ($P<0.05$). Two of these patients withdrew from the trial early—one because of acute hepatitis that was determined to be the cause of the increased alanine aminotransferase level, and one who developed the elevation after discontinuing the treatment. The increases in both bilirubin and alanine aminotransferase levels were transient.

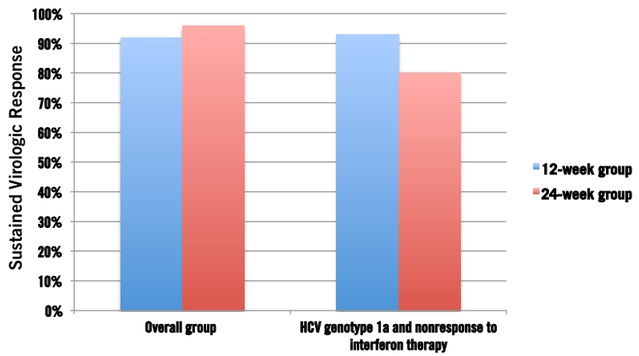


Figure. Sustained virologic response to ABT-450/ritonavir, ombitasvir, and dasabuvir plus ribavirin in the overall group of patients with genotype 1 HCV and cirrhosis, and in a subgroup with HCV genotype 1a and previous nonresponse to peginterferon-ribavirin treatment.

Data extracted from Poordad et al.[1]

Reference

1. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med.* 2014;370(21):1973-1982.

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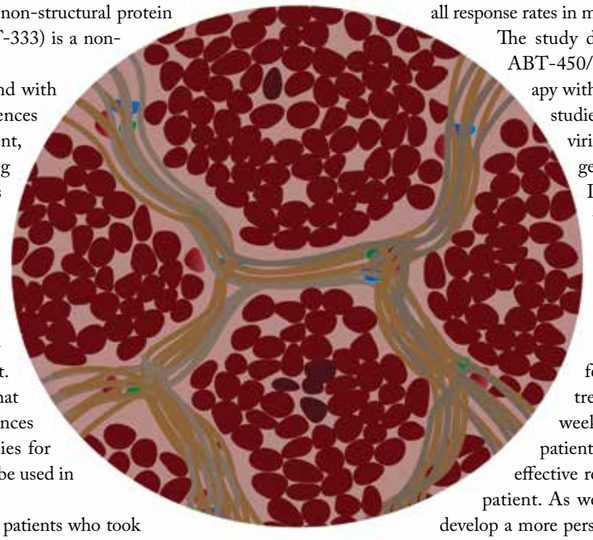
A recent study in the *New England Journal of Medicine* found that the new interferon (IFN)-free triple therapy regimen ABT-450/r-ombitasvir-dasabuvir with ribavirin was highly effective in treating patients with HCV genotype 1 who had compensated cirrhosis, or liver scarring. The open-label, phase 3 trial involved untreated and previously treated patients.

It is known that cirrhosis is difficult to treat. Researchers sought to examine the necessity of longer therapy duration (ie, 24 weeks) and whether the length of treatment was dependent on response to prior treatment. Patients with cirrhosis, regardless of prior treatment response, were randomized to 12 or 24 weeks of this 3-drug combination with ribavirin. Each of the IFN-free drugs act by inhibiting different proteins: paritaprevir, or ABT-450 with ritonavir (ABT-450/r), is a protease inhibitor, while ombitasvir (ABT-267) is a non-structural protein 5A inhibitor, and dasabuvir (ABT-333) is a non-nucleoside polymerase inhibitor.



This study is the first of its kind with adequate power to detect differences in treatment response to this potent, oral, triple-therapy regimen among patients with HCV and cirrhosis versus HCV patients without cirrhosis. The overall SVR rate was excellent.

The drugs were safe and well tolerated. Less than 2% of patients stopped therapy, and serious adverse events were infrequent. The findings clearly demonstrate that these new drugs offer huge advances over the prior IFN-based therapies for HCV with cirrhosis and they can be used in the majority of patients.

A higher SVR rate was seen in patients who took the regimen for 24 weeks versus 12 weeks, but the difference was not statistically significant. More importantly, only genotype 1a patients with cirrhosis who were prior nonresponders to treatment with IFN and ribavirin had improved SVR rates after 24 weeks compared with 12 weeks of treatment. This finding identifies a subgroup that may benefit from 24 weeks of treatment. The results also show that patients who have HCV genotype 1a, were prior null responders to IFN, or are former injection drug users had lower overall response rates in multivariable analyses.

> *"The findings clearly demonstrate that these new drugs offer huge advances over the prior interferon-based therapies for HCV with cirrhosis and they can be used in the majority of patients."*
>
> —Robert S. Brown, Jr., MD, MPH

The study did not look at the efficacy of the ABT-450/r–ombitasvir-dasabuvir triple therapy without ribavirin. However, other recent studies of this triple therapy without ribavirin show that that ribavirin is no longer necessary in easy-to-treat patients.[1] In some patient groups, such as those with advanced liver disease, ribavirin may still prove helpful.

Cost effectiveness is also a factor to consider in the continued use of ribavirin. Ribavirin is less expensive, and it may allow patients to take fewer drugs. If we use ribavirin, and treat using fewer drugs or for fewer weeks, we would be able to treat more patients. Our goal is to find the most cost-effective regimens that allow us to treat every patient. As we evolve as a medical field, we will develop a more personalized approach in which we find the most cost-effective regimens. Some of them may be ribavirin-free, but that remains to be seen.

Reference

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Dr. Brown disclosed financial relationships with Abbvie, Gilead Sciences, Janssen Pharmaceuticals, and Merck.

Sofosbuvir Plus Ribavirin Shows High Response Rates In Patients Coinfected With HCV and HIV

Source: *Journal of the American Medical Association*

Patients with comorbid hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infection who received combination treatment with sofosbuvir plus ribavirin had high rates of sustained HCV virologic response at 12 weeks (SVR_{12}) after cessation of therapy, according to an open-label, phase 3 study by Sulkowski et al.[1]

Coinfection with HCV and HIV affects up to 7 million people worldwide, and is associated with an increased risk for liver fibrosis, cirrhosis, hepatocellular carcinoma, and mortality, according to the study background. Treatment of HCV in patients with comorbid HIV infection has been limited due to a variety of factors including drug interactions between HCV and antiretroviral drugs, and because many coinfected patients are not eligible to take interferon-based therapies due to contraindications, the study authors noted.

Sofosbuvir Does Not Interact With Antiretroviral Agents

Sofosbuvir is an oral nucleotide analog HCV NS5B polymerase inhibitor recently approved for the treatment of HCV genotypes 1 through 4, including patients with HIV-1 coinfection. Sofosbuvir is not metabolized by the cytochrome P450 system of enzymes and, thus, does not interact with a range of antiretroviral agents.

This study involved 223 patients infected with HIV and HCV (genotypes 1, 2, or 3) infection who were given combination treatment with 400 mg of sofosbuvir and weight-based ribavirin for either 12 weeks (for treatment-naïve patients with genotype 2 or 3) or 24 weeks (for treatment-naïve patents with genotype 1, and treatment-experienced patents with genotype 2 or 3). Overall, 22 patients had cirrhosis. The trial was conducted at 34 treatment centers in the United States and Puerto Rico.

The primary outcome—SVR_{12}—was achieved in 67% to 88% of treatment-naïve and 92% to 94% of treatment-experienced patients with HCV and HIV.

Treatment-Experienced Patients Have Greater Response Rates

The primary outcome—SVR_{12}—was achieved in 67% to 88% of treatment-naïve and 92% to 94% of treatment-experienced patients (Table, page 25). Higher SVR_{12} rates were found with 24 weeks versus 12 weeks of treatment for patients with HCV genotype 3 (94% and 67%, respectively). In contrast, patients with HCV genotype 2 showed high response rates with both treatment durations and regardless of whether they were treatment-naïve or -experienced (Table, page 25).[1]

No adverse effect on HIV disease or its treatment was observed. Among the subgroup of patients not taking antiretrovirals during this study (n=11), no HIV-specific antiviral effects of sofosbuvir plus ribavirin were found. Two patients taking antiretrovirals during the study experienced HIV virologic rebound; however, one patient had a history of poor adherence to antiretroviral therapy, and the other patient showed resuppression of HIV RNA without any changes made to the antiretroviral therapy, the study authors reported.

The most commonly reported side effects in all groups were fatigue (38%), insomnia (17%), nausea (16%), and headache (13%). A total of 14 patients (6%) experienced serious adverse events, and 7 patients (3%) discontinued treatment because of an adverse event, with no between-group differences in these incidences found.

Decreases in hemoglobin to <10 mg/dL occurred in a total of 32 patients (14%)—21 treatment-naïve patients with HCV genotype 1 (18.4%), 8 treatment-naïve patients with genotype 2 or 3 (11.8%), and 3 treatment-experienced patients with genotype 2 or 3 (7.3%). An additional 3 treatment-naïve patients—2 in genotype 1 (1.8%) and 1 in genotype 2 and 3 (1.5%)—had decreases in hemoglobin to <8 mg/dL.

Increases in total bilirubin levels of >3.0 mg/dL occurred in 32 patients (14%). Most of these patients (30 of 32; 94%) were taking ritonavir-boosted atazanavir as part of their antiretroviral regimen; 4 of these patients elected to switch from atazanavir to darunavir because of increased bilirubin levels. All of the patients experienced a return to baseline bilirubin levels by week 12 after treatment cessation.

Reference

1. Sulkowski MS, Naggie S, Lalezari J, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA*. 2014;312(4):353-361.

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Treatment options have been limited for patients infected with both HCV and HIV due to drug interactions with antiretroviral therapies and the toxic effects of interferon. For these reasons, the new interferon (IFN)-free therapies offer unprecedented hope for improved treatment in this co-infected population.

In an important new study, treatment-naïve patients with HIV and HCV genotypes 2 or 3 received the oral, IFN-free combination of sofosbuvir and ribavirin for 12 weeks. Treatment-naïve coinfected patients with genotype 1, and treatment-experienced coinfected patients with genotypes 2 or 3 received the same treatment for 24 weeks.

This study by Sulkowski and colleagues is significant because it shows that coinfected individuals on a wide variety of antiretroviral therapies can take sofosbuvir without difficulty. Sofosbuvir plus ribavirin was well tolerated because the drug-drug interaction profile of sofosbuvir is very favorable. Sofosbuvir is a polymerase inhibitor, so it does not interact with antiretroviral therapies.

Moreover, the study enrolled a large number of individuals with additional comorbidities, including psychiatric illness, autoimmune disorders, seizure disorders, and diabetes. These patients, who were historically excluded from studies of new therapies, could be enrolled and treated because sofosbuvir is well-tolerated. The ability to eliminate IFN from the treatment regimen in this special population allows a large variety of coinfected patients to be treated.

This study also shows that high SVR rates can be achieved in coinfected patients when IFN is removed. The SVR rates in these patients were similar compared to those in other studies using sofosbuvir and ribavirin.

Also interesting, traditional predictors of SVR response did not hold up in this study against previously reported predictors of response in coinfected patients. The greatest predictor of SVR in this study was treatment completion. In this study, the efficacy of sofosbuvir and ribavirin in coinfected patients begins to break down the barriers of previously reported predictors of poor response. Based partly on these results, we should no longer consider HIV to be a special population. We can treat HCV patients with HIV as effectively as HCV patients without HIV.

"This study ... is significant because it shows that coinfected individuals on a wide variety of antiretroviral therapies can take sofosbuvir without difficulty."

—Paul Kwo, MD

Table. Sustained Virologic Response at 12 Weeks Following Treatment With Sofosbuvir plus Ribavirin in Patients with HCV and HIV

	Treatment Naïve			Treatment Experienced	
Outcomes	Genotype 1 (n=114)	Genotype 2 (n=26)	Genotype 3 (n=42)	Genotype 2 (n=24)	Genotype 3 (n=17)
SVR_{12}	87/114 (76%)	23/26 (88%)	28/42 (67%)	22/24 (92%)	16/17 (94%)

SVR_{12}, sustained HCV virologic response at 12 weeks

Data derived from Sulkowski et al.[1]

Adverse events were seen in the study, but almost all of them were related to the use of ribavirin. Only 22 (10%) of patients developed anemia, and fatigue was the most commonly reported adverse event. A total of 32 (14%) patients developed hemoglobin levels of less than 10 mg/dL.

As we study the efficacy of new agents, patients with HCV and HIV should only remain a special population to account for drug-drug integrations. As we bring other classes of therapies to the table, a careful examination of drug-drug interactions will help determine if these novel therapies are safe to use in HCV patients with comorbid HIV infection since the efficacy has been demonstrated.

Dr. Kwo has received consulting fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen, and Merck; he has received funds for research support from Abbvie, Bristol-Myers Squibb, Conatus, Gilead Sciences, Janssen, Merck, and Roche.

Median Cost of Telaprevir-Based Triple Therapy Nearly $190K Per Sustained Virologic Response

Source: *Hepatology*

A study using real-world data shows that the median cost of telaprevir-based triple therapy for treatment of hepatitis C virus (HCV) is almost $190,000, a cost of more than double the expense projected in prior randomized clinical trial data. The sustained virologic response (SVR) rate of 44% found in this study is lower than rates identified in phase 3 trials, as reported by Bichoupan et al.[1]

Published phase 3 clinical trials showed that the addition of telaprevir to standard therapy (pegylated interferon and ribavirin) boosted SVR rates from 35% to 45% with standard therapy to 64% to 75% with triple therapy. Telaprevir-based triple therapy was deemed to be cost effective, at approximately $70,364 per SVR.[2] Approved by the U.S. Food and Drug Administration in 2011, telaprevir is a first-generation, HCV nonstructural 3/4A protease inhibitor that is indicated, in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic HCV in adult patients with compensated liver disease, including cirrhosis.[3]

Findings Based on Real-World Clinical Data

In the first published real-world study on the outcomes and cost of telaprevir use, authors reviewed medical records from 147 patients (median age, 56 years) initiated on telaprevir-based triple therapy at Mount Sinai Medical Center in New York, NY, from May to December 2011. Costs were calculated in 2012 U.S. dollars, and the median cost per SVR was calculated by dividing the median cost by the SVR rate.

In the study group, 68% of patients were male, 36% had advanced fibrosis/cirrhosis, 19% were black, and 11% were co-infected with human immunodeficiency virus (HIV). The study population was more diverse than those assessed in clinical trials, thus more closely matching the characteristics of patients with HCV infection in the United States.

Most patients received 750 mg of telaprevir 3 times per day for 12 weeks, in combination with interferon (IFN) and weight-based ribavirin for 48 weeks. Patients with HIV-coinfection who were taking efavirenz were given higher telaprevir doses (1,125 mg 3 times daily) because of a known drug-drug interaction.

The median cost of care was $83,721 per patient, while the median cost per SVR was $189,338.

Treatment Response Rate Of 44% Found

A total of 65 patients (44%) achieved an SVR, which was defined as undetectable HCV RNA at 24 weeks post-treatment. Of the 82 patients (56%) who did not achieve an SVR, 42 had an inadequate response and stopped treatment according to predetermined rules, 18 relapsed after stopping treatment, 15 discontinued treatment because of adverse events, and 7 patients were lost to follow-up. Overall, 56% of patients experienced adverse events that required management.

The median cost of care was $83,721 per patient, while the median cost per SVR was $189,338. The high costs were primarily driven by the price of telaprevir and IFN, as well as the relatively low SVR. In fact, telaprevir and IFN accounted for approximately 85% of the total median cost (Table).[1]

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3. Incivek [package insert]. Cambridge, MA: Vertex Pharmaceuticals Incorporated; 2013.

Table. Breakdown of Cost for Telaprevir-Based Triple Therapy Based on a Median Cost per SVR of $189,338[1]

Factor	Percentage of Median Cost
Telaprevir	61%
Interferon	24%
Ribavirin	4%
Adverse event management	8%
Professional fees	2%
Laboratory tests	1%

SVR, sustained virological response

Cost per SVR = median cost per patient divided by the SVR rate

Data derived from Bichoupan K et al.[1]

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This study by Bichoupan and colleauges used the first-generation protease inhibitor telaprevir combined with pegylated IFN and ribavirin to treat the HCV population in a real-world setting. The authors assessed the cost of therapy to achieve SVR. The real world SVR in HCV patients was found to be 44%, a rate lower than seen in phase 3 trials. This difference is very likely due to the sicker population with more advanced liver disease included in this study compared to the population studied in clinical trials. The medical cost of care per patient was $83,721, and the calculated cost per SVR was $189,338.

The main drivers of cost in this study were the expense of the medications—telaprevir, ribavirin, and IFN. In addition, adverse event management accounted for approximately 8% of the costs.

The cost of HCV treatment is very topical right now. With the use of the newer, IFN-free, oral therapies, SVR rates should be markedly higher than 44%. These increases are seen in recent real-world data from the 65th Annual Meeting of the American Association for the Study of Liver Diseases using sofosbuvir-based therapies. Such improvements in care will drive the cost per SVR down in real-world settings.

"With the widespread use of all-oral therapies, SVR rates will be higher, and the rates of adverse events much lower. Therefore, the cost per SVR of treating patients with HCV, particularly those with advanced liver disease, is going to fall."

—Paul Kwo, MD

We will now be able to, and can offer, oral therapies without worrying about the tolerance of IFN since IFN-free combinations are much easier to tolerate. Phase 2 and 3 studies of the new combinations show SVR rates of higher than 95%. We do not expect to see much of a decline in SVR rates as the IFN-free medications are rolled out to larger numbers of patients.

A portion (8%) of the cost of telaprevir-based therapy was related to adverse event management. With the widespread use of new therapies, adverse events—and the cost of managing adverse events—will dramatically decrease.

Telaprevir played an important role in the improved treatment of patients with HCV. But use of telaprevir and boceprevir in the United States has now ceased. With the widespread use of all-oral therapies, SVR rates will be higher, and the rates of adverse events much lower. Therefore, the cost per SVR of treating patients with HCV, particularly those with advanced liver disease, is going to fall.

Dr. Kwo has received consulting fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen, and Merck; he has received funds for research support from Abbvie, Bristol-Myers Squibb, Conatus, Gilead Sciences, Janssen, Merck, and Roche.

Antivirals Improve Kidney and Cardiovascular Outcomes in Patients with Comorbid HCV and Diabetes

Source: *Hepatology*

Antiviral therapy for hepatitis C virus (HCV) improves kidney and cardiovascular outcomes for patients with diabetes, according to a population-based cohort study by Hsu et al.[1] The incidence of kidney disease, stroke, and heart attack was lower among patients with HCV who were treated with pegylated interferon and ribavirin compared with patients with HCV who were not treated with antivirals or diabetic patients not infected with the virus.

Previous research has suggested a link between diabetes and chronic HCV, with people infected with HCV having a greater chance of developing insulin resistance and diabetes.[2] Moreover, patients with HCV and insulin resistance, with or without diabetes, have a poor response to antiviral treatment, increased progression of liver fibrosis, and greater risk of developing hepatocellular carcinoma, according to the study background.

The authors examined data from the Taiwan National Health Insurance Research Database, which has collected health care data prospectively for all residents of the country since 1997. A total of 1,411 patients with diabetes and HCV who received pegylated interferon plus ribavirin (treated cohort) were enrolled in the study. These patients were matched 1:1 with 1,411 people with diabetes and untreated HCV (untreated group) and 1:4 with 5,644 patients with diabetes and without HCV (uninfected cohort). Follow-up was conducted from 2003 to 2011.

Antivirals may mitigate the insulin resistance and glucose abnormalities associated with HCV infection.

Antivirals Reduce Risk for Renal Disease, Stroke, Heart Attack

The 8-year cumulative incidence of end-stage renal disease (ESRD), stroke, and acute coronary syndrome were significantly higher in the untreated and uninfected groups than in the treated group (Table).[1] Multivariate adjusted analyses showed that antiviral treatment was associated with an 85% reduction in the risk of ESRD, 47% reduction in the risk of ischemic stroke, and 36% reduction in the risk of acute coronary syndrome (adjusted HRs, 0.16, 0.53, and 0.64, respectively).

The association between antiviral treatment and the reduced risk for ESRD was found across all patient subgroups. The reduced risk for ischemic stroke in treated patients was found among most subgroups, except for patients with peripheral arterial occlusive disease or who used metformin monotherapy. The reduced risk for acute coronary syndrome in antiviral-treated patients was found across all subgroups except among patients with peripheral artery disease.

"These findings imply that HCV infection may have a pathogenic role in the development of clinical complications related to diabetes mellitus," the study authors noted.

Furthermore, they suggested that antivirals may mitigate the insulin resistance and glucose abnormalities associated with HCV infection, as has been demonstrated in previous studies. This restoration of glucose homeostasis may underlie the association between improved kidney and cardiovascular outcomes in the patients who received antiviral treatment in this study. The mechanisms behind these effects are unknown, they added.

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1. Hsu YC, Lin JT, Ho HJ, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. *Hepatology*. 2014;59(4):1293-1302.
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Table. Cumulative Incidence of Renal and Cardiovascular Events (95% CI)[a]

	Treated	Untreated	Uninfected	*P* value[b]
End-stage renal disease	1.1% (0.3%-2.0%)	9.3% (5.9%-12.7%)	3.3% (2.3%-4.3%)	*P*<0.001
Ischemic stroke	3.1% (1.1%-5.0%)	5.3% (3.0%-7.5%)	6.1% (4.8%-7.4%)	*P*=0.01
Acute coronary syndrome	4.1% (2.1%-6.1%)	6.6% (3.7%-9.5%)	7.4% (5.9%-9.0%)	*P*=0.05

CI, confidence interval

[a]Treated cohort consisted of patients with diabetes and HCV who received pegylated interferon plus ribavirin, the untreated cohort consisted of people with diabetes and untreated HCV, and the uninfected cohort consisted of patients with diabetes and without HCV.

[b]Modified log-rank

Data extracted from Hsu et al.[1]

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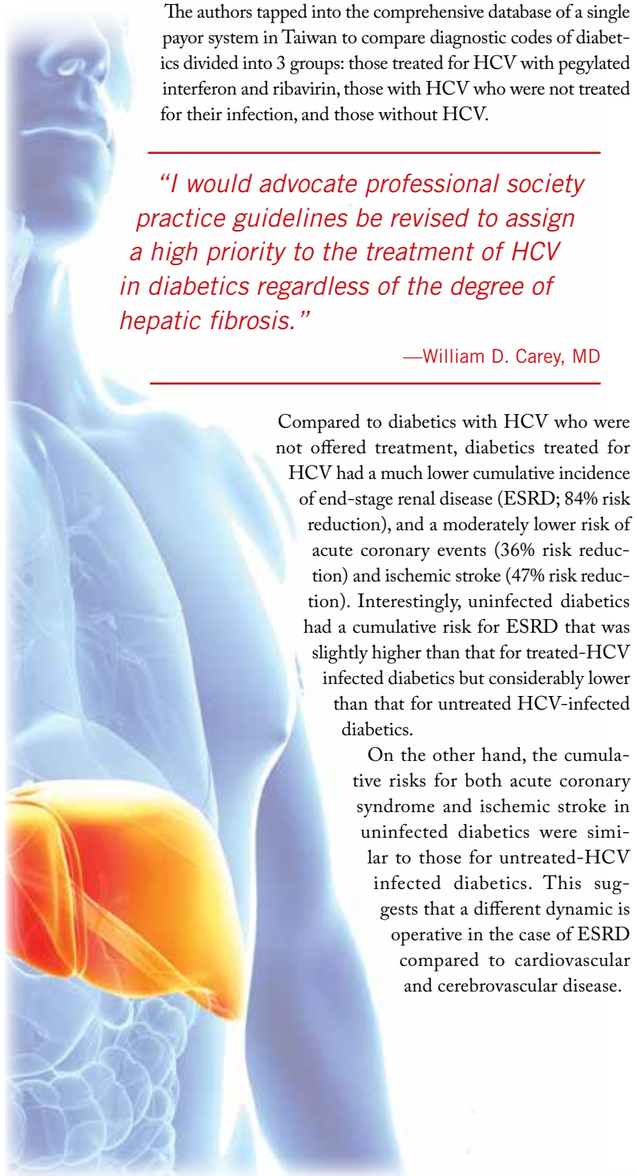
Interactions between HCV infection and diabetes mellitus are multifactorial and complex. The apparent lack of association between the 2 diseases is described in a study by Ruhl et al (see page 30).[1] The current article by Hsu and colleagues deals with the impact HCV may have on common diabetic complications, especially renal and cardiac disease. The authors tapped into the comprehensive database of a single payor system in Taiwan to compare diagnostic codes of diabetics divided into 3 groups: those treated for HCV with pegylated interferon and ribavirin, those with HCV who were not treated for their infection, and those without HCV.

"I would advocate professional society practice guidelines be revised to assign a high priority to the treatment of HCV in diabetics regardless of the degree of hepatic fibrosis."

—William D. Carey, MD



Compared to diabetics with HCV who were not offered treatment, diabetics treated for HCV had a much lower cumulative incidence of end-stage renal disease (ESRD; 84% risk reduction), and a moderately lower risk of acute coronary events (36% risk reduction) and ischemic stroke (47% risk reduction). Interestingly, uninfected diabetics had a cumulative risk for ESRD that was slightly higher than that for treated-HCV infected diabetics but considerably lower than that for untreated HCV-infected diabetics.

On the other hand, the cumulative risks for both acute coronary syndrome and ischemic stroke in uninfected diabetics were similar to those for untreated-HCV infected diabetics. This suggests that a different dynamic is operative in the case of ESRD compared to cardiovascular and cerebrovascular disease.

Risk reduction for ESRD was apparent and found to be independent of insulin use, hyperlipidemia, nonsteroidal anti-inflammatory drug use, and statin use. The benefit of HCV treatment in these subgroups was not as apparent for the outcomes of acute coronary syndromes and ischemic stroke. It is important to remember that advanced liver disease itself is a risk factor for ESRD and, most importantly, hepatorenal syndrome. However, these study data suggest even more protection from ESRD amongst non-cirrhotics than cirrhotics.

The authors provide solid evidence for their main conclusion: "Antiviral therapy for HCV infection is associated with improved renal and cardiovascular outcomes in diabetics." The data is clearest for ESRD. They further conclude that their "findings imply that HCV infection may have a pathogenic role in the development of clinical complications related to diabetes." A stickler might argue that such a conclusion is premature for a number of reasons. The study employed pegylated interferon, a drug with multiple immunologic properties, and with no direct antiviral effect. The fact that interferon appears to promote insulin resistance and is prodiabetic diminishes but does not eliminate the possibility that interferon may have a direct protective effect on the kidney in diabetics. There was no measurement of viral loads, therefore no estimate of viral elimination with treatment. These study results are tantalizing; the effect of direct-acting HCV antivirals of high efficacy will be required to clarify if viral elimination *per se* accounts for improved cardiovascular and renal outcomes.

While we have much to learn about the interactions between HCV, the cardiovascular system, the kidney, and pharmacologic agents used to treat HCV, for now it is reasonable to embrace the beneficial effect of HCV treatment on reducing the burden of end organ failure in diabetics. I would advocate professional society practice guidelines be revised to assign a high priority to the treatment of HCV in diabetics regardless of the degree of hepatic fibrosis.

Reference

1. Ruhl CE, Menke A, Cowie CC, Everhart JE. Relationship of hepatitis C virus infection with diabetes in the U.S. population. *Hepatology*. 2014;60(4):1139-1149.

Dr. Carey has no financial disclosures to report.

HCV Not Linked to Diabetes in a Population-Based Study

Source: *Hepatology*

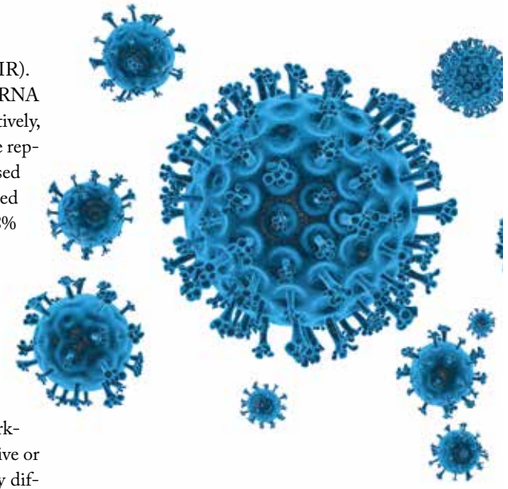
Hepatitis C virus (HCV) was not associated with diabetes or prediabetes in a population-based study involving more than 15,000 adults. Previous reports of an association between HCV and diabetes may be attributable to high levels of liver enzymes (in patients with diabetes) rather than viral infection of the liver, according to Ruhl et al.[1]

An association of HCV infection with diabetes has been reported in many studies, but few have been population-based, have used multivariate analysis, and/or have included level of liver enzymes in adjusted analyses, according to the study background. To further investigate a possible association, the authors analyzed information on diabetes status and serum HCV antibody (anti-HCV) or HCV RNA findings from the 1999-2010 National Health and Nutrition Examination Survey (NHANES) database. The population included 15,128 adult participants.

Diabetes and prediabetes was not associated with HCV status in adjusted multivariate analysis.

Prediabetes and diabetes were defined using standard American Diabetes Association criteria and confirmed by laboratory testing. Insulin resistance was measured by the traditional homeostatic model assessment (HOMA-IR).

The prevalence of anti-HCV and HCV RNA positive results was 1.7% and 1.1%, respectively, when the overall group was weighted to be representative of the U.S. population. Diagnosed diabetes was found in 1.7%, undiagnosed diabetes in 3.2%, and prediabetes in 32.8% of study participants.



Multivariate Analysis Shows No Association Between HCV and Diabetes

The unadjusted prevalence of diabetes and prediabetes among participants with markers of HCV infection (ie, anti-HCV positive or HCV RNA positive) was not significantly different from that of participants without HCV markers (Table).[1] Diabetes and prediabetes was not associated with HCV status in multivariate analysis that adjusted for patient demographics, body mass index, C-reactive protein, smoking, drinking, and blood transfusion before 1992.

Elevated Liver Enzymes Linked to Diabetes

Further analysis showed the prevalence of elevated plasma concentrations of the liver enzymes alanine aminotransferase and gamma-glutamyl transpeptidase were significantly higher in participants who were anti-HCV positive or HCV RNA positive. In multivariate analysis, elevated levels of these enzymes were associated with diabetes and insulin resistance (both in patients with normal glucose levels and prediabetes) regardless of HCV status ($P<0.05$).

The authors noted that increased concentrations of alanine aminotransferase and gamma-glutamyl transpeptidase are markers of fatty liver disease, which in turn is associated with diabetes. The nature of this latter relationship is unclear.

Reference

1. Ruhl CE, Menke A, Cowie CC, Everhart JE. Relationship of hepatitis C virus infection with diabetes in the U.S. population. *Hepatology*. 2014;60(4):1139-1149.

Table. Unadjusted Prevalence of HCV Status and Multivariate-Adjusted Odds Ratio For Diabetes and Prediabetes

HCV Status	Unadjusted Prevalence in Patients with Diabetes (Multivariate Adjusted OR[a])	Unadjusted Prevalence in Patients with Insulin Resistance (Multivariate Adjusted OR[a])
Anti-HCV negative	10.5 (1.0)	32.7 (1.0)
Anti-HCV positive	10.2 (1.00)	36.4 (1.06)
HCV RNA negative	10.5 (1.0)	32.7 (1.0)
HCV RNA positive	12.0 (1.06)	39.6 (1.17)

OR, odds ratio

N=13,630 for anti-HCV analysis and N=13,554 for HCV RNA analysis.

[a]Adjusted for age, sex, race-ethnicity, education, body mass index, elevated C-reactive protein, smoking, alcohol use, and blood transfusion before 1992.

Data derived from Ruhl et al.[1]

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Type 2 diabetes mellitus (T2DM) affects more than 26 million people in the United States. A staggering 43% of the U.S. population has either diabetes or prediabetes. Hepatitis C virus (HCV) infection affects 1.6% of the U.S. population.[1] By chance alone, more than 1 million diabetics would be expected to be infected with hepatitis C. High mortality rates and diabetes and liver-related events have been found in diabetics with HCV.[2,3]

As early as 1996, reports began to appear suggesting more than a chance association between these 2 common disorders. By 2008, 34 studies were available for meta-analysis that showed a modest association (odds ratio 1.67, 95% confidence interval [CI] 1.15-2.20 for retrospective studies; hazard ratio 1.67, 95% CI 1.28-2.06 for prospective studies).[4] The majority of studies in this meta-analysis by White et al, were based on non-U.S. populations.

The potential association of these 2 disorders is not a trivial research matter. The association of HCV infection with insulin resistance, impaired hepatic insulin signaling, and inflammation represent hepatitis-T2DM intersections of interest. Significant research has been conducted to elucidate a unified understanding of the inter-relationships between these disorders. Looked at through a clinical prism, the extent that HCV is considered a contributor to the development of T2DM would be a powerful argument for eradication of HCV regardless of hepatic fibrosis status in an attempt to prevent T2DM.

A rich source for investigation of disease prevalence and comorbidity in the United States is the U.S. National Health and Nutrition Examination Survey (NHANES), a 50-year-old continuous program designed to assess the health and nutritional status of U.S. adults and children. It combines interviews, examinations, and laboratory testing of 5,000 people annually across the country. Indeed, analysis of the 1988-1994 NHANES data also showed an association between HCV and T2DM, albeit a weak one.[5] This and other clinical studies seem to have cemented at least a probable association between the 2 disorders.

Ruhl et al have taken a fresh look and come to different conclusions. Examining NHANES data, and using the American Diabetes Association criteria for a definition of diabetes, this team of investigators has found an absence of association between T2DM and hepatitis C among 15,128 NHANES participants between 1999 and 2010. Key findings were the prevalence of anti-HCV in 1.7% of the overall population, HCV RNA in 1.1%, diabetes in 10.5%, and prediabetes in 32.8%. Prevalence of diabetes, prediabetes, and insulin-resistance did not differ by HCV status. There was an association, however, between T2DM and markers of liver cell damage (increased alanine aminotransferase and gamma glutamyltransferase levels), likely related to the presence of non-alcoholic fatty liver disease in diabetics.

The analysis by Ruhl et al represents a beacon of clarity in a previously murky area. It is worthwhile to try to understand the difference in outcomes of this study and those that suggest an association. First, it is clear that even studies showing an association between HCV and T2DM demonstrate only a modest association at best. Glucose dysregulation frequently manifesting as T2DM is a common accompaniment of advancing liver disease, especially cirrhosis. The study of individuals seeking health care, especially in liver clinics, may select for those with more advanced liver disease and skew the frequency of observed T2DM and HCV.

Lack of a clear definition of diabetes and reliance of patient self-reporting are additional methodological confounders, all avoided in the current study. Confirmation in other populations in the United States and elsewhere is warranted, as are analyses of possible effects of HCV genotypes, which vary considerably from country to country.

Even if there is not an increased representation of HCV among patients with T2DM compared to other groups, implications for the more than 1 million diabetics with HCV requires careful attention. Important considerations for HCV and diabetes comorbidities include aberrant activation of innate immune signaling and the activation of stellate cells that may alter the rate of progression to liver disease, the development of cirrhosis, end-stage liver disease, and hepatocellular carcinoma. This in turn will likely influence prioritization of HCV treatment for patients with HCV in T2DM. In summary, while HCV does not appear to cause diabetes, these comorbid conditions warrant additional study over the next decade, by which time HCV may become an uncommon disease.

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Dr. Carey has no financial disclosures to report.

MEETING CALENDAR 2015

Gastrointestinal Cancers Symposium
January 15-17, 2015
San Francisco, CA
http://gicasym.org/

European Fatty Liver Conference
March 5-6, 2015
Maastricht, The Netherlands
http://www.mintonline.org/eflc/default.asp

AASLD and Industry Colloquium: Novel Targets and Therapies in Liver Disease
March 20-21, 2015
Research Triangle Park, North Carolina
http://www.aasld.org/additionalmeetings/Pages/industrycolloquium.aspx

Digestive Disease Week (DDW)
May 16-19, 2015
Washington, DC
http://www.ddw.org/

The Global Viral Hepatitis Summit
June 25-28, 2015
Berlin, Germany
http://www.isvhld2015.org/

Clinical Hepatology: State-of-the-Art Management
June 27-28, 2015
Chicago, IL
http://www.aasld.org/additionalmeetings/Pages/midyearcourse.aspx

EASL Monothematic Conference: Autoimmune Hepatitis
September 3-5, 2015
London, United Kingdom
http://www.easl.eu/_events/easl-monothematic-conference/easl-monothematic-conference-autoimmune-hepatitis

The International Liver Cancer Association (ILCA)
September 4-6, 2015
Paris, France
http://www.ilca2015.org/

The Liver Meeting
November 13-17, 2015
San Francisco, CA
http://www.aasld.org/livermeeting/