Recommendations for Testing, Managing, and Treating Hepatitis C

Changes made April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

INTRODUCTION

NOTICE: Guidance for hepatitis C treatment in adults is changing constantly with the advent of new therapies and other developments. A static version of this guidance, such as printouts of this website material, booklets, slides, and other materials, may be outdated by the time you read this. We urge you to review this guidance on this website (www.hcvguidelines.org) for the latest recommendations.

The landscape of treatment for hepatitis C virus (HCV) infection has evolved substantially since the introduction of highly effective HCV protease inhibitor therapies in 2011. The pace of change is expected to increase rapidly, as numerous new drugs with different mechanisms of action will likely become available over the next few years. To provide healthcare professionals with timely guidance as new therapies are available and integrated into HCV regimens, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD), in collaboration with the International Antiviral Society–USA (IAS–USA), developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management. The IAS–USA provided the structure and assistance to sustain the process that represents the work of leading authorities in hepatitis C prevention, diagnosis, and treatment in adults, from 2013 to 2015.

The AASLD/IDSA Guidance on Hepatitis C addresses management issues ranging from testing and linkage to care, the crucial first steps toward improving health outcomes for HCV-infected persons, to the optimal treatment regimen in particular patient situations. Recommendations are based on evidence and are rapidly updated as new data from peer-reviewed evidence become available. For each treatment option, recommendations reflect the best possible management for a given patient and a given point of disease progression. Recommendations are rated with regard to the level of the evidence and strength of the recommendation. The AASLD/IDSA Guidance on Hepatitis C is supported by the membership-based societies and not by pharmaceutical companies or other commercial interests. The Boards of Directors of AASLD and IDSA have appointed an oversight committee of 5 co-chairs and have selected panel members from the 2 societies.

This Guidance should be considered a "living document" in that the Guidance will be updated frequently as new information and treatments become available. This continually evolving report provides guidance

on FDA-approved regimens. At times, it may also recommend off-label use of certain drugs or tests or provide guidance for regimens not yet approved by FDA. Readers should consult prescribing information and other resources for further information. Of note, the choice of treatment may, in the future, be further guided by data from cost-effectiveness studies.

Changes made on this page on January 14, 2016. Reviewed June 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

METHODS

The Guidance was developed by a panel of HCV experts in the fields of hepatology and infectious diseases, using an evidence-based review of information that is largely available to healthcare practitioners. The process and detailed methods for developing the Guidance are detailed in **Methods Table 1**. Recommendations were rated according to the strength of the recommendation and quality of the supporting evidence (see **Methods Table 2**). Commonly used abbreviations are expanded in **Methods Table 3**.

The Panel regularly reviews available data and decides whether a regimen should be classified as Recommended, Alternative, or Not Recommended for a particular subgroup of patients. Recommended regimens are those that are favored for most patients in that subgroup, based on optimal efficacy, favorable tolerability and toxicity profiles, duration, and pill burden. Alternative regimens are those that are effective but have, relative to Recommended regimens, potential disadvantages, limitations for use in certain patient populations, or less supporting data than Recommended regimens. In certain situations, an Alternative regimen may be an optimal regimen for a specific patient situation. Not Recommended regimens are clearly inferior compared to Recommended or Alternative regimens due to factors such as lower efficacy, unfavorable tolerability and toxicity, longer duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection.

Updated February 24, 2016. Reviewed June 2016.

Methods Table 1. Summary of the Process and Methods for the Guidance Development

Topic	Description
Statement of Need	Increased awareness of the rising number of complications of hepatitis C virus (HCV) infection, the recent screening initiatives by the Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force (USPSTF), and the rapid evolution of highly effective antiviral therapy for HCV infection have driven a need for timely guidance on how new developments change practice for health care professionals.
Goal of the Guidance	The goal of the Guidance is to provide up-to-date recommendations to health care practitioners on the optimal screening, management, and treatment for adults with HCV infection in the United States, considering the best available evidence. The Guidance is updated regularly, as new data, information, and tools and treatments become available.
Panel members	Panel members are chosen based on their expertise in the diagnosis, management, and treatment of HCV infection. Members from the fields of hepatology and infectious diseases are included, as well as HCV community representatives. Members were appointed by the respective Sponsor Societies after vetting by an appointed Sponsor Society committee. The Panel chairs are appointed by the Society boards, 2 each from the Sponsor Societies. All Panel chairs and members serve as volunteers (not compensated) for defined terms (2-3 years), which may be renewed based on panel needs.

Conflict of interest management	The panel was established with the goal of having no personal (ie, direct payment to the individual) financial conflicts of interest among its chairs and among fewer than half of its panel members. All potential panel members are asked to disclose any personal relationship with a pharmaceutical, biotechnology, medical device, or health-related company or venture that may result in financial benefit. Disclosures are obtained prior to the panel member appointments and for 1 year prior to the initiation of their work on the panel. Full transparency of potential financial conflicts is an important goal for the guidance that best ensures the credibility of the process and the recommendations. Individuals are also asked to disclose funding of HCV-related research activities to their institutional division, department, or practice group. Disclosures are reviewed by the HCV Guidance Chairs, who make assessments based on the conflict-of-interest policies of the sponsoring organizations (AASLD and IDSA). Personal and institutional financial relationships with commercial entities that have products in the field of hepatitis C are assessed. The following relationships are prohibited during membership on the guidance panel and are grounds for exclusion from the panel: • Employment with any commercial company with products in the field of hepatitis C. • An ownership interest in a commercial entity that produces hepatitis C products. • Participation in/payment for promotional or marketing activities sponsored by companies with HCV-related products including non-CME educational activities or speakers bureaus for audiences outside of the company. • Participation in any single-funder CME activity. • Participation on a marketing or medical affairs advisory board. The following relationships or activities are reportable but were not deemed to merit exclusion: • Commercial support of research that is paid to an organization or practice group. Due to the rapidly evolving nature of the subject matter, having individuals with expertise in the particular clinical topic is crucial to developing the highest-quality and most-informed recommendations. To that end, research support from commercial entities is not considered grounds for panel exclusion (an unresolvable conflict) if the funding of the research was paid to the institution or practice group, as opposed to the individual. In the instance of someone conducting clinical research in a community practice, research funds to the group practice were acceptable. • Participation on commercial company scientific advisory boards. Participation in advisory boards, data safety monitoring boards, or in consultancies sponsored by the research arm of a company (eg, study design or data safety monitoring board) is considered a potential personal conflict that should be reported but is not considered a criterion for exclusion. • CME honorarium earned in excess of $5000 (total per year, including travel costs). No need to report if total honorarium is less than $5000. The HCV Guidance Chairs achieved a majority of panel members with no personal financial interests. Panel members are asked to inform the group of any changes to their disclosure status and are given the opportunity to recuse themselves (or be recused) from the discussion where a perceived conflict of interest that cannot be resolved exists. Financial disclosures for each Panel member can be accessed here.

Intended Audience	Medical practitioners especially those who provide care to or manage patients with hepatitis C.
Sponsors, funding, and collaborating partner	The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) are the sponsors of the Guidance and provide ongoing financial support. Grant support was sought and obtained from the Centers for Disease Control and Prevention (CDC) for the initial gathering and review of evidence related to hepatitis C screening and testing recommendations and interventions to implement HCV screening in clinical settings.
Evidence identification and collection	The Guidance is developed using an evidence-based review of information that is largely available to health care practitioners. Data from the following sources are considered by Panel members when making recommendations: research published in the peer-reviewed literature or presented at major national or international scientific conferences; safety warnings from the US Food and Drug Administration (FDA) or other regulatory agencies or from manufacturers; drug interaction data; prescribing information from FDA-approved products; and registration data for new products under FDA review. Press releases, unpublished reports, and personal communications are generally not considered. Literature searches are conducted regularly and before each major revision to ensure that the Panel addresses all relevant published data. Medical subject headings and free text terms are combined to maximize retrieval of relevant citations from the PubMed, Scopus, EMBASE, and Web of Science databases. To be considered for inclusion, articles were required to have been published in English from 2010 to the present. Data from abstracts presented at national or international scientific conferences are also considered
Rating of the evidence and RECOMMENDATIONS	The Guidance is presented in the form of RECOMMENDATIONS. Each RECOMMENDATION is rated in terms of the level of the evidence and strength of the recommendation, using a modification of the scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (American Heart Association, 2014); (Shiffman, 2003). A summary of the supporting (and conflicting) evidence follows each RECOMMENDATION or set of RECOMMENDATIONS.
Data review and synthesis and preparation of RECOMMENDATIONS and supporting information	Draft RECOMMENDATIONS are developed by subgroups of the full Panel with interest and expertise in particular sections of the Guidance. Following development of supporting text and references, the sections are reviewed by the full Panel and Chairs. A penultimate draft is submitted to the AASLD and IDSA Governing Boards for final review and approval before posting online on the website, www.hcvguidelines.org. Subgroups of the Panel meet regularly by conference call as needed to update RECOMMENDATIONS and supporting evidence. Updates may be prompted by new publications or presentations at major national or international scientific conferences, new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety warnings, or other information that may have a substantial impact on the clinical care of patients. Updates and changes in the Guidance are indicated by highlighted text on the online site and a notice of update is posted on the Home Page.
Abbreviations	Commonly used abbreviations in the text with their expansions are listed in Methods Table 3.

Opportunity for Comments	Evidence-based comments may be submitted to the Panel by email to stynes@aasld.org, or by clicking on the "Send a comment to the Panel" button on www.hcvguidelines.org/contact-us. The Panel considers evidence-based comments about the RECOMMENDATIONS, ratings, and evidence summary but should not be contacted for individual patient management questions.

Changes to this page made on November 28, 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Methods Table 2. Rating System Used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation

Recommendations are based on scientific evidence and expert opinion. Each recommended statement includes a Roman numeral (**I**, **II**, or **III**) that represents the level of the evidence that supports the recommendation, and a letter (**A**, **B**, or **C**) that represents the strength of the recommendation.

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful
Level of Evidence	**Description**
Level A*	Data derived from multiple randomized clinical trials, meta-analyses, or equivalent
Level B*	Data derived from a single randomized trial, nonrandomized studies, or equivalent
Level C	Consensus opinion of experts, case studies, or standard of care

Adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (American Heart Association, 2014); (Shiffman, 2003).

*In some situations, such as for IFN-sparing HCV treatments, randomized clinical trials with an existing standard-of-care arm cannot ethically or practicably be conducted. The US Food and Drug Administration (FDA) has suggested alternative study designs, including historical controls or immediate versus deferred, placebo-controlled trials. For additional examples and definitions see FDA link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf. In those instances for which there was a single pre-determined, FDA-approved equivalency established, panel members considered the evidence as equivalent to a randomized controlled trial for levels A or B.

Reviewed June 2016.

Methods Table 3. Commonly Used Abbreviations and Their Expansions

Abbreviation	Expansion or Notes
These terms are not expanded in text	
HCV	hepatitis C virus. In this Guidance "hepatitis C virus" and HCV refer to the virus. Hepatitis C and HCV infection or HCV disease refer to the resulting disease.
IFN	interferon alfa
PEG	peginterferon alfa
These terms are expanded at first mention in text	

ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BOC	boceprevir
CBC	complete blood cell (eg, complete blood cell count)
CrCl	creatinine clearance
CTP	Child Turcotte Pugh (see below)
DAA	direct-acting antiviral
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
IDU	injection drug use or user
INR	international normalized ratio
MELD	model for end-stage liver disease
MSM	men who have sex with men
NAT	nucleic acid testing
NIH	National Institutes of Health
OATP	organic anion-transporting polypeptide
P-gp	p-glycoprotein
PrOD	paritaprevir/ritonavir/ombitasvir plus dasabuvir
RAS	resistance-associated substitution
RBC	red blood cell (eg, red blood cell count)
RBV	ribavirin
RGT	response-guided therapy
RVR	rapid virologic response
sAg	surface antigen
SMV	simeprevir; used for the treatment of those with genotype 1 of hepatitis C virus (HCV) who have compensated liver disease, including cirrhosis
SOF	sofosbuvir; a nucleoside analogue used in combination with other drugs for the treatment of HCV infection
SVR12 (or 24 or 48, etc)	sustained virologic response at 12 weeks (or at 24 weeks, or at 48 weeks, etc)
TSH	thyroid-stimulating hormone
TVR	telaprevir; an antiviral agent to treat hepatitis C

Definition of Terms

Child Turcotte Pugh (CTP) classification of the severity of cirrhosis

	Class A	Class B	Class C
Total points	5–6	7–9	10–15
Factor	**1 Point**	**2 Points**	**3 Points**
Total bilirubin (μmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time/international normalized ratio	< 1.7	1.71–2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

IFN ineligible

IFN ineligible is defined as one or more of the below:
- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- Major uncontrolled depressive illness
- A baseline neutrophil count below 1500/μL, a baseline platelet count below 90,000/μL or baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

Relapser

a person who has achieved an undetectable level of virus during a prior treatment course of PEG/RBV and relapsed after treatment was stopped

Changes made September 16, 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

HCV TESTING AND LINKAGE TO CARE

Expansions and notes for abbreviations used in this section can be found in Methods Table 3.

A summary of recommendations for Testing and Linkage to Care is found in the BOX.

Recommendations for One-time HCV Testing

- **One-time HCV testing is recommended for persons born between 1945 and 1965,* without prior ascertainment of risk.**
  Rating: Class I, Level B

- **Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.**

1. Risk behaviors
   - Injection-drug use (current or ever, including those who injected once)
   - Intranasal illicit drug use
2. Risk exposures
   - Persons on long-term hemodialysis (ever)
   - Persons with percutaneous/parenteral exposures in an unregulated setting
   - Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
   - Children born to HCV-infected women
   - Prior recipients of transfusions or organ transplants, including persons who:
     - Were notified that they received blood from a donor who later tested positive for HCV infection
     - Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
     - Received clotting factor concentrates produced before 1987
   - Persons who were ever incarcerated
3. Other considerations

- HIV infection
- Sexually active persons about to start pre-exposure prophylaxis (PreP) for HIV
- Unexplained chronic liver disease and/or chronic hepatitis including elevated alanine aminotransferase levels
- Solid organ donors (deceased and living)

Rating: Class I, Level B

*Regardless of country of birth

There are an estimated 3.5 million HCV-infected persons in the United States, 2.7 million in the general non-institutionalized population (Denniston, 2014), plus an additional 800,000 incarcerated, institutionalized, or homeless (Edlin, 2015); about half of all infected people are unaware they are infected (Denniston, 2012); (Holmberg, 2013).

HCV testing is recommended in select populations based on demography, prior exposures, high-risk behaviors, and medical conditions. Recommendations for testing are based on HCV prevalence in these populations, proven benefits of care and treatment in reducing the risk of hepatocellular carcinoma and all-cause mortality, and the potential public health benefit of reducing transmission through early treatment, viral clearance, and reduced risk behaviors (Smith, 2012); (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998).

HCV is primarily transmitted through percutaneous exposure to blood. Other modes of transmission include mother-to-infant and contaminated devices shared for noninjection drug use; sexual transmission also occurs but generally seems to be inefficient except among HIV-infected men who have unprotected sex with men (Schmidt, 2014). The most important risk for HCV infection is injection drug use, accounting for at least 60% of acute HCV infections in the United States. Healthcare exposures are important sources of transmission, including the receipt of blood products before 1992 (after which routine screening of blood supply was implemented), receipt of clotting factor concentrates before 1987, long-term hemodialysis, needlestick injuries among healthcare workers, and patient-to-patient transmission resulting from poor infection control practices. Other risk factors include having been born to an HCV-infected mother, having been incarcerated, and percutaneous or parenteral exposures in an unregulated setting: examples are tattoos received outside of licensed parlors and medical procedures done internationally or domestically where strict infection control procedure may not have been followed (eg surgery before the implementation of universal precautions) (Hellard, 2004).

The importance of these risk factors might differ based on geographic location and population (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998). An estimated 29% of incarcerated persons in North America are anti-HCV positive, supporting the recommendation to test this population for HCV (Larney, 2013). Because of shared transmission modes, persons with HIV infection are at risk for HCV; sexual transmission is a particular risk for HIV-infected men who have unprotected sex with men (Hosein, 2013); (van de Laar, 2010). Screening sexually active non-HIV-infected persons before they start pre-exposure prophylaxis (PreP) for prevention of HIV infection should also be considered (Volk, 2015). Recent data also support testing in all deceased and living solid-organ donors because of the risk of HCV infection posed to the recipient (Seem, 2013); (Lai, 2013). Although Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force hepatitis C testing guidelines do not specifically recommend testing immigrants from countries with a high

prevalence (eg, Egypt or Pakistan) of hepatitis C virus infection, such persons should be tested if they were born from 1945 through 1965 or if they have risk factors (listed in **Summary Box**) for infection.

In 2012, CDC expanded its guidelines originally issued in 1998 (Centers for Disease Control and Prevention, 1998) for risk-based HCV testing with a recommendation to offer a one-time (see **Summary Box**) HCV test to all persons born from 1945 through 1965, without prior ascertainment of HCV risk-factors. This recommendation was supported by evidence demonstrating that a risk-based strategy alone failed to identify more than 50% of HCV infections in part due to patient underreporting of their risk and provider limitations in ascertaining risk-factor information. Furthermore, persons in the 1945 to 1965 birth cohort accounted for nearly three-fourths of all HCV infections, with a five-times higher prevalence (3.25%) than other persons, reflecting a higher incidence of HCV infections in the 1970s and 1980s (peaking at 230,000, compared with 15,000 in 2009). A recent retrospective review showed that 68% of persons with HCV infection would have been identified through a birth cohort testing strategy, whereas only 27% would have been screened with the risk-based approach (Mahajan, 2013). The cost-effectiveness of one-time birth cohort testing is comparable to that of current risk-based screening strategies (Smith, 2012).

CDC and the US Preventive Services Task Force (USPSTF) both recommend a one-time HCV test in asymptomatic persons belonging to the 1945 to 1965 birth cohort and other persons based on exposures, behaviors, and conditions that increase risk for HCV infection.

Recommendation for HCV Testing Those with Ongoing Risk Factors

- **Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.**
  Rating: Class IIA, Level C

Evidence regarding the frequency of testing in persons at risk for ongoing exposure to HCV is lacking; therefore, clinicians should determine the periodicity of testing based on the risk of reinfection. Because of the high incidence of HCV infection among persons who inject drugs and among HIV-infected MSM who have unprotected sex (Aberg, 2013); (Linas, 2012); (Wandeler, 2012); (Witt, 2013); (Bravo, 2012); (Williams, 2011), at least annual HCV testing is recommended in these subgroups.

Implementation of clinical decision support tools or prompts for HCV testing in electronic health records could facilitate reminding clinicians of HCV testing when indicated (Hsu, 2013); (Litwin, 2012); (http://nvhr.org/EMR).

Recommendations for Follow-up of Initial Testing

- **An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive HCV RNA test.**
  Rating: Class I, Level A

- **Among persons with a negative anti-HCV test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past six months; testing for HCV RNA can also be considered in persons who are immunocompromised.**
  Rating: Class I, Level C

- **Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an anti-HCV test is expected to be positive.**
  Rating: Class I, Level C

- **Quantitative HCV-RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).**
  Rating: Class I, Level A

- **Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen.**
  Rating: Class I, Level A

- **If found to have positive results for anti-HCV test and negative results for HCV RNA by polymerase chain reaction (PCR), persons should be informed that they do not have evidence of current (active) HCV infection.**
  Rating: Class I, Level A

All persons recommended for HCV testing should first be tested for HCV antibody (anti-HCV) (Centers for Disease Control and Prevention [CDC], 2013); (Alter, 2003) using an FDA-approved test. FDA-approved tests include laboratory-based assays and a point-of-care assay (ie, OraQuick HCV Rapid Antibody Test [OraSure Technologies]) (Lee, 2011). The latter is an indirect immunoassay with a sensitivity and specificity similar to those of FDA-approved laboratory-based HCV antibody assays.

A positive test result for anti-HCV indicates either current (active) HCV infection (acute or chronic), past infection that has resolved, or a false-positive test result (Pawlotsky, 2002). Therefore, an HCV nucleic acid test (NAT) to detect viremia is necessary to confirm current (active) HCV infection and guide clinical management, including initiation of HCV treatment. HCV RNA testing should also be performed in persons with a negative anti-HCV test who are either immunocompromised (eg, persons receiving chronic hemodialysis) (KDIGO, 2008) or who might have been exposed to HCV within the last six months because these persons may be anti-HCV negative. An HCV RNA test is also needed to detect reinfection in anti-HCV–positive persons after previous spontaneous or treatment-related viral clearance.

An FDA-approved quantitative or qualitative NAT with a detection level of 25 IU/mL or lower should be used to detect HCV RNA. **Testing and Linkage to Care Table 1** lists FDA-approved, commercially available anti-HCV screening assays. **Testing and Linkage to Care Figure 1** shows the CDC-recommended testing algorithm.

Persons who have positive results for an anti-HCV test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have laboratory evidence of current (active) HCV infection. Additional HCV testing is typically unnecessary. The HCV RNA test can be repeated when

there is a high index of suspicion for recent infection or in patients with ongoing risk factors for HCV infection.

Practitioners or persons may seek additional testing to learn if the HCV antibody test represents a remote HCV infection that has resolved or a false-positive result. For patients with no apparent risk for HCV infection, the likelihood of a false-positive HCV antibody test is directly related to the HCV prevalence in the tested population; false-positive test results for anti-HCV are most common for populations with a low prevalence of HCV infection (Alter, 2003). If further testing is desired to distinguish between true positivity and biologic false positivity for HCV antibody, testing may be done with a second FDA-approved HCV antibody assay that is different from the assay used for initial antibody testing. A biologic false result should not occur with two different tests (Vermeersch, 2008); (Centers for Disease Control and Prevention [CDC]), 2013). Prior to the initiation of HCV therapy, quantitative HCV RNA testing may be used to determine the baseline level of viremia (ie, viral load) in order to define the duration of treatment for certain regimens. The degree of viral load decline after initiation of treatment is less predictive of sustained virologic response in the era of direct-acting antiviral therapy (see **Pretreatment and On-Treatment Monitoring**). Testing for HCV genotype helps to guide selection of the most appropriate treatment regimen.

Recommendations for Counseling Those with Current (Active) HCV Infection

- **Persons with current (active) HCV infection should receive education and interventions aimed at reducing progression of liver disease and preventing transmission of HCV.**
  Rating: Class IIa, Level B

1. *Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.*
   Rating: Class IIa, Level B
2. *Evaluation for other conditions that may accelerate liver fibrosis, including HBV and HIV infections, is recommended for all persons with HCV infection.*
   Rating: Class IIb, Level B
3. *Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) (see When and in Whom to Initiate HCV Therapy).*
   Rating: Class I, Level A
4. *Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection.*
   Rating: Class IIa, Level C
5. *Vaccination against pneumococcal infection is recommended to all patients with cirrhosis* (Marrie, 2011).
   Rating: Class IIa, Level C
6. *All persons with HCV infection should be provided education on how to avoid HCV transmission to others.*
   Rating: Class I, Level C

In addition to receiving therapy, HCV-infected persons should be educated about how to prevent further

damage to their liver. Most important is prevention of the potential deleterious effect of alcohol. Numerous studies have found a strong association between the use of excess alcohol and the development or progression of liver fibrosis and the development of hepatocellular carcinoma (Poynard, 1997); (Harris, 2001); (Wiley, 1998); (Corrao, 1998); (Bellentani, 1999); (Noda, 1996); (Safdar, 2004).

The daily consumption of more than 50 grams of alcohol has a high likelihood of worsening fibrosis. Some studies indicate that daily consumption of smaller amounts of alcohol also has a deleterious effect on the liver; however, these data are controversial (Westin, 2002). Excess alcohol intake may also cause steatohepatitis. Alcohol screening and brief interventions such as those outlined by the National Institute of Alcohol Abuse and Alcoholism (http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm) have been demonstrated to reduce alcohol consumption and episodes of binge drinking in the general population and among HCV-infected persons who consume alcohol heavily (Whitlock, 2004); (Dieperink, 2010); (Proeschold-Bell, 2012). Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist.

Hepatitis B virus (HBV) and human immunodeficiency virus-1 (HIV) coinfection have been associated with poorer prognosis of HCV in cohort studies (Thein, 2008a); (Zarski, 1998). Owing to overlapping risk factors for these infections and additional benefits of their identification and treatment, persons with HCV should be tested for HIV antibody and hepatitis B surface antigen (HBsAg) using standard assays for screening (Moyer, 2013); (Centers for Disease Control and Prevention [CDC], 2008); (http://www.aafp.org/afp/2008/0315/p819.html and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm) and counseled on how to reduce their risk of acquiring these infections, including through HBV vaccination (see below).

Patients with obesity and metabolic syndrome having underlying insulin resistance are more prone to have nonalcoholic fatty liver disease, which is a risk factor for fibrosis progression in HCV-infected persons (Hourigan, 1999); (Ortiz, 2002). Therefore, HCV-infected persons who are overweight or obese (defined by a body mass index 25 kg/m^2 or higher or 30 kg/m^2 or higher, respectively) should be counseled regarding strategies to reduce weight and improve insulin resistance via diet, exercise, and medical therapies (Musso, 2010); (Shaw, 2006). Patients with HCV infection and hyperlipidemia or cardiovascular comorbidities may also benefit from various hypolipidemic drugs. Prospective studies have demonstrated the safety and efficacy of statins in patients with chronic HCV and others with compensated chronic liver disease (Lewis, 2007). Therefore, these agents should not be withheld in HCV-infected patients.

The severity of liver disease associated with chronic HCV infection is a key factor in determining the initial and follow-up evaluation of patients. Although patients with more advanced disease may have a lower response to HCV therapy, they are also most likely to derive the greatest survival benefit (Ghany, 2011). A liver biopsy can provide objective, semiquantitative information regarding the amount and pattern of collagen or scar tissue in the liver that can assist with treatment and monitoring plans. The Metavir fibrosis score (F0-F4) and Ishak fibrosis score (0-6) are commonly used to score the amount of hepatic collagen. A liver biopsy can also help assess the severity of liver inflammation, or of hepatic steatosis, and help exclude competing causes of liver injury (Kleiner, 2005). However, the procedure has a low but real risk of complications, and sampling artifact makes its serial use in most patients less desirable (Regev, 2002). Noninvasive methods frequently used to estimate liver disease severity include a liver-directed physical exam (normal in most patients), routine blood tests (eg, serum alanine aminotransferase [ALT] and aspartate aminotransferase [AST], albumin, bilirubin, international

normalized ratio levels, and complete blood cell counts with platelets), serum fibrosis marker panels, liver imaging (eg, ultrasound, computed tomography scan), and transient elastography. Simple blood tests (eg, serum AST-to-platelet ratio index [APRI]), (Wai, 2003); (http://www.hepatitisc.uw.edu/page/clinical-calculators/apri) FIB-4, (Sterling, 2006) and assessment of liver surface nodularity and spleen size by liver ultrasound or other cross-sectional imaging modalities can help determine if patients with HCV have occult portal hypertension, which is associated with a greater likelihood of developing future hepatic complications in untreated patients (Chou, 2013); (Rockey, 2006). Liver elastography can provide instant information regarding liver stiffness at the point of care and can reliably distinguish patients with a high versus low likelihood of cirrhosis (Castera, 2012); (Bonder, 2014). A more detailed discussion regarding fibrosis assessment is found in the section When and In Whom to Initiate Therapy. Because persons with known or suspected bridging fibrosis and cirrhosis are at increased risk of developing complications of advanced liver disease, they require more frequent follow-up; these persons should also avoid hepatotoxic drugs (eg, excessive acetaminophen [ie, > 2 g/d] or certain herbal supplements) or nephrotoxic drugs (eg, nonsteroidal antiinflammatory drugs) and receive ongoing imaging surveillance for liver cancer and gastroesophageal varices (Sangiovanni, 2006); (Fontana, 2010). Persons with cirrhosis are also more susceptible to invasive pneumococcal infection (Marrie, 2011) and should receive pneumococcal vaccination (Centers for Disease Control and Prevention [CDC], 2012).

Exposure to infected blood is the primary mode of HCV transmission. HCV-infected persons must be informed of the precautions needed to avoid exposing others to infected blood. This is particularly important for persons who use injection drugs, given that HCV transmission in this population primarily results from the sharing of needles and other infected implements. Recently, epidemics of acute HCV due to sexual transmission in HIV-infected men who have sex with men have also been described (van de Laar, 2009); (Urbanus, 2009); (Fierer, 2008). **Testing and Linkage to Care Table 2** outlines measures to avoid HCV transmission. HCV is not spread by sneezing, hugging, holding hands, coughing, or sharing eating utensils or drinking glasses, nor is it transmitted through food or water.

Recommendation for Linkage to Care

- **All persons with current active HCV infection should be linked to a practitioner who is prepared to provide comprehensive management.**
  Rating: Class IIa, Level C

Improvement in identification of current (active) HCV infection and advances in treatment regimens will have limited impact on HCV-related morbidity and mortality without concomitant improvement in linkage to care. All patients with current HCV infection and a positive HCV RNA test result, should be evaluated by a practitioner with expertise in assessment of liver disease severity and HCV treatment. Subspecialty care and consultation are required for persons with HCV infection who have advanced fibrosis or cirrhosis (stage F3 or above on Metavir scale), including possible referral for consideration of liver transplantation. In the United States, only an estimated 13% to 18% of HCV-infected persons had received treatment by 2013 (Holmberg, 2013). Lack of appropriate practitioner assessment and delays in linkage to care can result in negative health outcomes. Further, patients who are lost to follow-up fail to benefit from evolving evaluation and treatment options.

Commonly cited patient-related barriers to treatment initiation include contraindications to treatment (eg, medical or psychiatric comorbidities), lack of acceptance of treatment (eg, asymptomatic nature of disease, competing priorities, low treatment efficacy, and long treatment duration and adverse effects), and lack of access to treatment (eg, cost and distance to specialist) (Khokhar, 2007); (Arora, 2011); (Clark, 2012). Common practitioner-related barriers include perceived patient-related barriers (eg, fear of adverse effects, treatment duration, cost, and effectiveness), lack of expertise in HCV treatment, lack of specialty referral resources, resistance to treating persons currently using illicit drugs or alcohol, and concern about cost of HCV treatment (Morrill, 2005); (Reilley, 2013); (McGowan, 2013). Data are lacking to support exclusion of HCV-infected persons from considerations for hepatitis C therapy based on the amount of alcohol intake or the use of illicit drugs. Based on data from IFN-based treatment, SVR rates among people who inject drugs are comparable to those among people who do not inject drugs (Aspinall, 2013). Some possible strategies to address these barriers are listed in **Testing and Linkage to Care Table 3**. One strategy that addresses several barriers is colocalization or integrated care of HCV screening, evaluation, and treatment with other medical or social services. Colocalization has already been applied to settings with a high prevalence of HCV infection (eg, correctional facilities and programs providing needle exchange, substance abuse treatment, and methadone maintenance) but is not uniformly available (Islam, 2012); (Stein, 2012); (Bruggmann, 2013). Integrated care, consisting of multidisciplinary care coordination and patient case management, increased the proportion of patients with HCV infection and psychiatric illness or substance use who begin antiviral therapy and achieve an SVR, without serious adverse events (Ho, 2015).

A strategy that addresses lack of access to specialists (a primary barrier to hepatitis C care) is participation in models involving close collaboration between primary care practitioners and subspecialists (Arora, 2011); (Rossaro, 2013); (Miller, 2012). Such collaborations have used telemedicine and knowledge networks to overcome geographic distances to specialists (Arora, 2011); (Rossaro, 2013). For example, Project ECHO (Extension for Community Healthcare Outcomes [http://echo.unm.edu]) uses videoconferencing to enhance primary care practitioner capacity in rendering HCV care and treatment to New Mexico's large rural and underserved population (Arora, 2011). Through case-based learning and real-time feedback from a multidisciplinary team of specialists (ie, gastroenterology, infectious diseases, pharmacology, and psychiatry practitioners), Project ECHO has expanded access to HCV infection treatment in populations that might have otherwise remained untreated. The short duration of therapy and few serious adverse events related to the new hepatitis C medications present an opportunity to expand the number of mid-level practitioners and primary care physicians in the management and treatment of HCV infection.

Additional strategies for enhancing linkage to and retention in care could be adapted from other fields, such as tuberculosis and HIV. For example, use of directly observed therapy has enhanced adherence to tuberculosis treatment, and use of case managers and patient navigators has reduced loss of follow-up in HIV care (Govindasamy, 2012). Recent hepatitis C test and care programs have identified the use of patient navigators or care coordinators to be an important intervention in overcoming challenges to linkage to, and retention in care (Trooskin, 2015); (Coyle, 2015). Ongoing assessment of efficacy and comparative effectiveness of this and additional strategies is a crucial area of future research for patients with HCV infection. Replication and expansion of best practices and new models for linkage to HCV care will also be crucial to maximize the public health impact of newer treatment paradigms.

Changes made on July 6, 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Summary of Recommendations for HCV Testing and Linkage to Care

Recommendations for One-time HCV Testing

- **One-time HCV testing is recommended for persons born between 1945 and 1965,* without prior ascertainment of risk.**
  Rating: Class I, Level B

- **Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.**

1. Risk behaviors
   - Injection-drug use (current or ever, including those who injected once)
   - Intranasal illicit drug use
2. Risk exposures
   - Persons on long-term hemodialysis (ever)
   - Persons with percutaneous/parenteral exposures in an unregulated setting
   - Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
   - Children born to HCV-infected women
   - Prior recipients of transfusions or organ transplants, including persons who:
     - Were notified that they received blood from a donor who later tested positive for HCV infection
     - Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
     - Received clotting factor concentrates produced before 1987
   - Persons who were ever incarcerated
3. Other considerations
   - HIV infection

- Sexually active persons about to start pre-exposure prophylaxis (PreP) for HIV
- Unexplained chronic liver disease and/or chronic hepatitis including elevated alanine aminotransferase levels
- Solid organ donors (deceased and living)

Rating: Class I, Level B

*Regardless of country of birth

Recommendation for HCV Testing Those with Ongoing Risk Factors

- **Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.**
  Rating: Class IIA, Level C

Recommendations for Follow-up of Initial Testing

- **An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive HCV RNA test.**
  Rating: Class I, Level A

- **Among persons with a negative anti-HCV test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past six months; testing for HCV RNA can also be considered in persons who are immunocompromised.**
  Rating: Class I, Level C

- **Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an anti-HCV test is expected to be positive.**
  Rating: Class I, Level C

- **Quantitative HCV-RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).**
  Rating: Class I, Level A

- **Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen.**
  Rating: Class I, Level A

- **If found to have positive results for anti-HCV test and negative results for HCV RNA by polymerase chain reaction (PCR), persons should be informed that they do not have evidence of current (active) HCV infection.**
  Rating: Class I, Level A

Recommendations for Counseling Those with Current (Active) HCV Infection

- **Persons with current (active) HCV infection should receive education and interventions**

aimed at reducing progression of liver disease and preventing transmission of HCV.
Rating: Class IIa, Level B

1. *Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.*
   Rating: Class IIa, Level B
2. *Evaluation for other conditions that may accelerate liver fibrosis, including HBV and HIV infections, is recommended for all persons with HCV infection.*
   Rating: Class IIb, Level B
3. *Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) (see When and in Whom to Initiate HCV Therapy).*
   Rating: Class I, Level A
4. *Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection.*
   Rating: Class IIa, Level C
5. *Vaccination against pneumococcal infection is recommended to all patients with cirrhosis* (Marrie, 2011).
   Rating: Class IIa, Level C
6. *All persons with HCV infection should be provided education on how to avoid HCV transmission to others.*
   Rating: Class I, Level C

Recommendation for Linkage to Care

- **All persons with current active HCV infection should be linked to a practitioner who is prepared to provide comprehensive management.**
  Rating: Class IIa, Level C

Changes made July 6, 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Testing and Linkage to Care Table 1. FDA-approved, Commercially Available Anti-HCV Screening Assays

Assay	Manufacturer	Format
Abbott HCV EIA 2.0	Abbott Laboratories, Abbott Park, IL, USA	EIA (Manual)
Advia Centaur HCV	Siemens, Malvern, PA, USA	CIA (Automated)
ARCHITECT Anti-HCV	Abbott Laboratories, Abbott Park, IL, USA	CMIA (Automated)
AxSYM Anti-HCV	Abbott Laboratories, Abbott Park, IL, USA	MEIA (Automated)
OraQuick HCV Rapid Antibody Test	OraSure Technologies, Inc, Bethlehem, PA, USA	Immunochromatographic (Manual)
Ortho HCV Version 3.0 EIA	Ortho	EIA (Manual)
VITROS Anti-HCV	Ortho	CIA (Automated)

Anti-HCV = HCV antibody; EIA = enzyme immunoassay; CIA = chemiluminescent immunoassay; MEIA = microparticle enzyme immunoassay; CMIA = chemiluminescent microparticle immunoassay

Table prepared by Saleem Kamili, PhD, Centers for Disease Control and Prevention.

Reviewed June 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Testing and Linkage to Care Table 2. Measures to Prevent Transmission of HCV

- Persons with HCV infection should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound to prevent the possibility of others coming into contact with their blood.
- Persons should be counseled to stop using illicit drugs and enter substance abuse treatment. Those who continue to inject drugs should be counseled to avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment; use new sterile syringes and filters and disinfected cookers; clean the injection site with a new alcohol swab; and dispose of syringes and needles after one use in a safe, puncture-proof container.
- Persons with HCV infection should be advised not to donate blood and to discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
- Persons with HIV infection and those with multiple sexual partners or sexually transmitted infections should be encouraged to use barrier precautions to prevent sexual transmission. Other persons with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection.
- Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

Reviewed June 2016.

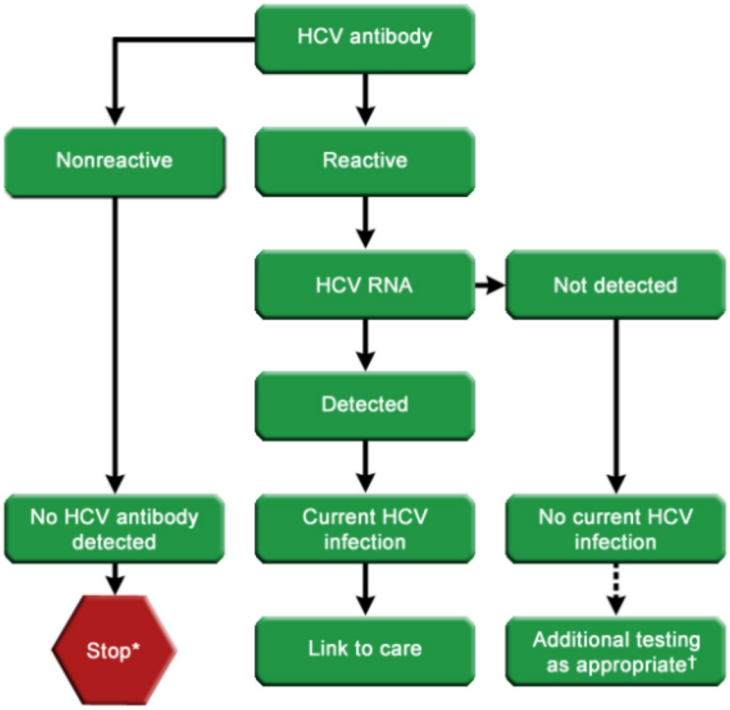
Testing and Linkage to Care Table 3. Common Barriers to HCV Treatment and Potential Strategies

Barrier	Strategy
Contraindications to treatment (eg, comorbidities, substance abuse, and psychiatric disorders)	• Counseling and education • Referral to services (eg, psychiatry and opioid substitution therapy) • Optimize treatment with simpler and less toxic regimens
Competing priority and loss to follow-up	• Conduct counseling and education • Engage case managers and patient navigators (HIV model) • Co-localize services (eg, primary care, medical homes, and drug treatment)
Long treatment duration and adverse effects	• Optimize treatment with simpler and better tolerated regimens • Education and monitoring • Directly observed therapy (tuberculosis model)
Lack of access to treatment (high cost, lack of insurance, geographic distance, and lack of availability of specialists)	• Leverage expansion of coverage through the Patient Protection and Affordable Care Act • Participate in models of care involving close collaboration between primary care practitioners and specialists • Pharmaceutical patient assistance programs • Co-localize services (primary care, medical homes, drug treatment)

Lack of practitioner expertise	• Collaboration with specialists (eg, via Project ECHO-like models and telemedicine) • Develop accessible and clear HCV treatment guidelines • Develop electronic health record performance measures and clinical decision support tools (eg, pop-up reminders and standing orders)

Reviewed June 2016.

Testing and Linkage to Care Figure 1. CDC Recommended Testing Sequence for Identifying Current HCV Infection



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody should be performed. For persons who are immunocompromised, testing for HCV RNA should be performed.

†To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Adapted from Centers for Disease Control and Prevention (CDC), 2013 (Centers for Disease Control and Prevention [CDC], 2013).

Reviewed June 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

WHEN AND IN WHOM TO INITIATE HCV THERAPY

Successful hepatitis C treatment results in sustained virologic response (SVR), which is tantamount to virologic cure, and as such, is expected to benefit nearly all chronically infected persons. When the US Food and Drug Administration (FDA) approved the first IFN-sparing treatment for HCV infection, many patients who had previously been "warehoused" sought treatment, and the infrastructure (experienced practitioners, budgeted health-care dollars, etc) did not yet exist to treat all patients immediately. Thus, the panel offered guidance for prioritizing treatment first to those with the greatest need. Since that time, there have been opportunities to treat many of the highest-risk patients and to accumulate real-world experience of the tolerability and safety of newer HCV medications. More importantly, from a medical standpoint, data continue to accumulate that demonstrate the many benefits, within the liver and extrahepatic, that accompany HCV eradication. Therefore, the panel continues to recommend treatment for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Accordingly, prioritization tables are now less useful and have been removed from this section.

Despite the strong recommendation for treatment for nearly all HCV-infected patients, pretreatment assessment of a patient's understanding of treatment goals and provision of education on adherence and follow-up are essential. A well-established therapeutic relationship between practitioner and patient remains crucial for optimal outcomes with new direct-acting antiviral (DAA) therapies. Additionally, in certain settings there remain factors that impact access to medications and the ability to deliver them to patients. In these settings, practitioners may still need to decide which patients should be treated first. The descriptions below of unique populations may help physicians make more informed treatment decisions for these groups (See **Unique Patient Populations: Patients with HIV/HCV Coinfection**, **Unique Patient Populations: Patients with Decompensated Cirrhosis**, **Unique Patient Populations: Patients who Develop Recurrent HCV Infection Post-Liver Transplantation**, and **Unique Patient Populations: Patients with Renal Impairment**).

Expansions and notes for abbreviations used in this section can be found in Methods Table 3.

A summary of recommendations for When and in Whom to Initiate HCV Therapy is found in the BOX.

Goal of Treatment

- **The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.**
  Rating: Class I, Level A

Recommendations for When and in Whom to Initiate Treatment

- **Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.**
  Rating: Class I, Level A

Clinical Benefit of Cure

The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA at least 12 weeks after completion of therapy. SVR is a marker for cure of HCV infection and has been shown to be durable, in large prospective studies, in more than 99% of patients followed up for 5 years or more (Swain, 2010); (Manns, 2013). Patients in whom an SVR is achieved have HCV antibodies but no longer have detectable HCV RNA in serum, liver tissue, or mononuclear cells, and achieve substantial improvement in liver histology (Marcellin, 1997); (Coppola, 2013); (Garcia-Bengoechea, 1999). Assessment of viral response, including documentation of SVR, requires use of an FDA-approved quantitative or qualitative nucleic acid test (NAT) with a detection level of 25 IU/mL or lower.

Patients who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation as reflected by improved aminotransferase (ie, alanine aminotransferase [ALT], aspartate aminotransferase [AST]) levels and a reduction in the rate of progression of liver fibrosis (Poynard, 2002b). Of 3010 treatment-naive HCV-infected patients with pretreatment and posttreatment biopsies from 4 randomized trials of 10 different IFN-based regimens (biopsies separated by a mean of 20 months), 39% to 73% of patients who achieved an SVR had improvement in liver fibrosis and necrosis (Poynard, 2002b), and cirrhosis resolved in half of the cases. Portal hypertension, splenomegaly, and other clinical manifestations of advanced liver disease also improved. Among HCV-infected persons, SVR is associated with a more than 70% reduction in the risk of liver cancer (hepatocellular carcinoma [HCC]) and a 90% reduction in the risk of liver-related mortality and liver transplantation (Morgan, 2013); (van der Meer, 2012); (Veldt, 2007).

Cure of HCV infection also reduces symptoms and mortality from severe extrahepatic manifestations, including cryoglobulinemic vasculitis, a condition affecting 10% to 15% of HCV-infected patients (Fabrizi, 2013); (Landau, 2010); (Sise, 2016). HCV-infected persons with non-Hodgkin lymphoma and other lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful therapy for HCV infection (Gisbert, 2005); (Takahashi, 2012); (Svoboda, 2005); (Mazzaro,

2002); (Hermine, 2002). These reductions in disease severity contribute to dramatic reductions in all-cause mortality (van der Meer, 2012); (Backus, 2011). Lastly, patients who achieve SVR have substantially improved qualities of life, which include physical, emotional, and social health (Boscarino, 2015); (Neary, 1999); (Younossi, 2013). Because of the many benefits associated with successful HCV treatment, clinicians should treat HCV-infected patients with antiviral therapy with the goal of achieving an SVR, preferably early in the course of chronic HCV infection before the development of severe liver disease and other complications.

Benefits of Treatment at Earlier Fibrosis Stages (Metavir Stage Below F2)

Initiating therapy in patients with lower-stage fibrosis augments the benefits of SVR. In a long-term follow-up study, 820 patients with Metavir stage F0 or F1 fibrosis confirmed by biopsy were followed up for up to 20 years (Jezequel, 2015). The 15-year survival rate was statistically significantly better for those who experienced an SVR than for those whose treatment had failed or for those who remained untreated (93%, 82%, and 88%, respectively; $P = .003$). The study results argue for consideration of earlier initiation of treatment. Several modeling studies also suggest a greater mortality benefit if treatment is initiated at fibrosis stages prior to F3 (Øvrehus, 2015); (Zahnd, 2015); (McCombs, 2015).

Treatment delay may decrease the benefit of SVR. In a report of long-term follow-up in France, 820 patients with biopsy-confirmed Metavir stage F0 or F1 fibrosis were followed up for as long as 20 years (Jezequel, 2015). The authors noted rapid progression of fibrosis in 15% of patients during follow-up, and in patients treated successfully, long-term survival was better. Specifically, at 15 years, survival rate was 92% for those with an SVR versus 82% for treatment failures and 88% for those not treated. In a Danish regional registry study, investigators modeled treatment approaches with the aim of evaluating the benefit to the region in terms of reductions in morbidity and mortality and HCV prevalence (Øvrehus, 2015). Although they note that in their situation of low HCV prevalence (0.4%), with approximately 50% undiagnosed, a policy that restricts treatment to those with Metavir fibrosis stage F3 or higher would decrease mortality from HCC and cirrhosis, the number needed to treat to halve the prevalence of the disease is lower if all eligible patients receive treatment at diagnosis. A modeling study based on the Swiss HIV Cohort Study also demonstrated that waiting to treat HCV infection at Metavir fibrosis stages F3 and F4 resulted in 2- and 5-times higher rates of liver-related mortality, respectively, compared with treating at Metavir stage F2 (Zahnd, 2015).

A US Veterans Administration dataset analysis that used very limited end points of virologic response dating from the IFN-treatment era suggested that early (at a Fibrosis-4 [FIB-4] score of < 3.25) initiation of therapy increased the benefit attained with respect to likelihood of treatment success and mortality reduction and ultimately decreased the number of patients needed to treat to preserve 1 life by almost 50% (McCombs, 2015).

Considerations in Specific Populations

Despite the recommendation for treatment of nearly all patients with HCV infection, it remains important for clinicians to understand patient- and disease-related factors that place individuals at risk for HCV-related complications (liver and extrahepatic) as well as for HCV transmission. Although these groups are no longer singled out for high prioritization for treatment, it is nonetheless important that practitioners recognize the unique dimensions of HCV disease and its natural history in these populations. The discussions offered below may assist clinicians in making compelling cases for insurance coverage of treatment when necessary.

Persons With Advanced Liver Disease

For persons with advanced liver disease (Metavir stage F3 or F4), the risk of developing complications of liver disease such as hepatic decompensation (Child Turcotte Pugh [CTP] Class B or C [**Methods Table 3**]) or HCC is substantial and may occur in a relatively short timeframe. A large prospective study of patients with cirrhosis resulting from HCV infection examined the risk of decompensation, including HCC, ascites, jaundice, bleeding, and encephalopathy, and found that the overall annual incidence rate was 3.9% (Sangiovanni, 2006). The National Institutes of Health (NIH)-sponsored HALT–C study included a group of 220 patients with cirrhosis resulting from HCV infection who were observed for approximately 8 years. A primary outcome of death, hepatic decompensation, HCC, or increase in CTP score of 2 or higher occurred at a rate of 7.5% per year (Everson, 2006); (Di Bisceglie, 2008). Patients with a CTP score of 7 or higher experienced a death rate of 10% per year.

Numerous studies have demonstrated that hepatitis C therapy and the achievement of an SVR in this population results in dramatic decreases in hepatic decompensation events, HCC, and liver-related mortality (Morgan, 2013); (van der Meer, 2012); (Backus, 2011); (Dienstag, 2011); (Berenguer, 2009); (Mira, 2013). In the HALT-C study, patients with advanced fibrosis secondary to HCV infection who achieved an SVR, compared with patients with similarly advanced liver fibrosis who did not achieve an SVR, had a decreased need for liver transplantation (hazard ratio [HR], 0.17; 95% confidence interval [CI], 0.06–0.46), decreased development of liver-related morbidity and mortality (HR, 0.15; 95% CI, 0.06–0.38) and decreased HCC (HR, 0.19; 95% CI, 0.04–0.80) (Dienstag, 2011). Importantly, persons with advanced liver disease also require long-term follow-up and HCC surveillance regardless of treatment outcome (see **Monitoring Patients who are Starting Hepatitis C Treatment, are on Treatment, or have Completed Therapy**).

Given the clinical complexity and the need for close monitoring, patients with advanced liver disease that has already decompensated (CTP Class B or C [**Methods Table 3**]) should be treated by physicians with experience in treating HCV in conjunction with a liver transplantation center if possible (see Unique Patient Populations: Patients with Decompensated Cirrhosis).

Persons Who Have Undergone Liver Transplantation

In HCV-infected individuals, HCV infection of the liver allograft occurs universally in those with viremia at the time of transplantation. Histologic features of hepatitis develop in about 75% of recipients in the first 6 months following liver transplantation (Neumann, 2004). By the fifth postoperative year, up to 30% of untreated patients have progressed to cirrhosis (Neumann, 2004); (Charlton, 1998). A small proportion of patients (4%-7%) develop an accelerated course of liver injury (cholestatic hepatitis C, associated with very high levels of viremia) with subsequent rapid allograft failure. Recurrence of HCV infection posttransplantation is associated with decreased graft survival for recipients with HCV infection compared to recipients who undergo liver transplantation for other indications (Forman, 2002).

Effective HCV therapy pretransplantation resulting in an SVR (virologic cure) prevents HCV recurrence posttransplantation (Everson, 2003). In addition, complete HCV viral suppression prior to transplantation prevents recurrent HCV infection of the graft in the majority of cases (Forns, 2004); (Everson, 2005). Preliminary data from a study of patients with complications of cirrhosis secondary to HCV infection, who were wait-listed for liver transplantation, that included patients with MELD scores up to 14 and CTP scores up to 8 found that treatment with sofosbuvir and weight-based ribavirin for up to 48 weeks was well tolerated and was associated with an overall posttransplant SVR rate of 70% (Curry, 2015).

Posttransplant SVR was nearly universal among patients who had undetectable HCV RNA for 28 days or longer prior to transplantation.

Treatment of established HCV infection posttransplantation also yields substantial improvements in patient and in graft survival (Berenguer, 2008); (Picciotto, 2007). The availability of effective IFN-free HCV treatments has addressed the major hurdles to treating HCV recurrence posttransplantation: poor tolerability and efficacy. In a multicenter, open-label study that evaluated the ability of sofosbuvir plus ribavirin to induce virologic suppression in 40 patients post–liver transplant with compensated recurrence of HCV infection, daily sofosbuvir and ribavirin for 24 weeks achieved an SVR at 12 weeks (SVR12) in 70% (Charlton, 2015). No deaths, graft losses, or episodes of rejection occurred. Six patients had serious adverse events, all of which were considered unrelated to study treatment. There were no drug interactions reported between sofosbuvir and any of the concomitant immunosuppressive agents. In contrast, treatment with sofosbuvir plus ribavirin with or without PEG-IFN in 64 patients with severe, decompensated cirrhosis resulting from recurrence of HCV infection following liver transplantation was associated with an overall SVR12 rate of 59% and a mortality rate of 13% (Forns, 2015). On an intent-to-treat basis, treatment was associated with clinical improvement in 57% and stable disease in 22% of patients. Given the clinical complexity including drug interactions and the need for close monitoring, patients with liver transplant should be treated by physicians with experience in treating this population (see Unique Patient Populations: Patients who Develop Recurrent HCV Infection Post-Liver Transplantation).

Persons at Greater Risk for Rapidly Progressive Fibrosis and Cirrhosis

Fibrosis progression is variable across different patient populations as well as within the same individual over time. Many of the components that determine fibrosis progression and development of cirrhosis in an individual are unknown. However, certain factors, such as coinfection with HIV or hepatitis B virus (HBV) and prevalent coexistent liver diseases (eg, nonalcoholic steatohepatitis [NASH]), are well-recognized contributors to accelerated fibrosis progression.

HIV coinfection. HIV coinfection accelerates fibrosis progression among HCV-infected persons, (Benhamou, 1999); (Macias, 2009); (Konerman, 2014) although control of HIV replication and restoration of CD4+ cell counts may mitigate this to some extent (Benhamou, 2001); (Bräu, 2006). However, antiretroviral therapy is not a substitute for HCV treatment. In the largest paired-biopsy study, 282 HIV/HCV-coinfected patients with 435 paired biopsies were prospectively evaluated; (Konerman, 2014) one-third of patients showed fibrosis progression of at least one Metavir stage at a median of 2.5 years. Importantly, 45% of patients with no fibrosis on initial biopsy had progression. Finally, a more rapid progression to death following decompensation combined with a lack of widespread access to liver transplantation and poor outcomes following transplantation highlight the need for treatment in this population regardless of current fibrosis stage (see Unique Patient Populations: Patients with HIV/HCV Coinfection) (Pineda, 2005); (Merchante, 2006); (Terrault, 2012).

HBV coinfection and other coexistent liver diseases. The prevalence of HBV/HCV coinfection is estimated at 1.4% in the United States and 5% to 10% globally (Tyson, 2013); (Chu, 2008). Persons with HBV/HCV coinfection and detectable viremia of both viruses are at increased risk for disease progression, decompensated liver disease, and the development of HCC.

HBV/HCV coinfected individuals are susceptible to a process called viral interference wherein one virus may interfere with the replication of the other virus. Thus, when treating one or both viruses with

antiviral drugs, periodic retesting of HBV DNA and HCV RNA levels during and after therapy is prudent, particularly if only one of the viruses is being treated at a time. Treatment of HCV infection in such cases utilizes the same genotype-specific regimens as are recommended for HCV monoinfection **(see Initial Treatment of HCV Infection)**. HBV infections in such cases should be treated as recommended for HBV monoinfection (Lok, 2009).

Persons with other chronic liver diseases who have coincident chronic HCV infection should be considered for hepatitis C therapy, given the potential for rapid progression of liver disease. An IFN-free regimen is generally preferred for immune-mediated liver diseases such as autoimmune hepatitis, because of the potential for IFN-related exacerbation.

Persons With Extrahepatic Manifestations of Chronic HCV Infection

Severe renal impairment. Chronic hepatitis C is associated with a syndrome of cryoglobulinemia and an immune complex and lymphoproliferative disorder that produces arthralgias, fatigue, palpable purpura, renal disease (eg, membranoproliferative glomerulonephritis), neurologic disease (eg, peripheral neuropathy, central nervous system vasculitis), and reduced complement levels (Agnello, 1992). Because patients with chronic hepatitis C frequently have laboratory evidence of cryoglobulins (more than 50% in some series), antiviral treatment is imperative for those with the syndrome of cryoglobulinemia and symptoms or objective evidence of end-organ manifestations. IFN-based regimens can produce clinical remission; however, the adverse effects of IFN may mimic manifestations of cryoglobulinemia (Saadoun, 2014). Although clinical data are not yet available, the use of IFN-free DAA regimens is an attractive option for these patients. Organ-threatening disease (eg, severe neuropathy, renal failure, digital ischemia), in addition to antiviral HCV therapy, should be treated more acutely with immunosuppressive agents or plasmapheresis to clear immune complexes.

Glomerular disease results from deposition of HCV-related immune complexes in the glomeruli (Johnson, 1993). Successful treatment of HCV using IFN-based regimens can reverse proteinuria and nephrotic syndrome but usually does not fully ameliorate azotemia (Johnson, 1994). No clinical trial data are yet available on IFN-free regimens, but the high rates of SVR (virologic cure) with antiviral therapy support their use in management of hepatitis C–related renal disease and cryoglobulinemia.

Nonhepatic Manifestations of Chronic HCV Infection

The relationship between chronic hepatitis C and diabetes (most notably type 2 diabetes and insulin resistance) is complex and incompletely understood. The prevalence and incidence of diabetes is increased in the context of hepatitis C (White, 2008). In the United States, type 2 diabetes occurs more frequently in HCV-infected patients, with a more than 3-fold greater risk in persons older than 40 years (Mehta, 2000). The positive correlation between quantity of plasma HCV RNA and established markers of insulin resistance confirms this relationship (Yoneda, 2007). Insulin resistance and type 2 diabetes are independent predictors of a more rapid progression of liver fibrosis and an impaired response to IFN-based therapy (Petta, 2008). Patients with type 2 diabetes and insulin resistance are also at increased risk for HCC (Hung, 2010).

Successful antiviral treatment has been associated with improved markers of insulin resistance and greatly reduced incidence of new onset of type 2 diabetes and insulin resistance in HCV-infected patients (Arase, 2009). Most recently, antiviral therapy for HCV infection has been shown to improve clinical outcomes related to diabetes. In a large prospective cohort from Taiwan, the incidence rates of end-stage renal disease, ischemic stroke, and acute coronary syndrome were greatly reduced in HCV-infected

patients with diabetes who received antiviral therapy compared with untreated, matched controls (Hsu, 2014). Therefore, antiviral therapy may prevent progression to diabetes in patients with prediabetes who have hepatitis C and may reduce renal and cardiovascular complications in patients with established diabetes who have hepatitis C.

In patients with chronic hepatitis C, fatigue is the most frequently reported symptom and has a major effect on quality of life and activity level evidenced by numerous measures of impaired quality of life (Foster, 1998). The presence and severity of fatigue appears to correlate poorly with disease activity, although it may be more common and severe in HCV-infected individuals with cirrhosis (Poynard, 2002a). Despite difficulties in separating fatigue symptoms associated with hepatitis C from those associated with other concurrent conditions (eg, anemia, depression), numerous studies have reported a reduction in fatigue after cure of HCV infection (Bonkovsky, 2007). In the Virahep-C study, 401 patients with HCV infection were evaluated for fatigue prior to and after treatment, using validated scales to assess the presence and severity of fatigue (Sarkar, 2012). At baseline, 52% of patients reported having fatigue, which was more frequent and severe in patients with cirrhosis than in those without cirrhosis. Achieving an SVR was associated with a substantial decrease in frequency and severity of fatigue. A recent analysis of 413 patients from the NEUTRINO and FUSION trials who were treated with a sofosbuvir-containing regimen and who achieved an SVR12 demonstrated improvement in patient fatigue (present in 12%) from the pretreatment level (Younossi, 2014). After achieving an SVR12, participants had marked improvements in fatigue over their pretreatment scores measured by 3 separate validated questionnaires. Additional studies support and extend these findings beyond fatigue, with improvements in overall health-related quality of life and work productivity observed following successful HCV therapy (Gerber, 2016); (Younossi, 2015b); (Younossi, 2015c); (Younossi, 2015d).

The reported prevalence of HCV infection in patients with porphyria cutanea tarda approximates 50% and occurs disproportionately in those with cirrhosis (Gisbert, 2003). The treatment of choice for active porphyria cutanea tarda is iron reduction by phlebotomy and maintenance of a mildly iron-reduced state without anemia. However, although improvement of porphyria cutanea tarda during HCV treatment with IFN has frequently been described (Takikawa, 1995), there are currently insufficient data to determine whether treating HCV infection with DAAs and achievement of SVR improve porphyria cutanea tarda.

Lichen planus is characterized by pruritic papules involving mucous membranes, hair, and nails. Antibodies to HCV are present in 10% to 40% of patients with lichen planus, but a causal link with chronic infection is not established. Resolution of lichen planus has been reported with IFN-based regimens, but there have also been reports of exacerbation of lichen planus with these treatments. Although it is unknown whether DAAs will have more success against lichen planus, treatment with IFN-free regimens would appear to be a more advisable approach to addressing this disorder (Gumber, 1995).

Benefit of Treatment to Reduce Transmission

Persons who have successfully achieved an SVR (virologic cure) no longer transmit the virus to others. As such, successful treatment of HCV infection benefits public health. Several health models have shown that even modest increases in successful treatment of HCV infection among persons who inject drugs can decrease prevalence and incidence (Martin, 2013a); (Durier, 2012); (Martin, 2013b); (Hellard, 2012). Models developed to estimate the impact of HCV testing and treatment on the burden of hepatitis C at a country level reveal that large decreases in HCV prevalence and incidence are possible as more persons are successfully treated (Wedemeyer, 2014). There are also benefits to eradicating HCV infection between couples and among families, and thus eliminating the perception that an individual might be

contagious. In addition, mother-to-child transmission of HCV does not occur if the woman is not viremic, providing an additional benefit of curing a woman before she becomes pregnant (Thomas, 1998). However, the safety and efficacy of treating women who are already pregnant to prevent transmission to the fetus have not yet been established, and thus treatment is not recommended for pregnant women.

The Society for Healthcare Epidemiology of America (SHEA) advises that health-care workers who have substantial HCV viral replication (≥104 genome equivalents/mL) be restricted from performing procedures that are prone to exposure (Henderson, 2010) and that all health-care workers with confirmed chronic HCV infection should be treated. For reasons already stated above, the achievement of an SVR in such individuals will not only eliminate the risk of HCV transmission to patients but also decrease circumstantial loss of experienced clinicians. Given concerns about underreporting of infection and transmission (Henderson, 2010), the availability of effective, all-oral regimens should lead to greater willingness on the part of exposure-prone clinicians to be tested and treated.

Successful treatment of HCV-infected persons at greatest risk for transmission represents a formidable tool to help stop HCV transmission in those who continue to engage in high-risk behaviors. To guide implementation of hepatitis C treatment as a prevention strategy, studies are needed to define the best candidates for treatment to stop transmission, the additional interventions needed to maximize the benefits of HCV treatment (eg, preventing reinfection), and the cost-effectiveness of the strategies when used in target populations.

Persons who inject drugs. Injection drug use (IDU) is the most common risk factor for HCV infection in the United States and Europe, with an HCV seroprevalence of 10% to 70%; (Amon, 2008); (Nelson, 2011) IDU also accounts for the majority of new HCV infections (approximately 70%) and is the key driving force in the perpetuation of the epidemic. Given these facts and the absence of an effective vaccine against HCV, testing and linkage to care combined with treatment of HCV infection with potent IFN-free regimens has the potential to dramatically decrease HCV incidence and prevalence (Martin, 2013b). However, treatment-based strategies to prevent HCV transmission have yet to be studied, including how to integrate hepatitis C treatment with other risk-reduction strategies (eg, opiate substitution therapy, needle and syringe exchange programs) (Martin, 2013a).

In studies of IFN-containing treatments in persons who inject drugs, adherence and efficacy rates are comparable to those of patients who do not use injection drugs. A recent meta-analysis of treatment with PEG-IFN with or without ribavirin in active or recent injection drug users showed SVR rates of 37% and 67% for HCV genotype 1 or 4 and 2 or 3, respectively (Aspinall, 2013). As shorter, better-tolerated, and more efficacious IFN-free therapies are introduced, these SVR rates are expected to improve. Importantly, the rate of reinfection in this population is lower (2.4/100 person-years of observation) than that of incident infection in the general population of injection drug users (6.1-27.2/100 person-years), although reinfection increases with active or ongoing IDU (6.44/100 person-years) and available data on follow-up duration are limited (Aspinall, 2013); (Grady, 2013).

Ideally, treatment of HCV-infected persons who inject drugs should be delivered in a multidisciplinary care setting with services to reduce the risk of reinfection and for management of the common social and psychiatric comorbidities in this population. Regardless of the treatment setting, recent and active IDU should not be seen as an absolute contraindication to HCV therapy. There is strong evidence from various settings in which persons who inject drugs have demonstrated adherence to treatment and low rates of reinfection, countering arguments that have been commonly used to limit access to this patient population (Aspinall, 2013); (Hellard, 2014); (Grebely, 2011). Indeed, combining HCV treatment with

needle exchange and opioid agonist therapy programs in this population with a high prevalence of HCV infection has shown great value in decreasing the burden of HCV disease. Elegant modeling studies illustrate the high return on the modest investment of addressing this often-ignored segment of the HCV-infected population (Martin, 2013b). These conclusions were drawn before the introduction of the latest DAA regimens. Conversely, there are no data to support the utility of pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned, because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from therapy. Scale up of HCV treatment in persons who inject drugs is necessary to positively impact the HCV epidemic in the United States and globally.

HIV-infected men who have sex with men (MSM) who engage in high-risk sexual practices. Over the past decade, a dramatic increase in incident HCV infections among HIV-infected MSM who did not report IDU as a risk factor has been demonstrated in several US cities (van de Laar, 2010). Recognition and treatment of HCV infection (including acute infection) in this population may represent an important step in preventing subsequent infections. As with persons who inject drugs, HIV/HCV-coinfected MSM who engage in ongoing high-risk sexual practices should be treated for their HCV infection in conjunction with continued education on risk-reduction strategies. In particular, safer-sex strategies should be emphasized given the high rates of reinfection after SVR, which may approach 30% over 2 years, in HIV-infected MSM with acute HCV infection (Lambers, 2011).

Incarcerated persons. Among incarcerated individuals, the rate of HCV seroprevalence ranges from 30% to 60% (Post, 2013) and the rate of acute infection is approximately 1% (Larney, 2013). Screening for HCV infection is relatively uncommon in state prison systems. Treatment uptake has been limited in part because of the toxic effects and long treatment duration of older IFN-based therapies as well as concerns about cost (Spaulding, 2006). In particular, truncation of HCV treatment owing to release from prison has been cited as a major limitation to widespread, effective HCV treatment in correctional facilities (Post, 2013); (Chew, 2009). Shorter (12- to 24-week) HCV therapies reduce duration of stay-related barriers to HCV treatment in prisons. Likewise, the improved safety of newer, all-oral regimens diminishes concerns of toxic effects. Coordinated treatment efforts within prison systems would likely rapidly decrease the prevalence of HCV infection in this at-risk population, although research is needed in this area.

Persons on hemodialysis. The prevalence rate of HCV infection is markedly elevated in persons on hemodialysis and ranged from 2.6% to 22.9% in a large multinational study (Fissell, 2004). Studies in the United States found a similarly elevated prevalence rate of 7.8% to 8.9% (Centers for Disease Control and Prevention, 2001); (Finelli, 2005). Importantly, the seroprevalence of HCV was found to increase with time on dialysis, suggesting that nosocomial transmission, among other risk factors, plays a role in HCV acquisition in these patients (Fissell, 2004). Improved education and strict adherence to universal precautions can drastically reduce nosocomial HCV transmission risks for persons on hemodialysis, (Jadoul, 1998) but clearance of HCV viremia through treatment-induced SVR eliminates the potential for transmission.

HCV-infected persons on hemodialysis have a decreased quality of life and increased mortality compared with uninfected persons on hemodialysis (Fabrizi, 2002); (Fabrizi, 2007); (Fabrizi, 2009). HCV infection in this population also has a deleterious impact on kidney transplantation outcomes with decreased patient and graft survival (Fabrizi, 2014). The increased risk for nosocomial transmission and the substantial clinical impact of HCV infection in those on hemodialysis are compelling arguments for HCV therapy as

effective antiviral regimens that can be used in persons with advanced renal failure become available (see Unique Patient Populations: Patients with Renal Impairment).

Populations Unlikely to Benefit From HCV Treatment

Patients with a limited life expectancy that cannot be remediated by treating HCV, by transplantation, or by other directed therapy do not require treatment. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert. Chronic hepatitis C is associated with a wide range of comorbid conditions (Butt, 2011); (Louie, 2012). Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) owing to non–liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence (Holmes, 2006); (Maddison, 2011).

Recommendations for Pretreatment Assessment

- **Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) (see HCV Testing and Linkage to Care).**
  Rating: Class I, Level A

An accurate assessment of fibrosis remains vital, as degree of hepatic fibrosis is one of the most robust prognostic factors used to predict HCV disease progression and clinical outcomes (Everhart, 2010). Individuals with severe fibrosis require surveillance monitoring for liver cancer, esophageal varices, and hepatic function (Garcia-Tsao, 2007); (Bruix, 2011). In some instances, the recommended duration of treatment is also longer.

Although liver biopsy is the diagnostic standard, sampling error and observer variability limit test performance, particularly when inadequate sampling occurs. Up to one-third of bilobar biopsies had a difference of at least 1 stage between the lobes (Bedossa, 2003). In addition, the test is invasive and minor complications are common, limiting patient and practitioner acceptance. Serious complications such as bleeding, although rare, are well recognized.

Noninvasive tests to stage the degree of fibrosis in patients with chronic HCV infection include models incorporating indirect serum biomarkers (routine tests), direct serum biomarkers (components of the extracellular matrix produced by activated hepatic stellate cells), and vibration-controlled transient liver elastography. No single method is recognized to have high accuracy alone and each test must be interpreted carefully. A recent publication of the Agency for Healthcare Research and Quality found evidence in support of a number of blood tests; however, at best, they are only moderately useful for identifying clinically significant fibrosis or cirrhosis (Selph, 2014).

Vibration-controlled transient liver elastography is a noninvasive way to measure liver stiffness and correlates well with measurement of substantial fibrosis or cirrhosis in patients with chronic HCV infection. The measurement range does overlap between stages (Ziol, 2005); (Afdhal, 2015); (Castera, 2005).

The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography (Boursier, 2012); (European Association for the Study of the Liver and Asociacion Latinoamericana para el Estudio del Higado, 2015). A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making. For example, one shows cirrhosis and the other does not. The need for liver biopsy with this approach is markedly reduced.

Alternatively, if direct biomarkers or vibration-controlled transient liver elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can help, (Sebastiani, 2009); (Castera, 2010); (Chou, 2013) although neither test is sensitive enough to rule out substantial fibrosis (Chou, 2013). Biopsy should be considered in those in whom more accurate fibrosis staging would impact treatment decisions. Individuals with clinically evident cirrhosis do not require additional staging (biopsy or noninvasive assessment).

Recommendations for Repeat Liver Disease Assessment

- **Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.**
  Rating: Class I, Level C

When therapy is deferred, it is especially important to monitor liver disease in these patients. In line with evidence-driven recommendations for treatment of nearly all HCV-infected patients, several factors must be taken into consideration if treatment deferral is entertained or mandated by lack of medication access. As noted, strong and accumulating evidence argue against deferral because of decreased all-cause morbidity and mortality, prevention of onward transmission, and quality-of-life improvements for patients treated regardless of baseline fibrosis. Additionally, treatment of HCV infection may improve or prevent extraheptatic complications, including diabetes mellitus, cardiovascular disease, renal disease, and B-cell non-Hodgkin lymphoma, (Conjeevaram, 2011); (Hsu, 2015); (Torres, 2015) which are not tied to fibrosis stage (Allison, 2015); (Petta, 2016). Deferral practices based on fibrosis stage alone are inadequate and shortsighted.

Fibrosis progression varies markedly between individuals based on host, environmental, and viral factors (**Table 1**) (Feld, 2006). Fibrosis may not progress linearly. Some individuals (often those aged ≥50 years) may progress slowly for many years followed by an acceleration of fibrosis progression. Others may never develop substantial liver fibrosis despite longstanding infection. The presence of existing fibrosis is a strong risk factor for future fibrosis progression. Fibrosis results from chronic hepatic necroinflammation, and thus a higher activity grade on liver biopsy and higher serum transaminase values are associated with more rapid fibrosis progression (Ghany, 2003). However, even patients with normal ALT levels may develop substantial liver fibrosis over time (Pradat, 2002); (Nutt, 2000). The limitations of transient elastography and liver biopsy in ascertaining the progression of fibrosis must be recognized.

Host factors associated with more rapid fibrosis progression include male sex, longer duration of infection, and older age at the time of infection (Poynard, 2001). Many patients have concomitant nonalcoholic fatty liver disease, and the presence of hepatic steatosis with or without steatohepatitis on liver biopsy, elevated body mass index, insulin resistance, and iron overload are associated with fibrosis

progression (Konerman, 2014); (Everhart, 2009). Chronic alcohol use is an important risk factor because alcohol consumption has been associated with more rapid fibrosis progression (Feld, 2006). A safe amount of alcohol consumption has not been established. Cigarette smoking may also lead to more rapid fibrosis progression. For more counseling recommendations, please see Testing and Linkage to Care.

Immunosuppression leads to more rapid fibrosis progression, particularly HIV/HCV coinfection and solid organ transplantation (Macias, 2009); (Konerman, 2014); (Berenguer, 2013). Therefore, immunocompromised patients should be treated even if they have mild liver fibrosis at presentation.

Level of HCV RNA does not correlate with stage of disease (degree of inflammation or fibrosis). Available data suggest that fibrosis progression occurs most rapidly in patients with HCV genotype 3 infection (Kanwal, 2014); (Bochud, 2009). Aside from coinfection with HBV or HIV, no other viral factors are consistently associated with disease progression.

Although an ideal interval for assessment has not been established, annual evaluation is appropriate to discuss modifiable risk factors and to update testing for hepatic function and markers for disease progression. For all individuals with advanced fibrosis, liver cancer screening dictates a minimum of evaluation every 6 months.

When and in Whom to Initiate HCV Therapy Table 1. Factors Associated With Accelerated Fibrosis Progression

Host	Viral
Nonmodifiable	HCV genotype 3
Fibrosis stage	Coinfection with hepatitis B virus or HIV
Inflammation grade	
Older age at time of infection	
Male sex	
Organ transplant	
Modifiable	
Alcohol consumption	
Nonalcoholic fatty liver disease	
Obesity	
Insulin resistance	

Changes made July 6, 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Summary of Recommendations for When and in Whom to Initiate HCV Therapy

Goal of Treatment

- **The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.**
  Rating: Class I, Level A

Recommendations for When and in Whom to Initiate Treatment

- **Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.**
  Rating: Class I, Level A

Recommendations for Pretreatment Assessment

- **Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) (see HCV Testing and Linkage to Care).**
  Rating: Class I, Level A

Recommendations for Repeat Liver Disease Assessment

- **Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.**

Rating: Class I, Level C

When and in Whom to Initiate HCV Therapy Table 1. Factors Associated With Accelerated Fibrosis Progression

Host	Viral
Nonmodifiable	HCV genotype 3
Fibrosis stage	Coinfection with hepatitis B virus or HIV
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Male sex	
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Alcohol consumption	
Nonalcoholic fatty liver disease	
Obesity	
Insulin resistance	

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OVERVIEW OF COST, REIMBURSEMENT, AND COST-EFFECTIVENESS CONSIDERATIONS FOR HEPATITIS C TREATMENT REGIMENS

The Hepatitis C Guidance describes how to diagnose, link to care, and treat most groups of patients with HCV (AASLD-IDSA, 2016). However, a common challenge is reduced access to treatment caused by restrictions on drug reimbursement. This section summarizes the US payer system, explains the concepts of cost, price, cost-effectiveness, value, and affordability, and reviews current evidence of the cost-effectiveness of strategies to improve access to treatment. Although these may sound similar and are often confused, the following discussion will seek to clarify these terms with regard to HCV therapy. To be clear, this section is informational. As explained below, actual costs are rarely known. Accordingly, the HCV Guidance does not utilize cost-effectiveness analysis to guide recommendations at this time.

Table. Abbreviations Specific to Overview of Cost, Reimbursement, and Cost-Effectiveness Considerations for Hepatitis C Treatment Regimens

Abbreviation	Expanded Name
ACA	Affordable Care Act
AMP	Average manufacturer price
AWP	Average wholesale price[a]
CEA	Cost-effectiveness analysis
Cn	Cost of new therapy
Co	Cost of old therapy
ICER	Incremental cost-effectiveness ratio
PBM	Pharmacy benefit manager
QALY	Quality-adjusted life-year

QALYn	Quality-adjusted life-year of new therapy
QALYo	Quality-adjusted life-year of old therapy
WAC	Wholesale acquisition cost[b]

[a] "List price" for wholesale pharmacies to purchase drugs.

[b] Typically, approximately 17% off of AWP.

Drug Cost and Reimbursement

There are many organizations involved with the distribution of hepatitis C drugs and each can impact costs, as well as the decision of which regimens are reimbursed (US Government Accountability Office, 2015); (Congress of the United States Congressional Budget Office, 2015). The roles these organizations have in determining the actual price paid for drugs and who has access to treatment include the following:

- Pharmaceutical companies determine the wholesale acquisition cost (WAC) of a drug (like a "sticker price"). The company negotiates contracts with other organizations within the pharmaceutical supply chain that allow for rebates or discounts that decrease the actual price paid.
- Pharmacy benefit managers (PBMs) often negotiate contracts with pharmaceutical companies on behalf of health insurance companies. Such contracts may include restrictions on who can be reimbursed for treatment and may offer exclusivity (restrictions on which medications can be prescribed) in exchange for lower prices, often provided in the form of WAC discounts.
- Private insurance companies often have separate pharmacy and medical budgets and use PBMs or negotiate drug pricing directly with pharmaceutical companies. Insurance companies determine formulary placement, which impacts choice of regimens and out-of-pocket expenses for patients. An insurance company can cover private, managed care Medicaid, and Medicare plans and can have different formularies for each line of business.
- Medicaid is a heterogeneous compilation of insurance plans that includes fee-for-service and managed care options. Most plans negotiate rebates with pharmaceutical manufacturers (through PBMs or individually). Differences in negotiated contracts between plans have led to Medicaid patients in different states having widely varied access to HCV therapy (Canary, 2015). Disparities may even exist between patients enrolled in different Medicaid plans within the same state (Barua, 2015). State Medicaid programs have benefited from the Patient Protection and Affordable Care Act (ACA), although such benefits are mitigated in states that have opted out of expanding Medicaid coverage under the ACA. In general, for single-source drugs such as the currently available hepatitis C treatments, Medicaid plans receive the lowest price offered to any other payer (outside certain government agencies), and the minimum Medicaid drug rebate is 23.1% of the average manufacturer price (AMP; another payment benchmark).
- Medicare covers HCV drugs through Part D benefits and is prohibited by law from directly negotiating drug prices. These drug plans are offered through PBMs or commercial health plans, which may negotiate discounts or rebates with pharmaceutical companies.
- The Veterans Health Administration receives mandated rebates through the Federal Supply Schedule, which sets drug prices for a number of government agencies, including the Department of Veterans Affairs, federal prisons, and the Department of Defense, and typically receives substantial discounts over average wholesale price (AWP; another payment benchmark).

- State prisons and jails are usually excluded from Medicaid-related rebates and often do not have the negotiating leverage of larger organizations and may end up paying higher prices than most other organizations.
- Specialty pharmacies receive dispensing fees and may receive additional payments from contracted insurance companies, PBMs, or pharmaceutical companies to provide services such as adherence support, management of adverse effects, and outcomes measurements such as early discontinuation rates and sustained virologic response rates.
- Patients incur costs (eg, copayment or coinsurance) determined by their pharmacy plan. Patient assistance programs through pharmaceutical companies or foundations can cover many of these out-of-pocket expenses or provide drugs at no cost to qualified patients who are unable to pay.

With the exception of mandated rebates, negotiations of drug prices are considered confidential business contracts and, therefore, there is almost no transparency regarding the actual prices paid for hepatitis C drugs (Saag, 2015). However, the average negotiated discount of 22% in 2014 increased to 46% off the WAC in 2015, implying that many payers are paying well below the WAC price for HCV regimens (Committee on Finance United States Senate, 2016).

Cost-effectiveness

Cost-effectiveness analysis (CEA) compares the relative costs and outcomes of two or more interventions. CEA explicitly recognizes budget limitations for healthcare spending and seeks to maximize public health benefits within those budget constraints. CEA is typically expressed as an incremental cost-effectiveness ratio (ICER), the ratio of change in costs between two or more interventions to the change in effects. In short, CEA provides a framework for comparing the healthcare costs and societal benefits of different technologies or therapies.

To make such comparisons, three questions first need to be answered:

1. How much more will we spend on a new intervention? This is not as simple as determining the cost of a new medication, but also the cost of the intervention over the course of a person's lifetime and the cost savings from the prevention or attenuation of disease complications. Further, the cost of current standard therapy and the cost of the disease should be considered, so incremental cost-effectiveness requires understanding the incremental cost of new versus old. Given the lack of transparency in healthcare costs in the United States, this is at best an inexact estimate.
2. How much more benefit accrues from a new intervention? To compare health interventions using a single metric across diseases and interventions and to integrate both duration and quality of life gained, benefit is measured in terms of quality-adjusted life-years (QALYs). CEA asks: "If a new therapy is implemented, how many more QALYs will likely be gained from the new medications?"
3. How much is society willing to pay to gain one additional QALY? This willingness-to-pay threshold typically varies by country and acknowledges opportunity costs. Spending more money on one disease may mean spending less money on other diseases. Similarly, spending more on health care means less spending for education, defense, or environment. Although it may seem inappropriate to set a monetary value on human life, willingness-to-pay thresholds only acknowledge that budgets are finite and provide a measure of societal value. They are not intended to be a moral valuation.

Once these questions are answered, CEA provides a simple rubric for making normative determinations about whether a new technology provides good value for its cost. First, the ICER of the new therapy is calculated as: $(Cn - Co) \div (QALYn - QALYo)$, where Cn is the cost of the new therapy, Co is the cost of the

old (comparison) therapy, and QALY is quality-adjusted life-year, shown as new (n) or old (o).

Once the ICER is determined, it is compared with the societal willingness-to-pay threshold (typically considered to be $50,000 to $100,000/QALY gained in the United States). ICERs that are less than the willingness-to-pay threshold represent a good value, and such interventions can be considered cost effective. Interventions with ICERs exceeding the willingness-to-pay threshold would be less efficient uses of limited budget resources.

Affordability

An intervention that is cost effective is not necessarily affordable. Affordability refers to whether a payer has sufficient resources in its annual budget to pay for a new therapy for all who might need or want it within that year. Several characteristics of CEA limit its ability to speak to the budget impact of interventions being implemented in the real world:

1. **Perspective on cost:** CEA seeks to inform decisions about how society should prioritize healthcare spending. As such, it typically assumes a societal perspective on costs and includes all costs from all payers, including out-of-pocket expenses for the patient. When making coverage decisions for therapy, however, an insurer considers only its own revenues and expenses.
2. **Time horizon:** CEA uses a lifetime time horizon, meaning that it considers lifetime costs and benefits, including those that occur in the distant future. Business budget planning, however, typically assumes a 1-year to 5-year perspective. Savings that may accrue 30 years from now have very little impact on spending decisions today, because they have little bearing on the solvency of the budget today.
3. **Weak association between willingness to pay and the real-world bottom line:** Societal willingness-to-pay thresholds in CEAs are not based on actual budget calculations and have little connection to a payer's bottom line. Given the rapid development of new technologies, funding all of them, even if they all fell below the societal willingness-to-pay threshold, would likely lead to uncontrolled growth in demand and would likely exceed the limited healthcare budget.

There is no mathematic formula that provides a good means of integrating the concerns of value and affordability. When new therapies for HCV are deemed cost effective, it indicates that such therapies provide excellent benefits for the resources invested in their use and that providing more therapy is a good investment in the long term. Determining the total resources that can be spent on HCV treatment, however, depends on political and economic factors that are not captured by cost-effectiveness determinations.

Cost-effectiveness of Current All-Oral Regimens for Hepatitis C Treatment

Recently published studies compared all-oral, direct-acting antiviral (DAA) regimens to previous standard-of-care regimens (usually IFN based) to calculate ICERs. In general, treating patients with more advanced fibrosis or cirrhosis provided better value (lower ICERs) than treating those with milder disease. Indeed, the ICERs of therapy for treatment-naïve patients who do not have cirrhosis are generally within the range of other widely used medical therapies. Although it is possible to make some general comments about cost-effectiveness for these new HCV drug regimens, it is important to recognize that this task is difficult, owing to the rapid changes in available drugs, the variability in cost (see above), and individual patient characteristics such as fibrosis stage, comorbidities, estimated life expectancy, and HCV genotype.

HCV Genotype 1

There are several cost-effectiveness studies of IFN-free, DAA therapy for HCV genotype 1 infection across various models that use independently derived assumptions about disease progression, costs, and quality of life. Most have shown ICERs within the range of other accepted medical practices. Published ICERs of all-oral regimens for treatment-naïve patients with HCV genotype 1 infection in the United States range from cost saving (less than $0) to $31,452 per QALY gained, depending on the presence or absence of cirrhosis (Chatwal, 2015); (Najafzadeh, 2015); (Linas, 2015); (Younossi, 2015a); (Tice, 2015); (Chidi, 2016). However, ICERs as high as $84,744 to $178,295 per QALY gained have been reported among the more recalcitrant IFN-experienced patients with fibrosis who are being retreated using an IFN-free regimen (Chatwal, 2015).

HCV Genotype 2

ICERs of all-oral regimens in HCV genotype 2–infected persons ranged from $35,500 to $238,000 per QALY gained, depending on the presence or absence of cirrhosis (Chatwal, 2015); (Najafzadeh, 2015); (Linas, 2015). In analyses among treatment-naïve patients without cirrhosis, the AWP of sofosbuvir led to ICERs being higher than US willingness-to-pay thresholds, but with the lower costs negotiated by some payers, the ICERs for all patient groups would fall within accepted pay thresholds for other accepted medical interventions in the United States (Najafzadeh, 2015); (Linas, 2015).

HCV Genotype 3

The ICERs of IFN-free therapy for HCV genotype 3 infection reflect the clinical reality that IFN-free regimens are less effective for treating patients with this genotype than any other genotype. As a result, ICERs of all-oral regimens ranged from being inferior (costing more with lower effectiveness) to $410,548 per QALY gained, depending on the presence or absence of cirrhosis (Chatwal, 2015); (Linas, 2015). In one analysis, the preferred therapy for HCV genotype 3 infection from a purely cost-effectiveness–based perspective was PEG-IFN, ribavirin, and sofosbuvir (Linas, 2015).

HCV Genotype 4

For HCV genotype 4 infection, ICERs of all-oral regimens ranged from $34,349 to $80,793 per QALY gained, depending on the presence or absence of cirrhosis (Chatwal, 2015). However, these findings are based on treatment efficacy from small studies and must be confirmed once better data on treatment response are available.

Limitations

These published CEAs considered a variety of all-oral and nonoral regimens, often for different treatment durations, and patient populations and were not always consistent with current treatment recommendations and guidelines. Some regimens recommended in the HCV Guidance have not yet been subjected to economic analyses. Analyses used published WAC prices, which are lower than AWP prices used in older CEAs but higher than the actual prices paid by many payers and reflect an upper threshold of ICER, but most also examined the impact of negotiated price discounts on cost-effectiveness conclusions. Other analyses that are not described here include, for example, the impact of immediate versus delayed treatment (Rein, 2015); (Chahal, 2016); (Martin, 2016) and HCV treatment as prevention (Harris, 2016); (He, 2016); (Martin, 2016).

Conclusions

Although the wholesale acquisition costs of HCV drugs often make treatment appear unaffordable, the reality is that insurers, PBMs, and government agencies negotiate pricing and few actually pay the much-publicized WAC (retail). However, the negotiated pricing and cost structure for pharmaceutical products in the United States are not transparent, and it is therefore difficult to estimate the true cost and cost-effectiveness of HCV drugs. Whatever the actual current cost of HCV DAAs, competition and negotiated pricing have not improved access to care for many persons with HCV infection and continue to limit the public health impact of these new therapies. Insurers, government, and pharmaceutical companies should work together to bring medication prices to the point where all of those in need of treatment are able to afford and readily access it.

Changes made July 6, 2016.

Published on Recommendations for Testing, Managing, and Treating Hepatitis C (http://www.hcvguidelines.org)

INITIAL TREATMENT OF HCV INFECTION

(Expansions and notes for abbreviations used in this section can be found in Methods Table 3. A summary of recommendations for initial treatment is found in the box.)

Initial treatment of HCV infection includes patients with chronic hepatitis C who have not been previously treated with IFN, PEG-IFN, ribavirin, or any HCV direct-acting antiviral (DAA) agent, whether experimental, investigational, or US Food and Drug Administration (FDA) approved.

The level of evidence available to inform the best regimen for each patient and the strength of the recommendation vary, and are rated accordingly (see Methods Table 2). In addition, specific recommendations are given when treatment differs for a particular group (eg, those infected with various genotypes). Recommended regimens are those that are favored for most patients in that subgroup, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration. Alternative regimens are those that are effective but have, relative to Recommended regimens, potential disadvantages, limitations for use in certain patient populations, or less supporting data than Recommended regimens. In certain situations, an Alternative regimen may be an optimal regimen for a specific patient situation. Not Recommended regimens are clearly inferior compared to Recommended or Alternative regimens due to factors such as lower efficacy, unfavorable tolerability and toxicity, longer duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection. Specific considerations of persons with HIV/HCV coinfection, decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C), HCV infection post-liver transplant, and those with severe renal impairment or end-stage renal disease (ESRD) are addressed in other sections of the Guidance.

Recommended and Alternative regimens are listed in order of level of evidence. When several regimens are offered at the same recommendation level, they are listed in alphabetical order. Choice of regimen should be determined based on patient-specific data, including drug interactions. As always, patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen (see Monitoring section).

I. Genotype 1

Six highly potent DAA oral combination regimens are Recommended for patients with HCV genotype 1 infection, although there are differences in the Recommended regimens based on the HCV subtype, the presence or absence of baseline NS5A resistance-associated substitutions (RASs), and the presence or absence of cirrhosis.

With certain regimens, patients infected with genotype 1a may have higher rates of virologic failure than those infected with genotype 1b. HCV genotype 1 infection that cannot be subtyped should be treated as genotype 1a infection.

Approximately 10%-15% of HCV genotype 1-infected patients without prior exposure to NS5A inhibitors will have detectable HCV NS5A RASs at the population level prior to treatment. While the clinical impact of NS5A RASs remains to be fully elucidated, in patients with genotype 1a infection the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (> 5 fold) adversely impacts response to NS5A-containing regimens (Zeuzem, 2015b); (Jacobson, 2015b). These RASs include substitutions at positions M28, Q30, L31, and Y93 in genotype 1a and are found by population sequencing in roughly 5%-10% of patients. Given that baseline NS5A RASs are one of the strongest pre-treatment predictors of treatment outcome with certain regimens, testing for these RASs prior to deciding on a therapeutic course is now recommended in select situations (Zeuzem, 2015c).

The introduction of DAAs into HCV treatment regimens increased the risk of drug interactions with concomitant medications, and now with combinations of DAAs, attention to drug interactions is all the more important (see Drug Interactions table). The product prescribing information and other resources (eg, http://www.hep-druginteractions.org) should be referenced regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all of the regimens discussed below.

A. Genotype 1a

Genotype 1a Treatment-Naïve Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis and in whom no baseline NS5A RASs[§] for elbasvir are detected. Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis. Rating: Class I, Level A. An 8-week duration is Recommended for treatment-naïve patients without cirrhosis who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL. Rating: Class I, Level B

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25

mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.
Rating: Class I, Level A

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.
  Rating: Class I, Level B

[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1a Treatment-Naïve Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis and in whom no baseline NS5A RASs[§] for elbasvir are detected.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.
§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a Treatment-Naïve Patients Without Cirrhosis - Alternative

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 16 weeks is an Alternative regimen for patients with HCV genotype 1a infection who do not have cirrhosis but have baseline NS5A RASs§ for elbasvir.
  Rating: Class IIa, Level B

§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a Treatment-Naïve Patients with Compensated Cirrhosis‡ - Alternative

Alternative regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.†
  Rating: Class I, Level A
- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis and in whom no Q80K substitution is detected.
  Rating: Class II, Level B
- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.
  Rating: Class IIa, Level B
- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 16 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis and have baseline NS5A RASs§ for elbasvir.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
† Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

For HCV genotype 1a-infected, treatment-naïve patients without cirrhosis, there are six regimens recommended based on comparable efficacy, as outlined above. For cirrhotic patients, some are classified as Alternative regimens because compared to the Recommended, they have longer duration, potentially reduced efficacy, and/or limited supporting data.

Elbasvir/grazoprevir

The fixed-dose combination of elbasvir (50 mg) and grazoprevir (100 mg) (hereafter elbasvir/grazoprevir) can be recommended based on data from the phase III C-EDGE trial, which assessed the efficacy and safety of elbasvir/grazoprevir for 12 weeks in treatment-naïve adults (genotypes 1, 4, and 6) (Zeuzem, 2017). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred and eighty-two patients (91% of study cohort) receiving 12 weeks of elbasvir/grazoprevir were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The sustained virologic response rate at 12 weeks (SVR12) was 92% in treatment-naïve patients with HCV genotype 1a infection (144/157) and 99% in genotype 1b (129/131) patients receiving 12 weeks of elbasvir/grazoprevir. Findings from this phase III study supported earlier phase II findings from the C-WORTHY trial in which SVR12 rates of 92% (48/52) and 95% (21/22) were demonstrated among genotype 1a and genotype 1b treatment-naïve non-cirrhotic HCV-infected patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin (Sulkowski, 2015b). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients. Recommendations for cirrhotic patients are based on 92 (22%) patients in the phase III C-EDGE trial who had Metavir F4 disease (Zeuzem, 2017). SVR12 was 97% in the subgroup of cirrhotic patients. A similar 97% (28/29) SVR12 rate had previously been demonstrated in genotype 1 cirrhotic treatment-naïve patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase II C-WORTHY trial (Lawitz, 2015c). Presence or absence of compensated cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen (Lawitz, 2015c); (Zeuzem, 2017).

Presence of certain baseline NS5A RASs significantly reduces rates of SVR12 with a 12-week course of the elbasvir/grazoprevir regimen in genotype 1a-infected patients (Zeuzem, 2017). NS5A RASs were identified at baseline in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study of which 58% (11/19) achieved SVR12 compared to an SVR12 rate of 99% (133/135) in patients without these RASs receiving 12 weeks of elbasvir/grazoprevir (Zeuzem, 2017). Among treatment-naïve patients, the presence of baseline NS5A RASs with a larger than 5-fold shift to elbasvir was associated with the most significant reductions in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12. Recommendations for prolonging duration of treatment to 16 weeks with inclusion of ribavirin for treatment-naïve genotype 1a patients with baseline NS5A RASs is based on extrapolation of data from the C-EDGE TE trial. In this phase III open-label trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, among 58 genotype 1a patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures (Kwo, 2017).

Subsequent integrated analysis of the elbasvir/grazoprevir phase II and III trials have demonstrated SVR12 rates of 100% (6/6 patients) in genotype 1 patients with pre-treatments NS5A RASs treated with elbasvir/grazoprevir for 16/18 weeks plus ribavirin (Jacobson, 2015b); (Thompson, 2015). Based on known inferior response in patients with presence of baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for therapy with elbasvir/grazoprevir. If baseline RASs are present, ie, substitutions at amino acid positions 28, 30, 31, or 93, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) is recommended to decrease relapse.

Lack of RAS testing results or lack of access to RAS testing should not be used as a means to limit access to HCV therapy.

Ledipasvir/sofosbuvir

The fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter, ledipasvir/sofosbuvir) was approved by the FDA for the treatment of HCV genotype 1 infection in treatment-naïve patients based on two registration trials: ION-1 (865 treatment-naïve patients; those with cirrhosis were included) and ION-3 (647 treatment-naïve patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 was 97% to 99% across all arms, with no difference in SVR based on length of treatment, use of ribavirin, or HCV genotype 1 subtype. Sixteen percent of subjects enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%). ION-3 excluded patients with cirrhosis and investigated shortening therapy from 12 weeks to 8 weeks (with or without ribavirin) (Kowdley, 2014). SVR12 rate was 93% to 95% across all arms, with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20/431) regardless of ribavirin use compared with the 12-week arm (3/216). Post-hoc analyses of the 2 ribavirin-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients receiving 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels below 6 million IU/mL (2%; 2/123), and was the same for patients with similar baseline HCV RNA levels who received 12 weeks (2%; 2/131). This analysis was not controlled and thus limits the generalizability of this approach to clinical practice. Published real-world cohort data generally show comparable effectiveness of 8 and 12 weeks in treatment-naïve patients without cirrhosis (Backus, 2016); (Ingiliz, 2016); (Ioannou, 2016); (Kowdley, 2016); (Terrault, 2016); however, only about half of patients "eligible" for 8 weeks received it, assignment of duration was not randomized, and baseline characteristics may have varied between 8- and 12-week groups. Based on available data, shortening treatment to less than 12 weeks is Not Recommended for HIV-infected patients (see HIV/HCV Coinfection section) and African-American patients (Su, 2016); (Wilder, 2016); (O'Brien, 2014). For others, it should be done at the discretion of the practitioner with consideration taken of other potential negative prognostic factors.

Paritaprevir/ritonavir/ombitasvir + dasabuvir

The daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) plus weight-based ribavirin was approved by the FDA for the treatment of HCV genotype 1a infection in treatment-naïve patients based on three registration trials: SAPPHIRE-I (322 treatment-naïve patients with genotype 1a HCV infection without cirrhosis),

PEARL-IV (305 treatment-naïve patients with genotype 1a without cirrhosis), and TURQUOISE-II (261 treatment-naïve and -experienced patients with HCV genotype 1a and cirrhosis). The SAPPHIRE-I trial reported a high SVR12 rate (95.3%) with 12 weeks of PrOD and ribavirin (Feld, 2014). Overall, virologic failure was higher for patients with HCV genotype 1a (7 of 8 failures had genotype 1a) than patients with HCV genotype 1b (1 virologic failure). PEARL-IV was specifically designed to determine the role of PrOD with or without weight-based ribavirin for treatment-naïve, HCV genotype 1a-infected patients without cirrhosis (Ferenci, 2014). SVR12 was lower in the ribavirin-free arm than in the ribavirin-containing arm (90% vs 97%, respectively) owing to higher rates of virologic failure (7.8% vs 2%, respectively), confirming the need for weight-based ribavirin for patients with HCV genotype 1a. TURQUOISE-II enrolled treatment-naïve and -experienced patients (261 patients with HCV genotype 1a) with CTP class A cirrhosis to receive either 12 weeks or 24 weeks of treatment with PrOD plus ribavirin. Overall, SVR12 rates were 89% in the 12-week arm and 95% in the 24-week arm (Poordad, 2014). This difference in SVR12 rate between arms was primarily driven by patients with null response to PEG-IFN/ribavirin; there was less difference in SVR rates in the patients with cirrhosis who were naïve to therapy (92% and 95%, respectively) (paritaprevir/ritonavir/ombitasvir prescribing information); (Poordad, 2014). In 2016, an extended release formulation of PrOD was approved allowing once daily dosing (RBV when needed remains twice daily) (Viekira XR PI).

In October 2015, the FDA released a warning regarding the use of the PrOD or PrO (without dasabuvir) in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.) PrOD and PrO are contraindicated in patients with Child Turcotte Pugh (CTP) class B or C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported rapid onset of liver injury and in some cases hepatic decompensation in patients with cirrhosis, including CTP class A compensated cirrhosis and decompensated cirrhosis, who were receiving PrOD or PrO. The liver injury and decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of PrOD or PrO resulted in resolution of injury, although some patients, including at least 2 patients with CTP class A compensated cirrhosis, died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and in many cases its resolution with discontinuation of treatment with PrOD or PrO is suggestive of drug-induced liver injury. Although PrOD and PrO are contraindicated in patients with CTP class B or C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.

For patients with CTP class A cirrhosis, the unlikely but real possibility of drug-induced liver injury should be discussed with the patient. If the decision is made to initiate treatment with PrOD or PrO, close monitoring of total and direct bilirubin and transaminase levels every 1 week or 2 weeks for the first 4 weeks is recommended to ensure early detection of drug-induced liver injury. Also, educating patients about the importance of reporting systemic symptoms such as jaundice, weakness, and fatigue is strongly recommended. The regimen should be discontinued immediately if drug-induced liver injury is detected. If a patient is already taking PrOD or PrO and is tolerating the regimen, laboratory monitoring as above without discontinuation is recommended unless there are signs or symptoms of liver injury. If heightened monitoring cannot be provided in the first 4 weeks of therapy with PrOD or PrO in patients with cirrhosis, the use of these regimens is not recommended.

Simeprevir + sofosbuvir

The OPTIMIST-1 and -2 trials investigated the safety and efficacy of simeprevir (150 mg) and sofosbuvir (400 mg) in chronically infected patients with HCV genotype 1 without and with cirrhosis, respectively. In the OPTIMIST-1 study, 310 treatment-naïve and -experienced patients without cirrhosis were randomly assigned to 12 vs 8 weeks of the simeprevir plus sofosbuvir regimen (Kwo, 2016). The overall SVR12 rate was 97% (150/155) versus 83% (128/155), respectively, with a statistically significantly greater relapse rate in the 8-week arm. In the 12-week arm there was no difference in SVR12; treatment-naïve and -experienced patients achieved SVR12 rates of 97% and 95%, respectively. There was also no difference in SVR12 based on genotype 1 subtype or presence of the baseline Q80K resistance substitution. A post-hoc analysis suggested that patients with a baseline HCV RNA level below 4 million IU/mL achieved the same SVR12 rate (96%) regardless of the length of treatment. This defined baseline HCV RNA level is different than the 6 million IU/mL defined in the ION-3 trial, suggesting these post-hoc analysis cut-offs are arbitrary and unlikely to translate to clinical practice. At this time an 8-week regimen of simeprevir and sofosbuvir cannot be recommended.

The OPTIMIST-2 study was a single-arm, open-label trial investigating 12 weeks of simeprevir plus sofosbuvir in 103 treatment-naïve and -experienced patients with cirrhosis (Lawitz, 2016b). The overall SVR12 rate was 83% (86/103), with 88% (44/50) of treatment-naïve and 79% (42/53) of treatment-experienced patients achieving SVR12. In addition, patients infected with HCV genotype 1a and 1b without the Q80K substitution had similar SVR12 rates (84% [26/31] and 92% [35/38], respectively). However, patients with HCV genotype 1a infection and the Q80K substitution had lower SVR12 rates (74% [25/34]). Thus, extending treatment to 24 weeks, with or without ribavirin, is recommended for patients with cirrhosis receiving simeprevir plus sofosbuvir to decrease the risk of relapse. At this time it is unclear whether extending treatment, with or without the addition of ribavirin, will increase efficacy in genotype 1a-infected patients with the Q80K substitution. Given the lower response rate in patients with cirrhosis, it is reasonable to avoid this regimen in patients with this baseline substitution.

Sofosbuvir/velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg) and velpatasvir (100 mg) (hereafter, sofosbuvir/velpatasvir) was approved by the FDA for the treatment of HCV genotype 1 infection in treatment-naïve patients based on ASTRAL-1, a placebo-controlled trial that gave 12 weeks of sofosbuvir/velpatasvir to 624 participants with HCV genotypes 1, 2, 4, 5, and 6 who were treatment-naïve (n= 423) or previously treated with interferon-based therapy with or without ribavirin or a protease inhibitor (n= 201) (Feld, 2015). Of the 328 genotype 1 patients included, 323 achieved SVR with no difference in SVR observed by HCV genotype (98% 1a and 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A resistance-associated substitutions (at 15% cut off), reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested, did not influence SVR rate for genotype 1 (Hezode, 2016). Of the 2 virologic failures in ASTRAL-1 (< 1% of treated participants), both were genotype 1 and had baseline RASs present. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir group and the placebo group.

Daclatasvir + sofosbuvir

Daclatasvir in combination with sofosbuvir for the treatment of HCV genotype 1 infection can be recommended based on data from the phase III ALLY-2 trial, which assessed the efficacy and safety of daclatasvir and sofosbuvir for 12 weeks in patients coinfected with HIV and HCV (genotypes 1-4) (Wyles, 2015). One hundred twenty-three (83%) patients receiving 12 weeks of therapy in the trial were infected with HCV genotype 1. Eighty-three (54%) of these patients were treatment-naïve. The sustained virologic response (SVR) rate was 96% in treatment-naïve patients with HCV genotype 1a infection (n= 71) receiving 12 weeks of therapy. However, only 9 treatment-naïve patients had cirrhosis. Similarly, in the phase IIb study of daclatasvir and sofosbuvir (A1444040) in 88 treatment-naïve patients with HCV genotype 1a infection, 21 were treated for 24 weeks (11 with ribavirin) and 67 were treated for 12 weeks (33 with ribavirin), and there were no virologic relapses. However, there were only 14 patients with cirrhosis in the 12-week and 24-week study arms (Sulkowski, 2014a). Because patients with cirrhosis were not adequately represented in these studies, the optimal duration of treatment for patients with cirrhosis remains unclear. Cohort studies of a compassionate-use program in Europe suggest that patients with cirrhosis may benefit from extension of therapy with daclatasvir and sofosbuvir to 24 weeks, with or without ribavirin (Welzel, 2016); (Pol, 2017). The phase III ALLY-1 trial investigated daclatasvir and sofosbuvir with ribavirin (initial dose of 600 mg, then titrated) in 60 patients with advanced cirrhosis (Poordad, 2016). Only 76% of patients with HCV genotype 1a (n= 34) and 100% of patients with HCV genotype 1b (n= 11) achieved an SVR at 12 weeks (SVR12). It is unclear how many treatment failures were among treatment-naïve patients or those with CTP class A cirrhosis. More data are needed; however, owing to the risk of the emergence of resistance to nonstructural protein 5A (NS5A) inhibitor treatment at the time of failure, extending treatment to 24 weeks for all patients with HCV genotype 1a infection and cirrhosis is recommended, and the addition of ribavirin may be considered. In patients with favorable characteristics, a 12-week treatment course that includes weight-based ribavirin (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) may be considered but is supported by limited data.

The safety profiles of all the Recommended regimens above appear favorable. Across numerous phase III programs, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in ribavirin-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

B. Genotype 1b

Genotype 1b Treatment-Naïve Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who

do not have cirrhosis. Rating: Class I, Level A. An 8-week duration is Recommended for treatment-naïve patients without cirrhosis who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL. Rating: Class I, Level B

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.
  Rating: Class I, Level B

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1b Treatment-Naïve Patients with Compensated Cirrhosis‡-Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen for treatment-naïve

patients with HCV genotype 1b infection who have compensated cirrhosis.[†]
Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.
  Rating: Class I, Level A

[‡] For decompensated cirrhosis, please refer to the appropriate section.
[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 1b Treatment-Naïve Patients with Compensated Cirrhosis[‡]- Alternative

Alternative regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.
  Rating: Class IIa, Level B

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.
  Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

For HCV genotype 1b-infected, treatment-naïve patients without cirrhosis, there are six regimens of comparable efficacy, as outlined above. For cirrhotic patients, some are classified as Alternative regimens, because compared to the Recommended, they have longer duration, potentially reduced efficacy, and/or limited supporting data.

There are no significant differences demonstrated to date in treatment responses to daclatasvir and sofosbuvir, ledipasvir/sofosbuvir, or sofosbuvir/velpatasvir for HCV genotype 1 subtypes, thus the supporting evidence remains the same as for HCV genotype 1a-infected patients (see Genotype 1a). In the ALLY-2 arm of daclatasvir and sofosbuvir for 12 weeks in treatment-naïve patients, only 12 were genotype 1b and all achieved SVR12 (Wyles, 2015). Furthermore, in the ALLY-1 study all 11 genotype 1b-infected patients with advanced cirrhosis achieved SVR12. Due to the limited numbers of genotype 1b patients represented in the phase III trials of this regimen, there is not enough evidence to support a different approach by subtype at this time.

For elbasvir/grazoprevir, 99% of genotype 1b (129/131) patients receiving 12 weeks achieved SVR in the

phase III C-EDGE trial (Zeuzem, 2015c). In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear to affect response to elbasvir/grazoprevir. Thus, current data do not support extending the duration or adding ribavirin in genotype 1b patients with NS5A resistance-associated substitutions. PrOD (plus ribavirin for those with cirrhosis) was approved by the FDA for the treatment of HCV genotype 1b infection in treatment-naïve patients based on three registration trials: SAPPHIRE-I (151 treatment-naïve patients with HCV genotype 1b and without cirrhosis), PEARL-III (419 treatment-naïve patients, all with genotype 1b and without cirrhosis), and TURQUOISE-II (119 treatment-naïve and -experienced patients with genotype 1b with cirrhosis). SAPPHIRE-I reported a high SVR12 rate (98%) with 12 weeks of PrOD and ribavirin in patients with HCV genotype 1b (Feld, 2014). Given the high SVR12 rates seen in SAPPHIRE-I, PEARL-III was specifically designed to determine the role of weight-based ribavirin with PrOD in treatment-naïve patients with HCV genotype 1b without cirrhosis (Ferenci, 2014). SVR12 rate was 99% in both arms, confirming that there is no added benefit from the use of weight-based ribavirin for patients without cirrhosis who have HCV genotype 1b infection. TURQUOISE-II enrolled treatment-naïve and -experienced patients with CTP class A cirrhosis to receive either 12 weeks or 24 weeks of treatment with PrOD and ribavirin. Overall, SVR12 rates were 98.5% in the 12-week arm and 100% in the 24-week arm (Poordad, 2014). To address the need for ribavirin with this regimen in patients with HCV genotype 1b and cirrhosis, the TURQUOISE-III study evaluated the safety and efficacy of PrOD without ribavirin for 12 weeks in patients with HCV genotype 1b infection and compensated cirrhosis. Sixty patients (62% men, 55% treatment-experienced, 83% with the IL28B non-CC genotype, 22% with platelet counts < 90 x 10^9/L, and 17% with albumin levels < 3.5 g/dL) were enrolled. All patients completed treatment, and all patients achieved an SVR12. On the basis of this study, treating patients with HCV genotype 1b with PrOD but without ribavirin is recommended, regardless of prior treatment experience or presence of cirrhosis (Feld, 2016). GARNET, a phase 3b single-arm study of 163 genotype 1b patients without cirrhosis, demonstrated a 98% SVR rate with an 8-week duration of PrOD. When considering the generalizability of these results, it is important to note that 91% of the GARNET participants had fibrosis stage F0-F2, 93% had HCV RNA levels < 6,000,000 IU/mL, and 96% were white. In addition, 2 of the 15 patients with fibrosis stage F3 experienced virologic relapse, suggesting that if used, an 8-week strategy should be reserved for those with early stage fibrosis (Welzel, 2016).

To date, there is no measurable difference demonstrated in treatment response to simeprevir plus sofosbuvir for HCV genotype 1 subtypes (with the exception of patients with genotype 1a with cirrhosis who also have the baseline Q80K substitution described above), thus the supporting evidence remains the same as for HCV genotype 1a-infected patients (see Genotype 1).

The safety profiles to date of all recommended regimens above appear favorable. Across numerous phase III programs, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in ribavirin-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

II. Genotype 2

Genotype 2 Treatment-Naïve Patients Without Cirrhosis - Recommended

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who do not have cirrhosis.
  Rating: Class I, Level A

Genotype 2 Treatment-Naïve Patients Without Cirrhosis - Alternative

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 2 infection who do not have cirrhosis.
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 2 Treatment-Naïve Patients with Compensated Cirrhosis‡- Recommended

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who have compensated cirrhosis.
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.

Genotype 2 Treatment-Naïve Patients with Compensated Cirrhosis‡- Alternative

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 16 weeks to 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 2 infection who have compensated cirrhosis.‡
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of HCV genotype 2 infection in patients with and without cirrhosis. ASTRAL-2 compared 12 weeks of sofosbuvir/velpatasvir to 12 weeks of sofosbuvir plus ribavirin in 266 treatment-naïve and -experienced subjects with and without cirrhosis and showed superior efficacy (99% compared to 94%) (Foster, 2015a). ASTRAL-1 also included 104 genotype 2 treatment-naïve and -experienced subjects with and without cirrhosis, all of whom achieved SVR12 (Feld, 2015). Pooled analysis of all genotype 2 subjects in ASTRAL-1 and -2, demonstrated 100% SVR12 in subjects with cirrhosis (29/29) and 99% SVR12 in naïve subjects (194/195). Among patients with HCV genotype 2 receiving sofosbuvir/velpatasvir, the presence of baseline NS5A or NS5B resistance-associated substitutions was not associated with virologic failure.

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients without and with cirrhosis. Although daclatasvir with sofosbuvir was not approved for the treatment of HCV genotype 2 infection, daclatasvir maintains adequate activity against HCV genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir with sofosbuvir was associated with high rates of SVR in treatment-naïve patients with HCV genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014a). It is unclear if there is a subgroup of HCV genotype 2-infected patients who would benefit from extending treatment. For patients who require treatment but cannot tolerate sofosbuvir/velpatasvir, a regimen of daclatasvir with sofosbuvir for 12 weeks is reasonable.

III. Genotype 3

Genotype 3 Treatment-Naïve Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who do not have cirrhosis.
  Rating: Class I, Level A

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 3 Treatment-Naïve Patients with Compensated Cirrhosis[‡]-Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who have compensated cirrhosis.[¶]
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 24 weeks with or without weight-based ribavirin is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who have compensated cirrhosis.[¶]
  Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.

[¶] RAS testing for Y93H is recommended for cirrhotic patients and ribavirin should be included in regimen if present.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Daclatasvir + sofosbuvir

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for treatment of HCV genotype 3 infection. The recommendation is based on ALLY-3, a phase III study of the once-daily NS5A inhibitor daclatasvir plus sofosbuvir for 12 weeks; the study included 101 treatment-naïve patients and demonstrated an SVR12 rate of 90%. In treatment-naïve patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12, and in treatment-naïve patients with cirrhosis (Metavir F4), 58% achieved SVR12 (Nelson, 2015). This suggests that patients with genotype 3 infection and cirrhosis are likely to benefit from an extension of therapy. This has been confirmed in cohort studies, including the European compassionate-use program, which reported SVR12 rates of 70% versus 86% when daclatasvir and sofosbuvir were used for 12 weeks and 24 weeks in HCV genotype 3-infected patients with cirrhosis, respectively. The role of ribavirin could not be clarified, as only 4 patients received daclatasvir plus sofosbuvir and ribavirin for 12 weeks, all or which achieved SVR12. SVR12 was comparable between the 24-week arms irrespective of the addition of ribavirin (85.9% [116/135] without compared to 81.3% [39/48] with ribavirin). SVR12 rates were also higher in those with compensated Child-Pugh A cirrhosis (85%-90% compared to 70.6% in Child B/C). Again the addition of ribavirin did not increase SVR12 rates in the 24-week arms (Hezode, 2017). 73% of patients were treatment-experienced, however earlier data suggested that SVR12 rates were higher in treatment-naïve patients (91%-100%) compared to experienced (81%-82%). SVR12 rates were similar in those that received ribavirin (88%, 29/33) and those that did not (86%, 42/49) (Hezode, 2015b).

The exact duration of therapy for a treatment-naïve genotype 3 patient with compensated cirrhosis is not known. The phase III study, ALLY3-+ , investigated the combination of daclatasvir plus sofosbuvir and ribavirin for 12 weeks or 16 weeks in treatment-naïve and -experienced genotype 3 patients with both

stage 3 and compensated cirrhosis. Overall SVR12 rates were 86% with cirrhosis, the majority of which were treatment experienced. Extending the duration to 16 weeks did not have a strong impact with 88% (15/17) achieving SVR12 with 12 weeks and 89% (16/18) achieving SVR12 with 16 weeks. All 14 patients with stage 3 disease achieved SVR12 irrespective of treatment duration (Leroy, 2016).

Presence of baseline NS5A RASs significantly reduces rates of SVR12 with a 12-week course of daclatasvir plus sofosbuvir in genotype 3-infected patients. In analysis of 175 subjects infected with HCV genotype 3 and nucleotide sequence data in the ALLY-3 trial, the presence of a NS5A Y93H substitution was associated with a reduced SVR12 rate; 54% (7/13) compared to 92% (149/162). Although the small numbers make interpretation difficult, only 7% (13/175) had NS5A Y93H substitution, all of which were subgenotype 3a. SVR rates were numerically lower in those with both cirrhosis and Y93H. In non-cirrhotic subjects with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) of those non-cirrhotic without Y93H. In those with both cirrhosis and Y93H, 25% (1/4) achieved SVR12 compared to 71% (24/34) in those with cirrhosis but without the substitution (Daklinza PI). Substitutions at A30K, L31F, L31I in genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daklinza PI). In the ALLY-3 trial, subjects with A30K and without cirrhosis achieved 100% SVR12 (9/9), however those with cirrhosis had lower SVR12 rates (1/5) (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 had compound substitutions with Y93H. Pending further data on optimal therapy in the setting of baseline Y93 substitution, the addition of ribavirin for patients with cirrhosis is recommended.

Additional real-world studies support the use of this regimen for treatment-naïve, genotype-3 infected patients with advanced liver disease (Welzel, 2016).

Sofosbuvir/velpatasvir

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients with and without cirrhosis. ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir to 24 weeks sofosbuvir plus ribavirin in 552 treatment- naïve and -experienced subjects with and without cirrhosis (Foster, 2015a). In treatment-naïve, non-cirrhotic subjects, SVR12 rates were 98% (160/163) compared to 90% (141/156), respectively. In those with cirrhosis SVR12 was 93% (40/43) compared to 73% (33/45), respectively. Of the 250 subjects that received sofosbuvir/velpatasvir 43 (16%) had baseline NS5A RASs; of which 88% achieved SVR12 compared to 97% without baseline substitutions. 84% (21/25) with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of baseline Y93 substitution, the addition of ribavirin for patients with cirrhosis is recommended.

Elbasvir/grazoprevir + sofosbuvir

C-SWIFT investigated the efficacy of triple therapy with the daily fixed-dose combination of elbasvir/grazoprevir and sofosbuvir (400 mg) for 8 weeks to 12 weeks in genotype 3 treatment-naïve patients with and without compensated cirrhosis. 93% (14/15) of non-cirrhotic patients achieved SVR12 with 8 weeks and 100% (14/14) with 12 weeks of this combination. 91% (10/11) compensated cirrhotic subjects achieved SVR12 with 12 weeks of therapy (Poordad, 2016).

IV. Genotype 4

Genotype 4 Treatment-Naïve Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.
  Rating: Class IIa, Level B

Genotype 4 Treatment-Naïve Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, who have compensated cirrhosis.[†]
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, who have compensated cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, who have compensated cirrhosis.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, who have compensated cirrhosis.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
† Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Paritaprevir/ritonavir/ombitasvir

PEARL-I was an open-label phase IIb study that included a cohort of 86 treatment-naïve patients with HCV genotype 4 infection without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir/ritonavir/ombitasvir (PrO) with or without weight-based ribavirin. SVR12 rates were 100% (42/42) in the group receiving ribavirin and 90.9% (40/44) in the group not receiving ribavirin. Adverse effects were generally mild, with headache, asthenia, fatigue, and nausea most commonly reported. There were no discontinuations owing to adverse events (Hezode, 2015). The AGATE-I trial, in its first phase, randomized 120 treatment-naïve and -experienced patients with genotype 4 HCV and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir (PrO) plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a). Similarly, the ongoing AGATE-II trial offered 100 treatment-naïve and -experienced non-cirrhotic patients with genotype 4, PrO plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. Additionally, AGATE-II randomized 60 treatment-naïve and -experienced genotype 4-infected patients with compensated cirrhosis to receive either 12 or 24 weeks of PrO plus weight-based ribavirin. The SVR12 rate from the 12-week arm was 97%. These data continue to support the use of PrO plus ribavirin for 12 weeks in treatment-experienced genotype 4 patients, including those with cirrhosis (Esmat, 2015).

Sofosbuvir/velpatasvir

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of HCV genotype 4 infection in patients with and without cirrhosis. ASTRAL-1 included 64 genotype 4 treatment-naïve subjects with and without cirrhosis, all of whom achieved SVR12 (100%) (Feld, 2015).

Elbasvir/grazoprevir

Sixty-six treatment-naïve genotype 4 patients have been treated with daily elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks with (n= 10) and without (n= 56) weight-based ribavirin in the phase 2/3 clinical program. 9.1% (n= 6) were cirrhotic and 42.4% (n= 28) had HIV/HCV coinfection. Overall 97% (64/66) achieved SVR12. There was 1 treatment failure and 1 subject was lost to follow-up. The impact of ribavirin could not be assessed, however the addition of ribavirin numerically increased the SVR12 rates

in treatment-experienced subjects. Baseline RASs and subgenotype did not appear to impact SVR12 rates (Asselah, 2015).

C-EDGE evaluated 18 treatment-naïve genotype 4 patients who were treated with 12 weeks of the fixed-dose combination therapy, elbasvir (50 mg)/grazoprevir (100 mg). All 18 achieved SVR12 (Zeuzem, 2015f).

Ledipasvir/sofosbuvir

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir/sofosbuvir in 21 HCV genotype 4-infected patients, of whom 60% were treatment-naïve and 43% had advanced fibrosis (Metavir stage F3 or F4) (Kohli, 2015). One patient took the first dose and then withdrew consent. All of the 20 patients who completed treatment achieved an SVR12; thus, the SVR12 rate was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Abergel and colleagues reported data from an open-label single-arm study including 22 HCV genotype 4-infected, treatment-naïve patients (only 1 with cirrhosis) with an SVR12 rate of 95% (21/22) (Abergel, 2016). These two pilot studies support the use of this regimen in patients with HCV genotype 4 infection.

V. Genotype 5 or 6

Genotype 5/6 Treatment-Naïve Patients with and Without Cirrhosis - Recommended

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 5 or 6 infection regardless of cirrhosis status.
  Rating: Class I, Level B
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 5 or 6 infection, regardless of cirrhosis status.
  Rating: Class IIa, Level B

Sofosbuvir/velpatasvir

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of HCV genotype 5 and 6 infection in patients with and without cirrhosis (Feld, 2015). ASTRAL-1 included 24 genotype 5 treatment-naïve subjects with and without cirrhosis, 23 of whom achieved SVR12 (96%), and 38 genotype 6 treatment-naïve subjects with and without cirrhosis, all of whom achieved SVR12 (100%).

Ledipasvir/sofobuvir

Although there are limited data on patients with HCV genotype 5 infection, the in vitro activity for sofobuvir and ledipasvir is quite good with EC_{50} of 15 nM and 0.081 nM, respectively. Abergel and colleagues reported data from an open-label, single-arm study that included 41 HCV genotype 5-infected patients with an overall SVR12 rate of 95% (39/41) (Abergel, 2016). The SVR12 rate was also 95% specifically in treatment-naïve patients (20/21), of whom only 3 had cirrhosis, but all of whom achieved SVR12.

Ledipasvir has in vitro activity against most HCV genotype 6 subtypes (except for 6e) (Wong, 2013); (Kohler, 2014). A small, two-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naïve and -experienced patients with HCV genotype 6 infection. Twenty-five patients (92% were treatment-naïve) who were primarily Asian (88%) had infection from seven different subtypes (32%, 6a; 24%, 6e; 12%, 6l; 8%, 6m; 12%, 6p; 8%, 6q; 4%, 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25), and the 1 patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events (Gane, 2015).

Elbasvir/grazoprevir

C-SCAPE evaluated the efficacy and safety of 12 weeks of elbasvir (50 mg)/grazoprevir (100 mg) with or without weight-based ribavirin for 12 weeks in treatment-naïve, non-cirrhotic genotype 2, 4, 5, and 6 patients. Eight genotype 5 and eight genotype 6 patients were included in this trial. In patients with HCV genotype 5 infection, administration of a 12-week regimen of elbasvir (50 mg)/grazoprevir (100 mg) plus ribavirin appears to be more active (SVR 100%, 4/4) than the same regimen without ribavirin (SVR12 25%, 1/4). Administration of a 12-week regimen of elbasvir (50 mg)/grazoprevir (100 mg) ± ribavirin to non-cirrhotic, treatment-naïve patients with HCV genotype 6 infection achieved an SVR12 of 75% irrespective of the addition of ribavirin (Brown, 2015).

C-EDGE evaluated 10 treatment-naïve genotype 6 patients who were treated with 12 weeks of the fixed-dose combination therapy, elbasvir (50 mg)/grazoprevir (100 mg). Eight of 10 (80%) achieved SVR12 (Zeuzem, 2015f).

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

> Click Here to Review Regimens Not Recommended in HCV Treatment <

Changes made April 12, 2017.

Published on Recommendations for Testing, Managing, and Treating Hepatitis C (http://www.hcvguidelines.org)

Summary of Recommendations for Patients Who Are Initiating Therapy for HCV Infection by HCV Genotype

Genotype 1a Treatment-Naïve Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis and in whom no baseline NS5A RASs[§] for elbasvir are detected.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis. Rating: Class I, Level A. An 8-week duration is Recommended for treatment-naïve patients without cirrhosis who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL. Rating: Class I, Level B

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.
  Rating: Class I, Level B

§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1a Treatment-Naïve Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis and in whom no baseline NS5A RASs§ for elbasvir are detected.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.
§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a Treatment-Naïve Patients Without Cirrhosis - Alternative

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 16 weeks is an Alternative regimen for patients with HCV genotype 1a infection who do not have cirrhosis but have baseline NS5A RASs§ for elbasvir.

Rating: Class IIa, Level B

[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a Treatment-Naïve Patients with Compensated Cirrhosis[‡] - Alternative

Alternative regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.[†]
  Rating: Class I, Level A

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis and in whom no Q80K substitution is detected.
  Rating: Class II, Level B

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 16 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis and have baseline NS5A RASs[§] for elbasvir.
  Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.
[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1b Treatment-Naïve Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who

do not have cirrhosis.
Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis. Rating: Class I, Level A. An 8-week duration is Recommended for treatment-naïve patients without cirrhosis who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL. Rating: Class I, Level B

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.
Rating: Class I, Level A

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.
Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.
Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.
Rating: Class I, Level B

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1b Treatment-Naïve Patients with Compensated Cirrhosis[‡]-Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.
Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.

Rating: Class I, Level A

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.[†]
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.
  Rating: Class I, Level A

[‡] For decompensated cirrhosis, please refer to the appropriate section.
[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 1b Treatment-Naïve Patients with Compensated Cirrhosis[‡] - Alternative

Alternative regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.
  Rating: Class IIa, Level B

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.
  Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 2 Treatment-Naïve Patients Without Cirrhosis - Recommended

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who do not have cirrhosis.
  Rating: Class I, Level A

Genotype 2 Treatment-Naïve Patients Without Cirrhosis - Alternative

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 2 infection who do not have cirrhosis.

Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 2 Treatment-Naïve Patients with Compensated Cirrhosis‡- Recommended

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who have compensated cirrhosis.
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.

Genotype 2 Treatment-Naïve Patients with Compensated Cirrhosis‡- Alternative

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 16 weeks to 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 2 infection who have compensated cirrhosis.‡
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 3 Treatment-Naïve Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who do not have cirrhosis.
  Rating: Class I, Level A

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 3 Treatment-Naïve Patients with Compensated Cirrhosis‡- Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who have compensated cirrhosis.¶
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 24 weeks with or without weight-based ribavirin is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who have compensated cirrhosis.¶
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
¶ RAS testing for Y93H is recommended for cirrhotic patients and ribavirin should be included in regimen if present.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 4 Treatment-Naïve Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a

Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.
Rating: Class IIa, Level B

Genotype 4 Treatment-Naïve Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, who have compensated cirrhosis.[†]
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, who have compensated cirrhosis.
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, who have compensated cirrhosis.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, who have compensated cirrhosis.
  Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.
[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 5/6 Treatment-Naïve Patients with and Without Cirrhosis - Recommended

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 5 or 6 infection regardless of cirrhosis status.
  Rating: Class I, Level B

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 5 or 6 infection, regardless of cirrhosis status.
  Rating: Class IIa, Level B

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Changes made April 12, 2017.

Published on Recommendations for Testing, Managing, and Treating Hepatitis C (http://www.hcvguidelines.org)

RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED

(Expansions and notes for abbreviations used in this section can be found in Methods Table 3. A summary of recommendations for retreatment is found in the box.)

This section provides guidance on the retreatment of a person with chronic HCV infection in whom prior therapy has failed. The level of the evidence available to inform the best regimen for each patient and the strength of the recommendation vary, and are rated accordingly (see Methods Table 2). In addition, specific recommendations are given when treatment differs for a particular group (eg, those infected with various genotypes). Recommended regimens are those that are favored for most patients in that subgroup, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration. Alternative regimens are those that are effective but have, relative to Recommended regimens, potential disadvantages, limitations for use in certain patient populations, or less supporting data than Recommended regimens. In certain situations, an Alternative regimen may be an optimal regimen for a specific patient. Not Recommended regimens are clearly inferior compared to Recommended or Alternative regimens due to factors such as lower efficacy, unfavorable tolerability and toxicity, longer duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection. Specific considerations of persons with HIV/HCV coinfection, decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C), HCV infection post-liver transplant, and those with severe renal impairment or end-stage renal disease are addressed in other sections of the Guidance.

Recommended and Alternative regimens are listed in order of level of evidence. When several regimens are offered at the same level of evidence, they are listed in alphabetical order. Choice of regimen should be determined based on patient-specific data, including drug interactions. As always, patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen (See Monitoring section).

I. Genotype 1

Six highly potent oral DAA combination regimens are Recommended for patients with HCV genotype 1

infection, although there are differences in the Recommended regimens based on the viral subtype and the presence or absence of baseline NS5A resistance-associated substitutions (RASs), and the presence or absence of cirrhosis. With certain regimens, patients infected with genotype 1a may have higher rates of virologic failure than those infected with genotype 1b. HCV genotype 1 infection that cannot be subtyped should be treated as genotype 1a infection.

Approximately 10%-15% of HCV genotype 1-infected patients without prior exposure to NS5A inhibitors will have detectable HCV NS5A RASs at the population level prior to treatment. While the clinical impact of NS5A RASs remains to be fully elucidated, in patients with genotype 1a infection the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (> 5 fold) adversely impacts response to NS5A-containing regimens (Zeuzem, 2015b); (Jacobson, 2015b). These RASs include substitutions at positions M28, Q30, L31, and Y93 in genotype 1a and are found by population sequencing in roughly 5%-10% of patients. Given that baseline NS5A RASs are one of the strongest pre-treatment predictors of treatment outcome with certain regimens in patients with genotype 1a infection, testing for these RASs prior to deciding on a therapeutic course is recommended in select situations (Zeuzem, 2015c).

The introduction of DAAs into HCV treatment regimens increased the risk of drug interactions with concomitant medications and now with combinations of DAAs, attention to drug interactions is all the more important (see Drug Interactions table). The product prescribing information and other resources (eg, http://www.hep-druginteractions.org) should be referenced regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all of the regimens discussed below.

A. Genotype 1a

Genotype 1a PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed, and in whom no baseline NS5A RASs[§] for elbasvir are detected.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom

prior PEG-IFN/ribavirin treatment has failed.
Rating: Class I, Level A

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level B

§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1a PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed, and in whom no baseline NS5A RASs§ for elbasvir are detected.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.
§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Alternative

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 16 weeks is an Alternative regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed, and who have baseline NS5A RASs[§] for elbasvir.
  Rating: Class IIa, Level B

[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis[‡] - Alternative

Alternative regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.[†]
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 16 weeks is an Alternative regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed, and who have baseline NS5A RASs[§] for elbasvir.
  Rating: Class I, Level B

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection, who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class IIa, Level B

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection with compensated cirrhosis who are negative for the Q80K substitution by commercially

available resistance assay, in whom prior PEG-IFN/ribavirin treatment has failed. Other Recommended or Alternative regimens should be used for patients with compensated cirrhosis and HCV genotype 1a infection in whom the Q80K substitution is present.
Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
†Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.
§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

B. Genotype 1b

Genotype 1b PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended

regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1b PEG-IFN/Ribavirin Treatment-Experienced with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.†
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.
† Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 1b PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Alternative

Alternative regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is an

Alternative regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1b infection, who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class IIa, Level B

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Elbasvir/grazoprevir

The fixed-dose, once-daily combination of elbasvir (50 mg) and grazoprevir (100 mg) (hereafter, elbasvir/grazoprevir) was evaluated in patients who had previously failed PEG-IFN/ribavirin in C-EDGE TE. In this phase III trial, patients were randomized to receive elbasvir/grazoprevir for 12 or 16 weeks with or without ribavirin. Genotype 1 patients treated for 12 weeks without ribavirin had an overall high SVR rate of 93.8% (90/96), which was similar to response rates in patients treated for 12 weeks with ribavirin (94.4%, 84/89). Response rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96). A subset analysis of patients with compensated cirrhosis revealed similar response rates to the population without cirrhosis when treated with elbasvir/grazoprevir without ribavirin for 12 weeks: SVR in cirrhosis 95% (19/20) vs no cirrhosis 94.9% (37/39).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A resistance-associated substitutions (RASs) when assessed by population sequencing (limit of detection 25%). These resistance-associated substitutions included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-patients with baseline NS5A RASs (> 5 fold), 11 patients achieved SVR (52.4%) due to higher relapse (Kwo, 2015). A subsequent integrated analysis of phase II and III trials confirmed a lower SVR in treatment-experienced genotype 1a patients with these specific baseline NS5A RASs (90%, 167/185) vs patients without baseline RASs (99%, 390/393) (Zeuzem, 2015b). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) of patients with baseline elbasvir NS5A RASs achieved SVR, compared to 96% (52/54) of those without baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased response rates to 100% regardless of presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen in the 12-week arms (Jacobsen, 2015b). Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for therapy with elbasvir/grazoprevir. If these RASs are present, treatment extension to 16

weeks with the addition of weight-based ribavirin (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) is recommended to decrease the risk of relapse. Lack of RAS testing results or lack of access to RAS testing should not be used as a means to limit access to HCV therapy.

Ledipasvir/sofosbuvir

The fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter, ledipasvir/sofosbuvir) has been evaluated in patients with and without cirrhosis in whom prior treatment with PEG-IFN/ribavirin, with or without HCV protease inhibitors (telaprevir or boceprevir), failed. In the ION-2 study, patients who had not responded to prior PEG-IFN/ribavirin were treated with ledipasvir/sofosbuvir. This regimen was given for 12 weeks or 24 weeks, with or without ribavirin. In the population without cirrhosis, the overall response rate was 98% (95% confidence interval [CI], 96%-99%). Specifically, in patients without cirrhosis who did not respond to PEG-IFN/ribavirin, 33 of 35 (94%) achieved an SVR after treatment with ledipasvir/sofosbuvir for 12 weeks, and 38 of 38 (100%) patients achieved SVR after treatment with ledipasvir/sofosbuvir and ribavirin for 12 weeks (Afdhal, 2014b). This regimen was well tolerated in all groups, with no serious adverse events reported in the 12-week regimen with or without ribavirn. In the population with cirrhosis, patients treated for 24 weeks had higher SVR rates than those treated for 12 weeks, supporting the recommendation that HCV treatment-experienced patients with cirrhosis receive 24 weeks of treatment without ribavirin.

In SIRIUS, a double-blind placebo-controlled French study, patients with cirrhosis who did not respond to PEG-IFN/ribavirin plus telaprevir or boceprevir, were randomized to receive placebo for 12 weeks followed by ledipasvir/sofosbuvir plus ribavirin for 12 weeks or ledipasvir/sofosbuvir plus placebo for 24 weeks. The SVR rate was similar in each group, 74 of 77 (96%) in the group that received ledipasvir/sofosbuvir plus ribavirin for 12 weeks (3 patients with relapse) and 75 of 77 (97%) in the group that received ledipasvir/sofosbuvir for 24 weeks (2 patients with relapse). This observation was further supported by a meta-analysis of treatment-naïve and -experienced patients with cirrhosis who were treated with ledipasvir/sofosbuvir in phase II and III studies (including the SIRIUS study). In this analysis, ledipasvir/sofosbuvir for 12 weeks was inferior to ledipasvir/sofosbuvir for 24 weeks and ledipasvir/sofosbuvir plus ribavirin for 12 weeks; no difference in SVR was detected between the latter two groups. Safety and tolerability were similar in each group, and with the exception of anemia, reported adverse events did not differ substantially between patients treated with or without ribavirin (Bourliere, 2015); (Reddy, 2015).

Baseline NS5A RASs adversely impact responses to ledipasvir/sofosbuvir therapy; though the magnitude of this impact varies based on a number of factors including virus (genotype subtype, specific RAS), regimen (companion drugs, use of ribavirin), and patient factors (treatment experience, presence of cirrhosis). In an analysis of over 350 HCV genotype 1 treatment-experienced patients with cirrhosis the presence of baseline ledipasvir RASs (defined as RASs resulting in a > 2.5 fold-shift in ledipasvir EC_{50}) detected at a 1% level resulted in lower SVR12 rates compared to those without baseline RASs (Zeuzem, 2015b). The SVR12 rates were 89% (RASs) versus 96% (no RASs) when ledipasvir/sofosbuvir plus ribavirin for 12 weeks was used and 87% versus 100%, respectively, with ledipasvir/sofosbuvir for 24 weeks. The impact is likely to be larger in a genotype 1a only population. Given the vulnerable nature of this population, baseline NS5A resistance testing should be considered in genotype 1a treatment-experienced patients with cirrhosis prior to use of ledipasvir/sofosbuvir. If ledipasvir associated RASs are detected consideration should be given to adding weight-based ribavirin to the regimen and extending therapy to 24 weeks. This is based on a 100% SVR12 rate in 14 patients with cirrhosis and baseline ledipasvir RASs treated with 24 weeks of ledipasvir/sofosbuvir plus ribavirin (Sarrazin, 2016).

Paritaprevir/ritonavir/ombitasvir + dasabuvir

In SAPPHIRE-2, the daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (hereafter, PrOD) with weight-based ribavirin (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) was investigated for treatment of patients with HCV genotype 1 infection, in whom previous PEG-IFN/ribavirin therapy failed (Zeuzem, 2014). In this phase III trial, patients who did not have cirrhosis and who were treated for a total of 12 weeks had a high overall rate of response with 286 of 297 (96.3%). Response rates did not differ substantially when stratified by subtype (genotype 1a, 96.0% [166/173]; genotype 1b, 96.7% [119/123]) or kinetics of prior response to PEG-IFN/ribavirin (relapse, 95.3% [82/86]; partial response, 100% [65/65]; null response, 95.2% [139/146]). In the PEARL-II study, 179 patients without cirrhosis and HCV genotype 1b infection, in whom previous therapy with PEG-IFN/ribavirin failed, were treated with PrOD with or without weight-based ribavirin for 12 weeks (Andreone, 2014). SVR rates were high in both arms: 100% (91/91) in the ribavirin-free arm and 96.6% (85/88) in the ribavirin-containing arm, supporting the recommendation that this regimen may be used without ribavirin for patients with HCV genotype 1b infection.

In the TURQUOISE-II study, patients with CTP class A cirrhosis were treated with PrOD and ribavirin for 12 weeks or 24 weeks (Poordad, 2014). Of the 380 patients enrolled in this study, 220 had received prior PEG-IFN/ribavirin therapy that failed. Among the treatment-experienced patients, SVR12 was achieved in 90.2% (110/122) of patients in the 12-week arm and 96.9% (95/98) of patients in the 24-week arm. In multivariate logistic regression analysis, both prior null response to PEG-IFN/ribavirin therapy and genotype 1a subtype were associated with lower likelihood of SVR in patients who received 12 weeks of therapy. Therefore, patients with HCV genotype 1a infection and cirrhosis should be treated for 24 weeks. Hemoglobin decline to less than 10 g/dL occurred in 7.2% of the 12-week arm and 11.0% of the 24-week arm; however, treatment discontinuation for adverse events was rare overall (2.1%). To address the need for ribavirin with this regimen in patients with HCV genotype 1b and cirrhosis, the TURQUOISE-III study evaluated the safety and efficacy of PrOD without ribavirin for 12 weeks in patients with HCV genotype 1b infection and compensated cirrhosis. Sixty patients (62% men, 55% treatment-experienced, 83% with the IL28B non-CC genotype, 22% with platelet counts < 90 x 10^9/L, and 17% with albumin levels < 3.5 g/dL) were enrolled. All patients completed treatment, and all patients achieved an SVR12. On the basis of this study, treating patients with HCV genotype 1b with PrOD without ribavirin is recommended, regardless of prior treatment experience or presence of cirrhosis (Feld, 2016). In 2016, an extended release formulation of PrOD was approved allowing once daily dosing (RBV when needed remains twice daily) (Viekira XR PI).

In October 2015, the FDA released a warning regarding the use of the PrOD or PrO (without dasabuvir) in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.) PrOD and PrO are contraindicated in patients with Child Turcotte Pugh (CTP) class B or C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported rapid onset of liver injury and in some cases hepatic decompensation in patients with cirrhosis, including CTP class A compensated cirrhosis and decompensated cirrhosis, who were receiving PrOD or PrO. The liver injury and decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of PrOD or PrO resulted in resolution of injury, although some patients, including at least 2 patients with CTP class A compensated cirrhosis, died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and in many cases its resolution with discontinuation of treatment with

PrOD or PrO, is suggestive of drug-induced liver injury. Although PrOD and PrO are contraindicated in patients with CTP class B or C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.
For patients with CTP class A cirrhosis, the unlikely but real possibility of drug-induced liver injury should be discussed with the patient. If the decision is made to initiate treatment with PrOD or PrO, close monitoring of total and direct bilirubin and transaminase levels every 1 week or 2 weeks for the first 4 weeks is recommended to ensure early detection of drug-induced liver injury. Also, educating patients about the importance of reporting systemic symptoms such as jaundice, weakness, and fatigue is strongly recommended. The regimen should be discontinued immediately if drug-induced liver injury is suspected. If a patient is already taking PrOD or PrO and is tolerating the regimen, laboratory monitoring as above without discontinuation is recommended unless there are signs or symptoms of liver injury. If heightened monitoring cannot be provided in the first 4 weeks of therapy with PrOD or PrO in patients with cirrhosis, the use of these regimens is not recommended.

Simeprevir + sofosbuvir

In the phase IIa COSMOS study, 167 participants received simeprevir (150 mg once daily) plus sofosbuvir (400 mg once daily) with or without weight-based ribavirin for 12 weeks or 24 weeks. Overall SVR12 was 92% (90% among 80 patients with prior PEG-IFN/ribavirin nonresponse and limited [Metavir F0-F2] fibrosis, and 94% among 87 patients with Metavir F3-F4 fibrosis), and the regimens were well tolerated confirming high efficacy and safety (54b). The OPTIMIST-1 and -2 phase III studies subsequently evaluated the combination of sofosbuvir plus simeprevir for 12 weeks in patients with HCV genotype 1 infection who were HCV treatment-naïve and -experienced and without or with cirrhosis, respectively (Kwo, 2016); (Lawitz, 2016b). In OPTIMIST-1, patients with HCV genotype 1 infection and no evidence of cirrhosis were randomized to 8 weeks or 12 weeks of treatment. Superiority in SVR12 was assessed for simeprevir plus sofosbuvir at 12 and 8 weeks versus a composite historical control SVR rate. The SVR12 in the 12-week arm was 97%, meeting superiority versus the historical control (87%); however, the 8-week arm only achieved an SVR12 of 83%, which did not meet superiority versus the historical control. Among those treated for 12 weeks, the SVR rate in PEG-IFN plus ribavirin treatment-experienced patients was 95% (38/40) and the SVR rate in patients with genotype 1a infection with the baseline Q80K substitution (96%; 44/46) was similar to that observed in patients without the Q80K substitution (97%; 68/70). In contrast, in the OPTIMIST-2 study (a single-arm study), 79% (42/53) of treatment-experienced patients with HCV genotype 1 infection and cirrhosis who were treated with 12 weeks of simeprevir and sofosbuvir achieved SVR. Overall, in this population of patients with cirrhosis, the SVR rate was lower in patients with HCV genotype 1a with the Q80K substitution (74%; 25/34) than in patients with HCV genotype 1a without the Q80K substitution (92%, 35/38). Taken together, these studies support the evaluation of treatment-experienced patients with cirrhosis and HCV genotype 1a for the presence of the Q80K substitution. If the Q80K substitution is detected, a different treatment regimen should be used. If Q80K substitutions are not detected then a 24-week regimen should be used (Janssen Therapeutics, 2013); (Lawitz, 2014b).

Sofosbuvir/velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve and treatment-experienced patients with HCV genotypes 1, 2, 4, 5, and 6 treated with sofosbuvir and velpatasvir (hereafter, sofosbuvir/velpatasvir) as a fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The response rate among genotype 1 treatment-experienced patients was 99.1% (109/110) overall with 100% (78/78)

in patients with subtype 1a infection and 96.9% (31/32) with subtype 1b. Specifically among patients previously treated with PEG-IFN/ribavirin, 50 of 51 (98%) achieved SVR, and among those previously treated with a DAA plus PEG-IFN/ribavirin, 48 of 48 (100%) achieved SVR. The single treatment-experienced patient who did not have a response to this regimen was a genotype 1b black patient with cirrhosis and IL28 TT genotype who had a persistently detectable HCV viral load during previous PEG-IFN/ribavirin therapy. This regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) when compared to the placebo group (77%).

Daclatasvir + sofosbuvir

The combination of daclatasvir and sofosbuvir has been studied in HCV genotype 1 treatment-experienced patients who have previously been treated with PEG-IFN/ribavirin in two observational early access programs in the United Kingdom and France (Foster, 2015); (Pol, 2017); (Foster, 2016). In the French cohort, patients were treated with daclatasvir and sofosbuvir with or without ribavirin for 12 weeks or 24 weeks. In patients treated with daclatasvir and sofosbuvir alone, a numerically higher rate of sustained virologic response at 4 weeks (SVR4) was seen in those treated for 24 weeks (12 weeks, 15/18 or [82.6%] vs 24 weeks, 75/78 or [96.1%]). Patients treated with daclatasvir, sofosbuvir, and ribavirin had high response rates in the 12-week and the 24-week treatment groups (100% and 97.1%, respectively), but only 4 patients were treated for 12 weeks. In the United Kingdom cohort, 235 HCV genotype 1-infected patients with decompensated cirrhosis (45% had prior IFN-based HCV treatment failures) were treated with 12 weeks of sofosbuvir plus ledipasvir or daclatasvir with or without ribavirin as part of a compassionate access program. The selection of daclatasvir or ledipasvir and the use of ribavirin was at the discretion of the treating physician; most patients (94.4%) had ribavirin in their regimen. Among patients treated with sofosbuvir plus ribavirin for 12 weeks, the SVR rate was 86% for those who received ledipasvir (n= 164) and 82% for those who received daclatasvir (n= 82). Based on these limited data, consideration should be given to the addition of ribavirin when treating more difficult-to-treat patients, such as those with cirrhosis.

Genotype 1 Sofosbuvir plus Ribavirin with or Without PEG-IFN Treatment-Experienced Patients - Recommended

- No Cirrhosis:
  Daily fixed-dose combination of ledipavir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom a previous sofosbuvir plus ribavirin-containing regimen with or without PEG-IFN has failed.
  Rating: Class IIa, Level B

- Compensated Cirrhosis:‡
  Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom a previous sofosbuvir plus ribavirin-containing regimen with or without PEG-IFN has failed.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

To date, clinical experience and trial data on the retreatment of sofosbuvir-experienced patients are very limited. However, retreatment after a sofosbuvir-containing treatment failure with a second course of treatment using sofosbuvir plus new agents, or retreatment with the same sofosbuvir-based regimen for a longer duration, have been reported.

Retreatment with ledipasvir/sofosbuvir in subjects with HCV genotype 1 infection, with or without cirrhosis, in whom a sofosbuvir-containing regimen failed has been evaluated in two small pilot studies utilizing ledipasvir/sofosbuvir for 12 weeks. With prior failures of 24 weeks of sofosbuvir plus ribavirin, high SVR rates were noted when patients were retreated with ledipasvir/sofosbuvir for 12 weeks (Osinusi, 2014). Ledipasvir/sofosbuvir plus ribavirin has also been evaluated in subjects in whom prior treatment with sofosbuvir plus PEG-IFN/ribavirin or sofosbuvir and ribavirin failed. In this study of 51 patients, retreatment with ledipasvir/sofosbuvir plus ribavirin for 12 weeks led to SVR12 in 100% of 50 patients with HCV genotype 1 infection; 1 virologic failure was observed in a patient determined to have HCV genotype 3 infection prior to retreatment (Wyles, 2015b). There are exceedingly limited data on the retreatment of such patients with cirrhosis. However, a post-hoc analysis of 352 previously treated patients with cirrhosis (240 of whom had prior protease inhibitor-based treatment failures) who were retreated with 12 weeks or 24 weeks of ledipasvir/sofosbuvir with or without ribavirin found that SVR12 was achieved in 95% to 98% (Reddy, 2015). Thus, for previously treated HCV genotype 1-infected patients with compensated cirrhosis, retreatment with 24 weeks of ledipasvir/sofosbuvir plus ribavirin is recommended.

There are no published data on retreatment of sofosbuvir-containing treatment failures with non-sofosbuvir based DAA regimens. In theory the lack of cross resistance between SOF and all other currently available DAAs suggests that such regimens may be efficacious in retreatment settings. However, given the lack of available data recommendations cannot be made. If use of non-sofosbuvir-based DAA regimens is being considered, those patients should be treated in line with the recommendations for pegylated interferon-experienced patients according to genotype subtype and cirrhosis status.

Genotype 1 HCV Nonstructural Protein 3 (NS3) Protease Inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed. Genotype 1a patients who have baseline NS5A RASs[§] for elbasvir should have this treatment extended to 16 weeks.
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1 HCV Nonstructural Protein 3 (NS3) Protease Inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom a prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed. Genotype 1a patients who have baseline NS5A RASs[§] for elbasvir should have this treatment extended to 16 weeks.
  Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Ledipasvir/sofosbuvir

The safety and efficacy of ledipasvir/sofosbuvir was evaluated in subjects in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus PEG-IFN/ribavirin has failed (Afdhal, 2014b). SVR12 rates with 12- and 24-week regimens were high during both treatment durations (94% and 98%, respectively). Relapse rates in the ION-2 retreatment trial were numerically higher in the 12-week arms than in the 24-week arms. The pretreatment presence of cirrhosis or nonstructural protein 5A (NS5A) resistance-associated substitutions (RASs) were the major reasons for the higher relapse rate in the 12-week arm. Thus, patients with cirrhosis in whom a prior regimen of PEG-IFN, ribavirin, and an HCV protease inhibitor has failed should receive 24 weeks of ledipasvir/sofosbuvir, and patients without cirrhosis should receive 12 weeks of ledipasvir/sofosbuvir. Based on data from the SIRIUS study, patients with cirrhosis in whom a prior protease inhibitor-containing regimen failed may also receive ledipasvir/sofosbuvir plus weight-based ribavirin for 12 weeks (Bourliere, 2015).

Sofosbuvir/velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve and treatment-experienced patients with HCV genotypes 1, 2, 4, 5, and 6 treated with sofosbuvir/velpatasvir as a fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The response rate among genotype 1 treatment-experienced patients was 99.1% (109/110) overall with 100% (78/78) in patients with subtype 1a infection and 96.9% (31/32) with subtype 1b. In this study, 100% (48/48) of subjects who had previously failed a protease inhibitor plus PEG-IFN/ribavirin achieved SVR12 (Feld, 2015). These data are supported by similarly high SVR rates seen in a preceding phase II open-label trail where 27/27 or 100% of patients achieved SVR12 after 12 weeks of therapy (Pianko, 2015).

Daclatasvir and sofosbuvir

The combination of daclatasvir and sofosbuvir was studied in 41 patients without cirrhosis in whom previous therapy with PEG-IFN, ribavirin, and an HCV protease inhibitor had failed. Of these patients, 21 were treated with daclatasvir and sofosbuvir for 24 weeks and 20 were treated with daclatasvir and sofosbuvir plus ribavirin for 24 weeks. Both groups had high cure rates and no additional benefit was seen with the inclusion of ribavirin (98% SVR12 overall) (Sulkowski, 2014a). Although data are limited,

the addition of ribavirin can be considered in difficult-to-treat situations, such as in patients with cirrhosis (Pol, 2017).

Elbasvir/grazoprevir

Grazoprevir is a next-generation protease inhibitor that retains activity in vitro against many common protease inhibitor resistant substitutions (Summa, 2012); (Howe, 2014). The combination of grazoprevir (100 mg) plus elbasvir (50 mg) with expanded weight-based ribavirin (800-1400 mg) was evaluated in an open-label phase II study of 79 patients who had failed prior interferon-based HCV therapy including a protease inhibitor (Forns, 2015a). The majority of enrolled subjects had failed prior PEG-IFN/ribavirin plus either boceprevir (35%, n= 28) or telaprevir (54%, n= 43); importantly 83% experienced virologic failure with their prior PI-containing regimen and 44% had detectable NS3 RASs to early-generation PIs at study entry. Sustained virologic response 12 weeks after completion of therapy was attained in 96% of patients including in 93% (28/30) of genotype 1a patient and 94% (32/34) of those with cirrhosis. Baseline NS3 RASs did not appear to have a large impact on responses with a SVR12 rate of 91% (31/34). Presence of NS5A or dual NS3/NS5A substitutions was associated with lower SVR12 rates of 75% and 66%, respectively, but with only 3 failures in the entire study firm conclusions cannot be drawn. Consistent with the recommendations for other populations, extension of therapy to 16 weeks with ribavirin is recommended in patients with baseline NS5A RASs resulting in a > 5-fold shift in elbasvir potency.

Genotype 1 Simeprevir plus Sofosbuvir Treatment-Experienced Patients - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Deferral of treatment is recommended, pending availability of data, for patients with HCV genotype 1 infection, regardless of subtype, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed (no prior NS5A treatment), who do not have cirrhosis, and do not have reasons for urgent retreatment.
  Rating: Class IIb, Level C

- Testing for resistance-associated substitutions that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1 infection, regardless of subtype, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed (no prior NS5A treatment), who have compensated cirrhosis,[‡] or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.
  Rating: Class II, Level C

- When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based ribavirin, unless contraindicated, should be added.
  Rating: Class II, Level C

- If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks (see text), and weight-based ribavirin, unless contraindicated, are recommended.
  Rating: Class II, Level C

‡ For decompensated cirrhosis, please refer to the appropriate section.

Recommended for Genotype 1 HCV NS5A Inhibitor Treatment-Experienced Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Deferral of treatment is recommended, pending availability of data for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, who do not have cirrhosis, and do not have reasons for urgent retreatment.
  Rating: Class IIb, Level C

- Testing for resistance-associated substitutions that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, and who have compensated cirrhosis,‡ or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.
  Rating: Class IIb, Level C

- When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based ribavirin, unless contraindicated, should be added.
  Rating: Class IIb, Level C

- If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks (see text), and weight-based ribavirin, unless contraindicated, are recommended.
  Rating: Class IIb, Level C

‡ For decompensated cirrhosis, please refer to the appropriate section.

Simeprevir + sofosbuvir failures

Data suggest that approximately 5% to 10% of patients without cirrhosis and with HCV genotype 1 infection treated for 12 weeks with simeprevir plus sofosbuvir will experience treatment failure, typically due to viral relapse (Kwo, 2015). Failure rates in patients with cirrhosis treated for 24 weeks with this regimen are limited; however, treatment failure appears to be more common in persons infected with HCV genotype 1a and those with cirrhosis. Data from the OPTIMIST-1 and -2 studies indicate that treatment failure following a regimen of simeprevir plus sofosbuvir is associated with resistance to simeprevir and cross-resistance to other HCV NS3 protease inhibitors such as paritaprevir, telaprevir, and boceprevir; grazoprevir cross-resistance may also occur in the setting of D168 or A156 substitutions (Kwo, 2015); (Lawitz, 2017). On the other hand, only a single patient developed the signature sofosbuvir

RAS S282T in the OPTIMIST trials supporting the rare occurrence of this substitution in clinical practice.

Data on retreatment of simeprevir plus sofosbuvir failures are extremely limited. Interim data from a cohort of 31 patients who had failed simeprevir plus sofosbuvir therapy indicated reasonable response rates to 12-24 weeks of ledipasvir/sofosbuvir therapy with or without ribavirin (Gonzales, 2015). In the subset of patients with SVR12 data available, 85% SVR12 was achieved in non-cirrhotic patients and 91% in cirrhotic patients. Given the lack of a standardized treatment approach and heterogeneous nature of the population, conclusions on the optimal retreatment regimen cannot be drawn.

Ledipasvir/sofosbuvir failures

Data on the retreatment of patients for whom prior treatment with ledipasvir/sofosbuvir has failed are very limited. In a pilot study, 41 patients with and without cirrhosis who did not achieve an SVR with 8 weeks or 12 weeks of ledipasvir/sofosbuvir were retreated with 24 weeks of ledipasvir/sofosbuvir (Lawitz, 2015b). SVR12 rates varied according to the presence or absence of NS5A inhibitor RASs. Among 11 patients for whom NS5A inhibitor RASs were not detected, SVR occurred in 11 of 11 (100%); in contrast, among 30 patients for whom NS5A inhibitor RASs were detected, SVR occurred in 18 of 30 (60%). Importantly, NS5B inhibitor RASs (eg, S282T) known to confer decreased activity of sofosbuvir were observed in 3 of 12 (25%) patients for whom the retreatment regimen was not successful (Lawitz, 2015b). Similarly, in the OPTIMIST-2 study in which patients with cirrhosis were treated with simeprevir and sofosbuvir, the presence of NS3 RASs, namely the Q80K substitution, led to a decreased SVR rate in patients with HCV genotype 1a infection. SVR occurred in 25 of 34 (74%) patients with HCV genotype 1a and the Q80K RAS and in 35 of 38 (92%) patients with HCV genotype 1a without the Q80K RAS (Lawitz, 2016b). Based on these data, retreatment for patients for whom an NS5A inhibitor-containing regimen has failed should be considered in the context of retreatment urgency and the presence or absence of RASs to inhibitors of NS3 and NS5A. Further, based on limited data, ribavirin is recommended as part of all retreatment regimens for patients in whom prior treatment with NS5A inhibitors has failed. Although no data exist, consideration may also be given to the addition of PEG-IFN to the retreatment regimen in patients who are eligible for this agent; PEG-IFN will have antiviral activity regardless of the RASs present.

Retreatment approach and potential regimens (including other NS5A regimen containing failures)

For patients with cirrhosis or other patients who require retreatment urgently, testing for RASs that confer decreased susceptibility to NS3 protease inhibitors (eg, Q80K) and to NS5A inhibitors should be performed using commercially available assays prior to selecting the next HCV treatment regimen. For patients with no NS5A inhibitor RASs detected, retreatment with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir, both with ribavirin, for 24 weeks is recommended. For patients who have NS5A inhibitor RASs detected and who do not have NS3 inhibitor RASs detected, treatment with simeprevir, sofosbuvir, and ribavirin for 24 weeks is recommended. For patients who have both NS3 and NS5A inhibitor RASs detected there are several small studies that provide some insight on salvage regimens. Limited data suggest a retreatment approach based on sofosbuvir combined with either elbasvir/grazoprevir or PrOD may be efficacious (Lawitz, 2015e); (Poordad, 2015a). In a retreatment arm of the C-SWIFT study, 23 patients who had failed shorter courses of elbasvir/grazoprevir plus sofosbuvir were retreated with 12 weeks of this combination plus weight-based ribavirin. In a per protocol analysis a 100% SVR12 rate was achieved (23/23), including SVR in 9/9 patients with dual NS3 and NS5A RASs (Lawitz, 2015e). A second phase II study of 22 patients, including 14 PrOD failures, evaluated retreatment with 12-24 weeks of PrOD plus sofosbuvir. Treatment duration and ribavirin usage were

determined by cirrhosis status, HCV RNA response on therapy, and genotype subtype. SVR12 data was available on 15 patients with 14/15 (93%) attaining SVR12. Based on these limited data, patients with dual NS3 and NS5A class RASs may be retreated with elbasvir/grazoprevir plus sofosbuvir with weight-based ribavirin for 12 weeks or PrOD plus sofosbuvir for 12 weeks in genotype 1b and 24 weeks with weight-based ribavirin in those with genotype 1a. If these regimens are unavailable, retreatment should be conducted in a clinical trial setting, as an appropriate treatment regimen cannot be recommended at this time. Another approach in patients with prior non-response to NS5A-containing therapy has been studied in genoptype 1, 2, and 3 patients who did not respond to velpatasvir-containing regimens including sofobuvir/velpatasvir and sofosbuvir/velpatasvir/GS-9857 (Gane, 2016). Retreatment with sofosbuvir/velpatasvir with ribavirin for 24 weeks yielded high overall response rates (91% or 59/65). Among genotype 1 patients, 97% (33/34) achieved SVR. Baseline NS5A RASs did not appear to effect SVR rates. In 34 genotype 1 patients, 6 patients had NS5A RASs prior to retreatment, all of whom achieved SVR. Although data are extremely limited, retreatment with sofosbuvir/velpatasvir + ribavirin for 24 weeks should be considered in genotype 1 patients who have not responded to prior NS5A-based therapy, especially if there is urgency for treatment.

II. Genotype 2

Genotype 2 PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

Genotype 2 PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Alternative

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is an Alternative regimen for patients with HCV genotype 2 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 2 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated

Cirrhosis‡ - Recommended

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.

Sofosbuvir/velpatasvir

In the randomized, open-label ASTRAL-2 study, patients with HCV genotype 2 infection were treated with either 12 weeks of sofosbuvir plus velpatasvir (hereafter, sofosbuvir/velpatasvir) or sofosbuvir plus ribavirin (Foster, 2015a). Of the total of 266 patients, a minority (15%) had previously failed PEG-IFN/ribavirin and a similar proportion (14%) had cirrhosis. Overall, the combination of sofosbuvir/velpatasvir yielded a statistically significant superior SVR12 rate, 99% vs 94%. The only failure in the sofosbuvir/velpatasvir arm was a man who withdrew from the study after one day due to side effects (anxiety). In contrast, there were 6 virologic failures in the sofosbuvir plus ribavirin arm. Fatigue and anemia were more commonly reported in patients receiving sofosbuvir plus ribavirin. In light of the high SVR12 rate and fewer side effects with sofosbuvir/velpatasvir, regimens with peginterferon and/or ribavirin are no longer recommended for genotype 2 infection.

Daclatasvir plus sofosbuvir

The once-daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 to 24 weeks has been shown to have efficacy in HCV genotype 2 infection, however available data in patients previously treated with PEG-IFN/ribavirin are very limited (Wyles, 2015); (Sulkowski, 2014a). For patients who require treatment and are unable to access sofosbuvir/velpatasvir, treatment with daclatasvir/sofosbuvir for 12 weeks is an alternative regimen with consideration of extension of therapy to 24 weeks in more difficult patients to treat such as those with cirrhosis.

Genotype 2 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Alternative

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 16 weeks to 24 weeks is an Alternative regimen for patients with HCV genotype 2 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 2 Sofosbuvir plus Ribavirin Treatment-Experienced Patients - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection, regardless of cirrhosis status,‡ in whom prior treatment with sofosbuvir and ribavirin has failed.
  Rating: Class IIa, Level C

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection, regardless of cirrhosis status, in whom prior treatment with sofosbuvir and ribavirin has failed.
  Rating: Class IIa, Level C

‡ For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

To date, there are few data available to guide therapy in patients with HCV genotype 2 infection in whom prior treatment with sofosbuvir and ribavirin has failed. Prior studies of genotype 1 or 3 treatment failures have shown that adding ribavirin to sofosbuvir/velpatasvir leads to higher cure rates than just sofosbuvir/velpatasvir alone (Pianko, 2015). Extrapolating from this study, the addition of ribavirin is recommended.

The combination of daclatasvir and sofosbuvir is effective in patients with HCV genotype 2 infection, but there are limited data about this therapy in treatment-experienced patients with HCV genotype 2 infection (Sulkowski, 2014a); (Wyles, 2015). For patients in whom prior treatment with sofosbuvir and ribavirin failed who are ribavirin ineligible, the decision to treat with daclatasvir and sofosbuvir should be made on an individual patient basis with consideration of extension of therapy to 24 weeks with the addition of ribavirin, especially in difficult-to-treat patients such as those with cirrhosis.

III. Genotype 3

Genotype 3 PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who do not have cirrhosis, in whom

prior treatment with PEG-IFN/ribavirin has failed.[¶]
Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed[¶].
  Rating: Class I, Level A

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

¶ RAS testing for Y93H is recommended and ribavirin should be included in regimen if present.

Genotype 3 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level B

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

Genotype 3 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis[‡] - Alternative

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Daclatasvir plus sofosbuvir

Data are limited for treatment-experienced HCV genotype 3-infected patients with cirrhosis. In the ALLY-3 study, a suboptimal response to 12 weeks of daclatasvir plus sofosbuvir (SVR12 69% [9/13]) was seen (Nelson, 2015). In contrast, treatment-experienced patients without cirrhosis did well in the ALLY-3 study with an SVR12 rate of 94% (32/34). In a follow-up study (ALLY-3+), 36 genotype 3 cirrhotic patients were randomized to daclatasvir plus sofosbuvir with ribavirin for 12 or 16 weeks. An on-treatment analysis showed similar SVR12 rates of 88% (15/17) and 89% (16/18), respectively, in the 12-week and 16-week treatment arms (Leroy, 2016). These data suggest at a minimum ribavirin should be included, if possible, for all cirrhotic patients treated with this regimen. For patients who are unable to access shorter duration or ribavirin-free regimens such as sofosbuvir plus elbasvir/grazoprevir or sofosbuvir/velpatasvir, treatment with daclatasvir plus sofosbuvir with ribavirin for 24 weeks is an alternative regimen that can be considered, especially for those who require immediate treatment.

Sofosbuvir/velpatasvir

The phase III ASTRAL-3 study evaluated the fixed-dose combination of sofosbuvir/velpatasvir for 12 weeks without ribavirin in 277 genotype 3-infected patients, including 71 with prior treatment experience and 80 with cirrhosis (Foster, 2015a). Despite a high combined SVR12 rate of 95% (264/277), both prior treatment (90% SVR) and cirrhosis (91% SVR) had a moderate negative impact on treatment responses. In the group with both cirrhosis and prior treatment the SVR12 rate was 89% (33/37). The addition of ribavirin did appear to increase SVR12 rates in a phase II study of treatment-experienced genotype 3 patients treated for 12 weeks with 25 or 100 mg of velpatasvir combined with sofosbuvir (Pianko, 2015). Based on this and analogous to the similar ALLY-3+ study, the addition of weight-based ribavirin (if not contraindicated) is recommended for cirrhotic genotype 3 patients when using sofosbuvir/velpatasvir pending additional data.

Baseline NS5A substitutions in genotype 3 also impact DAA treatment response, with the Y93H substitution being the most challenging. In the ALLY-3 study the Y93H was detected in 13 (9%) of patients with an SVR12 of 54% (7/13); including a 67% SVR12 in patients without cirrhosis. In the ASTRAL-3 study the Y93H was detected in 25 (9%) of patients with an SVR12 rate of 84% (21/25). Given that cirrhotic patients in whom prior treatment with PEG-IFN/ribavirin has failed are already recommended to have ribavirin added with or without extension of therapy depending on the specific regimen, baseline testing for NS5A RASs in genotype 3 would only impact treatment approaches for patients in whom prior treatment with PEG-IFN/ribavirin has failed without cirrhosis. Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced genotype 3 patients without cirrhosis. If the Y93H substitution is identified, weight-based ribavirin should be added to the treatment course.

Elbasvir/grazoprevir plus sofosbuvir

In the C-ISLE study, patients (N= 100) with genotype 3 infection and cirrhosis, including 53 who previously failed PEG-IFN/ribavirin, were randomized into 1 of 3 arms: elbasvir/grazoprevir plus sofosbuvir for 12 weeks, elbasvir/grazoprevir plus sofosbuvir plus weight-based ribavirin for 12 weeks, or elbasvir/grazoprevir plus sofosbuvir for 16 weeks (Foster, 2016b). All 3 arms had a 100% SVR on the per protocol analysis, with 17 patients in each arm. The efficacy was high regardless of the presence of

baseline resistance association substitutions, including 3 patients with the Y93H.

Genotype 3 Sofosbuvir-Based Treatment-Experienced Patients (No Prior NS5A Treatment) - Recommended

- Deferral of treatment is recommended, pending availability of data, for patients with HCV genotype 3, in whom previous treatment with a sofosbuvir-based regimen has failed (no prior NS5A treatment), who do not have cirrhosis,[‡] and do not have reasons for urgent retreatment.
  Rating: Class IIb, Level C

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 3 infection, regardless of cirrhosis status,[‡] in whom prior treatment with a sofosbuvir-based regimen has failed (no prior NS5A treatment) and require urgent retreatment.
  Rating: Class IIb, Level C

- Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg) for 12-16 weeks with or without weight-based ribavirin is a Recommended regimen for patients with HCV genotype 3 infection, regardless of cirrhosis status,[‡] in whom prior treatment with a sofosbuvir-based regimen has failed (no prior NS5A treatment) and require urgent retreatment.
  Rating: Class IIb, Level C

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) plus weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, regardless of cirrhosis status,[‡] in whom prior therapy with a sofosbuvir-based regimen has failed (no prior NS5A treatment) and require urgent retreatment.
  Rating: Class IIb, Level C

[‡] For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Daclatasvir plus sofosbuvir

In the ALLY-3 study, 7 patients previously treated with sofosbuvir-containing regimens (with ribavirin and/or PEG-IFN) were retreated with daclatasvir plus sofosbuvir for 12 weeks. Of these patients, 5 (71%) achieved an SVR12 (Nelson, 2015). Based on these limited data, 12 weeks of daclatasvir plus sofosbuvir may be insufficient, and extending the duration to 24 weeks of therapy and adding weight-based ribavirin is recommended.

Elbasvir/grazoprevir plus sofosbuvir plus ribavirin

The C-ISLE study included two patients who had failed prior sofosbuvir plus ribavirin. Both of these patients had a SVR12 (Foster, 2016b). Despite the paucity of data, this is a logical strategy, since all three directly acting antivirals in the regimen are known to have activity against genotype 3 infection and have shown high efficacy in other treatment-experienced patients with cirrhosis. The exact duration and need for ribavirin is not clear but due to the lack of extensive data, optimization with extended therapy and the addition of weight-based ribavirin is recommended when possible.

Sofosbuvir/velpatasvir

No data are available evaluating retreatment of patients with genotype 3 infection with sofosbuvir/velpatasvir, who previously failed treated with sofosbuvir plus ribavirin with or without PEG-IFN. However, retreatment with sofosbuvir/velpatasvir plus weight-based ribavirin for 12 weeks is a logical strategy in patients who require immediate treatment due to the general lack of treatment-emergent NS5B resistance substitutions in sofosbuvir regimen failures and the high efficacy of this regimen in phase 2 trials (Pianko, 2015).

IV. Genotype 4

Genotype 4 PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients who have HCV genotype 4 infection, who do not have cirrhosis, who experienced virologic relapse after prior PEG-IFN/ribavirin therapy. Genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on PEG-IFN/ribavirin should be treated with 16 weeks and have weight-based ribavirin added to the treatment regimen.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin treatment has failed.
  Rating: Class IIa, Level B

Genotype 4 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.†
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients who have HCV genotype 4 infection, who have compensated cirrhosis, and who experienced virologic relapse after prior PEG-IFN/ribavirin therapy. Genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on PEG-IFN/ribavirin should be treated with 16 weeks and have weight-based ribavirin added to the treatment regimen.
  Rating: Class IIa, Level B

- Daily ledipasvir (90 mg)/sofosbuvir (400 mg) and weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection with compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed, and who are eligible for ribavirin.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

†Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 4 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Alternative

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is an Alternative regimen for patients with HCV genotype 4 infection with compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

Paritaprevir/ritonavir/ombitasvir

PEARL-I was an open-label phase IIb study that included a cohort of 49 treatment-experienced patients with HCV genotype 4 infection without cirrhosis who received 12 weeks of paritaprevir, ritonavir, and ombitasvir (PrO) with or without weight-based ribavirin. In intention-to-treat analysis, SVR12 was achieved in 41 of 41 (100%) patients. This regimen was well tolerated with no serious adverse events reported (Hezode, 2015). The AGATE-I trial, in its first phase, randomized 120 treatment-naïve and -experienced patients with genotype 4 HCV and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir (PrO) plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a). Similarly, the ongoing AGATE-II trial offered 100 treatment-naïve and -experienced noncirrhotic patients with genotype 4 PrO plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. Additionally, AGATE-II randomized 60 treatment-naïve and -experienced genotype 4-infected patients with compensated cirrhosis to receive either 12 or 24 weeks of PrO plus weight-based ribavirin. The SVR12 rate from the 12-week arm, reported recently, was 97%. These data continue to support the use of PrO plus ribavirin for 12 weeks in treatment-experienced genotype 4 patients, including those with cirrhosis (Esmat, 2015a).

Ledipasvir/sofosbuvir

In the SYNERGY trial, 20 patients with HCV genotype 4 infection were treated with ledipasvir/sofosbuvir for 12 weeks. Of these patients, 40% were treatment-experienced and 40% had advanced fibrosis. Preliminary data demonstrate efficacy, with 95% achieving SVR12 based on an intention-to-treat analysis (Kohli, 2015).

Sofosbuvir/velpatasvir

Velpatasvir is also active in vitro against genotype 4 and the combination of sofosbuvir/velpatasvir for 12 weeks was evaluated in 116 genotype 4-infected patients included in the ASTRAL-1 study (Feld, 2015). 100% SVR12 was achieved, including 52 treatment-experienced patients.

Elbasvir/grazoprevir

An integrated analysis of all phase 2/3 elbasvir/grazoprevir studies demonstrated efficacy of this regimen for both treatment-naïve (n= 66) and -experienced (n= 37) patients with genotype 4 HCV infection (Asselah, 2015). The overall SVR12 rate among treatment-experienced genotype 4 infected patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure) and elbasvir/grazoprevir duration (12 vs 16 weeks) and/or ribavirin usage (no ribavirin vs ribavirin). Numbers within any specific subgroup are too small to make definitive recommendation; however, trends emerged that were used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior PEG-IFN/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the non-ribavirin-containing arms (12 weeks: 78%, 16 weeks: 60%) compared to ribavirin-containing treatment (12 weeks + ribavirin: 91%, 16 weeks + ribavirin: 100%). Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks plus ribavirin in genotype 4-infected patients with prior on-treatment virologic failure represents the most conservative approach.

V. Genotype 5 and 6

Few data are available to help guide decision making for patients infected with HCV genotype 5 or 6. Thus, for those patients for whom immediate treatment is required, the following recommendations have been drawn from available data.

Genotype 5 or 6 PEG-IFN/Ribavirin Treatment-Experienced Patients with or Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 5 or 6 infection regardless of cirrhosis status, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

- Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 5 or 6 infection regardless of cirrhosis status, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level C

In the phase III NEUTRINO trial (Lawitz, 2013a), treatment-naïve patients with HCV genotypes 1 (n= 291), 4 (n= 28), 5 (n= 1), and 6 (n= 6) were treated with sofosbuvir (400 mg daily) plus PEG-IFN (2a 180 µg weekly) and weight-based ribavirin (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 12 weeks. All six patients with HCV genotype 6 and the one patient with HCV genotype 5 achieved SVR12. The adverse event profile in these patients and in the larger study population was similar to that seen with PEG-IFN/ribavirin therapy.

Ledipasvir has in vitro activity against most HCV genotype 6 subtypes (exception 6e) (Wong, 2013); (Kohler, 2014). A small, two-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naïve and -experienced patients with HCV genotype 6 infection. Twenty-five patients (92% treatment-naïve) who were primarily of Asian descent (88%) were infected with different subtypes of HCV genotype 6 (32%, 6a; 24%, 6e; 12%, 6l; 8%, 6m; 12%, 6p; 8%, 6q; 4%, 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25). The 1 patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events.

Velpatasvir also has in vitro activity against HCV genotypes 5 and 6. The ASTRAL-1 study included 35 patients with genotype 5 and 41 patients with genotype 6, of those only 11 and 3, respectively, were treatment-experienced (Feld, 2015). All genotype 5 and 6 treatment-experienced patients treated with 12 weeks of sofosbuvir/velpatasvir achieved SVR12.

Because of their limited activity against HCV genotypes 5 and 6 in vitro and in vivo, neither boceprevir nor telaprevir should be used as therapy for patients with HCV genotype 5 or 6 infection.

Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

> Click Here to Review Regimens Not Recommended in HCV Treatment <

Changes made April 12, 2017.

Summary of Recommendations for Patients in Whom Previous Treatment Has Failed

Genotype 1a PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed, and in whom no baseline NS5A RASs[§] for elbasvir are detected.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.

Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level B

§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1a PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed, and in whom no baseline NS5A RASs§ for elbasvir are detected.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.
§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Alternative

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 16 weeks is an Alternative regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed, and who have baseline NS5A RASs[§] for elbasvir.
  Rating: Class IIa, Level B

[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis[‡] - Alternative

Alternative regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.[†]
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 16 weeks is an Alternative regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed, and who have baseline NS5A RASs[§] for elbasvir.
  Rating: Class I, Level B

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection, who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class IIa, Level B

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection with compensated cirrhosis who are negative for the Q80K substitution by commercially available resistance assay, in whom prior PEG-IFN/ribavirin treatment has failed. Other Recommended or Alternative regimens should be used for patients with compensated cirrhosis and HCV genotype 1a infection in whom the Q80K substitution is present.
  Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.

[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers

and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1b PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1b PEG-IFN/Ribavirin Treatment-Experienced with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.[†]
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

[‡] For decompensated cirrhosis, please refer to the appropriate section.
[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 1b PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis[‡] - Alternative

Alternative regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is an Alternative regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1b infection, who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class IIa, Level B

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1 Sofosbuvir plus Ribavirin with or Without PEG-IFN Treatment-Experienced Patients - Recommended

- No Cirrhosis:
  Daily fixed-dose combination of ledipavir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom a previous sofosbuvir plus ribavirin-containing regimen with or without PEG-IFN has failed.
  Rating: Class IIa, Level B

- Compensated Cirrhosis:‡
  Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom a previous sofosbuvir plus ribavirin-containing regimen with or without PEG-IFN has failed.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

Genotype 1 HCV Nonstructural Protein 3 (NS3) Protease Inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not

have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
Rating: Class IIa, Level B

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed. Genotype 1a patients who have baseline NS5A RASs[§] for elbasvir should have this treatment extended to 16 weeks.
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1 HCV Nonstructural Protein 3 (NS3) Protease Inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1

infection, regardless of subtype, who have compensated cirrhosis, in whom a prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed. Genotype 1a patients who have baseline NS5A RASs[§] for elbasvir should have this treatment extended to 16 weeks.
Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1 Simeprevir plus Sofosbuvir Treatment-Experienced Patients - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Deferral of treatment is recommended, pending availability of data, for patients with HCV genotype 1 infection, regardless of subtype, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed (no prior NS5A treatment), who do not have cirrhosis, and do not have reasons for urgent retreatment.
  Rating: Class IIb, Level C

- Testing for resistance-associated substitutions that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1 infection, regardless of subtype, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed (no prior NS5A treatment), who have compensated cirrhosis,[‡] or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.
  Rating: Class II, Level C

- When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based ribavirin, unless contraindicated, should be added.
  Rating: Class II, Level C

- If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks (see text), and weight-based ribavirin, unless contraindicated, are recommended.
  Rating: Class II, Level C

[‡] For decompensated cirrhosis, please refer to the appropriate section.

Recommended for Genotype 1 HCV NS5A Inhibitor Treatment-Experienced Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Deferral of treatment is recommended, pending availability of data for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, who do not have cirrhosis, and do not have reasons for urgent retreatment.
  Rating: Class IIb, Level C

- Testing for resistance-associated substitutions that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, and who have compensated cirrhosis,‡ or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.
  Rating: Class IIb, Level C

- When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based ribavirin, unless contraindicated, should be added.
  Rating: Class IIb, Level C

- If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks (see text), and weight-based ribavirin, unless contraindicated, are recommended.
  Rating: Class IIb, Level C

‡ For decompensated cirrhosis, please refer to the appropriate section.

Genotype 2 PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

Genotype 2 PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Alternative

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is an Alternative regimen for patients with HCV genotype 2 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients

on antiretroviral therapy.

Genotype 2 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Recommended

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.

Genotype 2 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Alternative

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 16 weeks to 24 weeks is an Alternative regimen for patients with HCV genotype 2 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 2 Sofosbuvir plus Ribavirin Treatment-Experienced Patients - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection, regardless of cirrhosis status,‡ in whom prior treatment with sofosbuvir and ribavirin has failed.
  Rating: Class IIa, Level C

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection, regardless of cirrhosis status, in whom prior treatment with sofosbuvir and ribavirin has failed.
  Rating: Class IIa, Level C

‡ For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 3 PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.¶
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed¶.
  Rating: Class I, Level A

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

¶ RAS testing for Y93H is recommended and ribavirin should be included in regimen if present.

Genotype 3 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level B

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

Genotype 3 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Alternative

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 3 Sofosbuvir-Based Treatment-Experienced Patients (No Prior NS5A Treatment) - Recommended

- Deferral of treatment is recommended, pending availability of data, for patients with HCV genotype 3, in whom previous treatment with a sofosbuvir-based regimen has failed (no prior NS5A treatment), who do not have cirrhosis,‡ and do not have reasons for urgent retreatment.
  Rating: Class IIb, Level C

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 3 infection, regardless of cirrhosis status,‡ in whom prior treatment with a sofosbuvir-based regimen has failed (no prior NS5A treatment) and require urgent retreatment.
  Rating: Class IIb, Level C

- Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg) for 12-16 weeks with or without weight-based ribavirin is a Recommended regimen for patients with HCV genotype 3 infection, regardless of cirrhosis status,‡ in whom prior treatment with a sofosbuvir-based regimen has failed (no prior NS5A treatment) and require urgent retreatment.
  Rating: Class IIb, Level C

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) plus weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, regardless of cirrhosis status,‡ in whom prior therapy with a sofosbuvir-based regimen has failed (no prior NS5A treatment) and require urgent retreatment.
  Rating: Class IIb, Level C

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 4 PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients who have HCV genotype 4 infection, who do not have cirrhosis, who experienced virologic relapse after prior PEG-IFN/ribavirin therapy. Genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on PEG-IFN/ribavirin should be treated with 16 weeks and have weight-based ribavirin added to the treatment regimen.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin treatment has failed.
  Rating: Class IIa, Level B

Genotype 4 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.[†]
  Rating: Class I, Level A

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients who have HCV genotype 4 infection, who have compensated cirrhosis, and who experienced virologic relapse after prior PEG-IFN/ribavirin therapy. Genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on PEG-IFN/ribavirin should be treated with 16 weeks and have

weight-based ribavirin added to the treatment regimen.
Rating: Class IIa, Level B

- Daily ledipasvir (90 mg)/sofosbuvir (400 mg) and weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection with compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed, and who are eligible for ribavirin.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
†Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 4 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Alternative

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is an Alternative regimen for patients with HCV genotype 4 infection with compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

Genotype 5 or 6 PEG-IFN/Ribavirin Treatment-Experienced Patients with or Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 5 or 6 infection regardless of cirrhosis status, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level B

- Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 5 or 6 infection regardless of cirrhosis status, in whom prior treatment with PEG-IFN/ribavirin has failed.
  Rating: Class IIa, Level C

> Click Here to Review Regimens Not Recommended in HCV Treatment <

Changes made on April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

MONITORING PATIENTS WHO ARE STARTING HEPATITIS C TREATMENT, ARE ON TREATMENT, OR HAVE COMPLETED THERAPY

(Expansions and notes for abbreviations used in this section can be found in Methods Table 3. A summary of recommendations for monitoring is found in the box.)

This section provides guidance on monitoring patients with chronic hepatitis C who are starting treatment, are on treatment, or have completed treatment. The section is divided into three parts: pretreatment and on-treatment monitoring, posttreatment follow-up for persons in whom treatment has failed to clear virus, and posttreatment follow-up for those who achieved a sustained virologic response (SVR; virologic cure).

Recommended Assessments Prior to Starting Antiviral Therapy

- Staging of hepatic fibrosis is essential prior to HCV treatment (see Testing and Linkage to Care and see When and in Whom to Treat).
- Assessment of potential drug-drug interactions with concomitant medications is recommended prior to starting antiviral therapy.
  - Patients should also be educated on the proper administration of medications (eg, dose, frequency of medicines, food effect, missed doses, adverse effects, etc), the crucial importance of adherence, and the necessity for close supervision and blood tests during and after treatment.

The following laboratory tests are recommended within 12 weeks prior to starting antiviral therapy:

- Complete blood count (CBC); international normalized ratio (INR)
- Hepatic function panel (albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels)
- Calculated glomerular filtration rate (GFR)
- Thyroid-stimulating hormone (TSH) if IFN is used

The following laboratory testing is recommended at any time prior to starting antiviral therapy:

- HCV genotype and subtype
- Quantitative HCV RNA (HCV viral load)

Rating for all statements above: Class I, Level C

- Patients scheduled to receive an HCV NS3 protease inhibitor (paritaprevir, simeprevir, grazoprevir) should be assessed for a history of decompensated liver disease and for severity of liver disease using CTP score. Patients with current or prior history of decompensated liver disease or with a current CTP score of 7 or greater should NOT receive treatment with regimens that contain NS3 protease inhibitors due to increased area under the curve (AUC) and/or lack of safety data. Similarly, patients with a CTP score of 5 or 6, who cannot be closely monitored for laboratory or clinical symptoms during treatment, should not receive treatment with a regimen that contains paritaprevir/ritonavir.
  Rating: Class I, Level A

- All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc.
  Rating: Class IIa, Level B

- Testing for the presence of resistance-associated substitutions (RASs) prior to starting treatment should be performed as recommended in the Initial Treatment and the Retreatment Sections.
  Rating: Class IIb, Level B

Table: NS5A Resistance-Associated Substitutions (RASs) with Potential for Clinical Significance

Wild-type Amino Acid (sensitive)	Position	Substitution Amino Acid
M	28	A/G/T
Q	30	D/E/H/G/K/L/R
L	31	F/M/V
Y	93	C/H/N/S

The role of NS5A resistance-associated substitutions (RASs) is emerging. NS5A RASs appear to have impact on treatment response with regimens that include an NS5A inhibitor and this impact occurs primarily with genotype 1a and genotype 3 infections. However, the magnitude of the impact on treatment response varies with the specific combination of direct acting antivirals. Recommendations on the need for NS5A testing, particularly at baseline prior to exposure to a NS5A inhibitor, will be made for individual regimens where there is sufficient data and it is felt the impact is great enough to be clinically

significant and warrant testing. This is a rapidly evolving part of the field and will be updated regularly to reflect new and emerging data.

Recommended Monitoring During Antiviral Therapy

- Clinic visits or telephone contact are recommended as clinically indicated during treatment to ensure medication adherence and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications.

- Complete blood count (CBC), creatinine level, calculated glomerular filtration rate (GFR), and hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated. Thyroid-stimulating hormone (TSH) is recommended every 12 weeks for patients receiving IFN. More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving ribavirin) is recommended as clinically indicated. Patients receiving elbasvir/grazoprevir should be monitored with hepatic function panel at 8 weeks (and again at 12 weeks if receiving 16 weeks of treatment).

- A 10-fold increase in alanine aminotransferase (ALT) activity at week 4 should prompt discontinuation of therapy. Any increase in ALT of less than 10-fold at week 4 and accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase, or international normalized ratio, should also prompt discontinuation of therapy. Asymptomatic increases in ALT of less than 10-fold elevated at week 4 should be closely monitored and repeated at week 6 and week 8. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.

Rating: Class I, Level B

- Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy. Antiviral drug therapy should NOT be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.

- Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy.

Rating: Class I, Level B

- Patients with compensated cirrhosis[‡] who are receiving paritaprevir/ritonavir-based regimens should be assessed for clinical signs of decompensated liver disease (eg, ascites, encephalopathy) and for biochemical evidence of liver injury with a hepatic function panel at week 2 and week 4 of treatment, and as needed during the remainder of treatment. Paritaprevir/ritonavir-based regimens should be discontinued if patients develop ascites or encephalopathy or a significant increase in direct bilirubin or ALT or AST.
  Rating: Class I, Level A

- For HBsAg+ patients who are not already on HBV suppressive therapy, monitoring of HBV DNA levels during and immediately after DAA therapy for HCV is recommended and antiviral treatment for HBV should be given if treatment criteria for HBV are met.

Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

Recommendations for Discontinuation of Treatment Because of Lack of Efficacy

- If HCV RNA is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment week 6). If quantitative HCV viral load has increased by greater than 10-fold (> 1 $\log_{10}$ IU/mL) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended.

- The significance of a positive HCV RNA test result at week 4 that remains positive, but lower, at week 6 or week 8 is unknown. No recommendation to stop therapy or extend therapy can be provided at this time.

Rating: Class III, Level C

Recommended Monitoring for Pregnancy-related Issues Prior to and During Antiviral Therapy that Includes Ribavirin

- Women of childbearing age should be counseled not to become pregnant while receiving ribavirin-containing antiviral regimens, and for up to 6 months after stopping.

- Male partners of women of childbearing age should be cautioned to prevent pregnancy while they are receiving ribavirin-containing antiviral regimens, and for up to 6 months after stopping.

Rating: Class I, Level C

- Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes ribavirin.

- Since the safety of DAA regimens that do not include ribavirin has not been established during pregnancy, counseling and serum pregnancy testing should be offered to women of childbearing age before beginning HCV treatment.

Rating: Class I, Level C

- Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for 6 months after) ribavirin treatment for women of childbearing potential, and for female partners of men who receive ribavirin treatment.

Rating: Class I, Level C

Pretreatment and On-Treatment Monitoring

The pretreatment testing described here assumes that a decision to treat with antiviral medications has already been made and that the testing involved in deciding to treat, including testing for HCV genotype and assessment of hepatic fibrosis, has already been completed (see When and in Whom to Initiate HCV Therapy).

Prior to starting treatment, patients should be evaluated for potential drug-drug interactions with selected antiviral medications (eg, http://www.hep-druginteractions.org).

Table: Drug Interactions with Direct-Acting Antivirals and Selected Concomitant Medications (x = assess potential drug interaction)

Concomitant Medications	Daclatasvir	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir	Elbasvir/ Grazoprevir	Velpatasvir
Acid-reducing agents*		X	X				X
Alfuzosin/tamsulosin			X				
Amiodarone	X	X	X	X	X		X
Anticonvulsants*	X	X	X	X	X	X	X
Antiretrovirals*	See HIV section	See HIV section	See HIV section	See HIV section	See HIV section	See HIV section	See HIV section
Azole antifungals*	X**		X	X		X	
Buprenorphine/naloxone			X				
Calcineurin inhibitors*			X	X		X	
Calcium channel blockers*	X		X	X		X	
Cisapride			X	X		X	
Digoxin	X	X		X		X	
Ergot derivatives			X				
Ethinyl estradiol–containing products			X				
Furosemide			X				
Gemfibrozil			X				
Glucocorticoids*	X		X (inhaled, intranasal)	X		X	
Herbals St. John's wort Milk thistle	X	X	X	X X	X	X X	X
HMG-CoA reductase inhibitors (statins)*	X	X	X	X		X	
Macrolide antimicrobials*	X**			X		X	
Other antiarrythmics*			X	X		X	
Phosphodiesterase inhibitors*			X	X		X	
Pimozide			X				
Rifamycin antimicrobials*	X	X	X	X	X	X	X
Salmeterol			X				
Sedatives*			X	X		X	

*Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
**Requires a daclatasvir dose modification.

During treatment, individuals should be followed up at clinically appropriate intervals to ensure medication adherence, assess adverse events and potential drug-drug interactions, and monitor blood test results necessary for patient safety. Frequency and type of contact (eg, clinic visit, phone call, etc) are variable, but need to be sufficient to assess patient safety and response to treatment, as outlined above.

The assessment of HCV viral load at week 4 of therapy is useful to determine initial response to therapy

and adherence. In phase III clinical trials, almost all patients who did not have cirrhosis had undetectable HCV RNA level at week 4; those with cirrhosis may require more than 4 weeks of treatment before HCV RNA level is undetectable. There are minimal data on how to use HCV RNA level during treatment to determine when to stop treatment for futility. The current recommendation to repeat quantitative HCV RNA testing at week 4 of treatment and to discontinue treatment if the quantitative HCV RNA level increases by more than 10-fold (> 1 $\log_{10}$ IU/mL) is based on expert opinion. There are no data to support stopping treatment based on detectable HCV RNA results at weeks 2, 3, or 4 of treatment, or that detectable HCV RNA level at these time points signifies medication nonadherence. Although HCV RNA testing is recommended at week 4 of treatment, the absence of an HCV RNA level at week 4 is not a reason to discontinue treatment. Quantitative HCV RNA level testing at the end of treatment will help to differentiate viral breakthrough from relapse, if necessary. Some may choose to forego end-of-treatment viral load testing, given the high rates of viral response with the newer regimens, and to focus on the week 12 posttreatment viral load. Virologic relapse is rare at 12 or more weeks after completing treatment. Nevertheless, repeat quantitative HCV RNA testing can be considered at 24 or more weeks after discontinuing treatment for selected patients.

During clinical trials with ELB/GRZ with or without ribavirin, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN), generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing therapy or completion of therapy. Higher rates of late ALT elevations occurred in females, Asians and those 65 years or older. Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12 (elbasvir and grazoprevir package insert). Patients who have compensated cirrhosis (Child's A) and are receiving paritaprevir/ritonavir-based regimens should be followed closely. (Please see above and statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.)

Patients who are being treated with amiodarone should not receive sofosbuvir-based regimens due to risk of life-threatening arrhythmias.

Pregnancy

Ribavirin causes fetal death and fetal abnormalities in animals and thus it is imperative for persons of childbearing potential who receive the drug to use at least two reliable forms of effective contraception during treatment and for a period of 6 months thereafter. Ethinyl estradiol-containing contraceptives should be avoided in those receiving paritaprevir/ritonavir/ombitasvir plus dasabuvir due to risk of developing elevated transaminases. It is recommended that the healthcare practitioner document the discussion of potential teratogenic effects of ribavirin in the patient's medical record. Sofosbuvir, ledipasvir, paritaprevir, ombitasvir, and dasabuvir are pregnancy category B, although there are limited data on the use of these drugs in pregnancy. It is recommended that female patients have a thorough discussion of potential pregnancy-related drug effects prior to starting antiviral treatment. Given the relatively short duration of treatment and the potential to use ribavirin-free regimens in many patients, the potential risks and benefits of delaying pregnancy until HCV antiviral treatment is completed should be considered. The education of patients and caregivers about potential adverse effects and their management is an integral component of treatment and is important for a successful outcome in all patient populations.

Reactivation of HBV

Cases of HBV reactivation, occasionally fulminant, during or after DAA therapy have been reported in HBV/HCV coinfected patients who were not already on HBV suppressive therapy (Hayashi, 2016); (Takayama, 2016); (Ende, 2015); (Collins, 2015); (De Monte, 2016); (Sulkowski, 2016); (Wang, 2016). In light of these observations, and consistent with general recommendations for the assessment of the HCV-infected patient, all patients initiating HCV DAA therapy should be assessed for HBV coinfection with testing for HBsAg, anti-HBs, and anti-HBc. HBV vaccination is recommended for all susceptible individuals. A test for HBV DNA should be obtained prior to DAA therapy in patients who are HBsAg positive. Patients meeting criteria for treatment of active HBV infection should be started on therapy at the same time (or before) HCV DAA therapy is initiated (AASLD Guidelines for Treatment of Chronic Hepatitis B). Patients with low or undetectable HBV DNA levels should be monitored at regular intervals (usually not more frequently than every 4 weeks) for HBV reactivation with HBV DNA, and those patients with HBV DNA levels meeting treatment criteria should initiate HBV therapy (AASLD Guidelines for Treatment of Chronic Hepatitis B). There are insufficient data to provide clear recommendations for the monitoring of patients testing positive either for anti-HBc alone (isolated anti-HBc) or for anti-HBs and anti-HBc (immune recovery). However, the possibility of HBV reactivation should be considered in these groups in the event of unexplained increases in liver enzymes during and/or after completion of DAA therapy.

Monitoring Patients Who Have Completed Treatment

Patients who do not achieve an SVR, because of failure of the treatment to clear, or to maintain clearance of HCV infection with relapse after treatment completion, have ongoing HCV infection and the possibility of continued liver injury and transmission. Such patients should be monitored for progressive liver disease and considered for retreatment when alternative treatments are available. Patients who have undetectable HCV RNA in the serum, when assessed by a sensitive polymerase chain reaction (PCR) assay, 12 or more weeks after completing treatment, are deemed to have achieved an SVR. In these patients, HCV-related liver injury stops, although the patients remain at risk for non-HCV-related liver disease, such as fatty liver disease or alcoholic liver disease. Patients with cirrhosis remain at risk for developing hepatocellular carcinoma.

Recommended Monitoring for Patients in Whom Treatment Failed to Achieve a Sustained Virologic Response

- Disease progression assessment every 6 months to 12 months with a hepatic function panel, complete blood count (CBC), and international normalized ratio (INR) is recommended.
  Rating: Class I, Level C

- Screening for hepatocellular carcinoma with ultrasound examination every 6 months is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4).
  Rating: Class I, Level C

- Endoscopic screening for esophageal varices is recommended if cirrhosis[‡] is present.
  Rating: Class I, Level A

- Evaluation for retreatment is recommended as effective alternative treatments become available.
  Rating: Class I, Level C

[†] For decompensated cirrhosis, please refer to the appropriate section.

The following monitoring is Not Recommended during or after therapy.

- Monitoring for HCV drug resistance-associated substituions during or after therapy is Not Recommended.
  Rating: Class IIb, Level C

Patients in whom treatment failed to achieve an SVR remain at risk for ongoing liver injury and progression of liver fibrosis (Dienstag, 2011). Thus, patients in whom treatment fails should be monitored for signs and symptoms of cirrhosis. There is currently no conclusive evidence to suggest that failure of antiviral treatment results in more severe liver injury or more rapidly progressive liver disease than would have occurred if the patient had not received treatment.

Patients in whom an initial antiviral treatment failed have achieved SVR when treated with the same drugs for a longer duration, or when treated with alternative antiviral regimens (Lawitz, 2014a). Thus, patients in whom treatment has failed to achieve an SVR should be considered for treatment when alternative antiviral regimens are available. Advice from a physician experienced in HCV treatment may be beneficial when considering retreatment after antiviral therapy failure.

Patients in whom antiviral therapy failed to achieve an SVR may harbor viruses that are resistant to one or more of the antivirals at the time of virologic "breakthrough" (Lawitz, 2014a); (Schneider, 2014). However, there is no evidence to date that the presence of resistance-associated substitutions (RASs) results in more progressive liver injury than would have occurred if the patient did not have resistant viruses. The presence of baseline RASs in treatment-naïve persons does not preclude achieving an SVR with a combination direct-acting antiviral regimen. Furthermore, RASs are often not detectable with routine (population sequencing) detection methods, nor with more sensitive tests of HCV substitutions, after patients are followed up for several months (Schneider, 2014). Subsequent retreatment with combination antivirals, particularly regimens containing antiviral drugs that have a high barrier to resistance, such as nonstructural protein 5B (NS5B) nucleotide polymerase inhibitors (eg, sofosbuvir), may overcome the presence of resistance to one or more antivirals.

There are three situations in which baseline testing for RASs is recommended in the treatment of HCV genotype 1 infection. First, for those patients whose prior treatment regimen containing an NS5A inhibitor failed and who have cirrhosis or require urgent retreatment, testing for RASs that confer decreased susceptibility to NS3 protease inhibitors (eg, Q80K) and to NS5A inhibitors should be performed using commercially available assays. In a pilot study of 41 patients with or without cirrhosis who did not achieve an SVR with 8 weeks or 12 weeks of therapy with the daily fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) who were retreated with 24 weeks of ledipasvir/sofosbuvir, rates of SVR at 12 weeks varied according to the presence or absence of certain NS5A inhibitor RASs. Among 11 patients in whom NS5A inhibitor RASs were not detected, SVR occurred in 11 of 11 (100%); in contrast, among 30 patients in whom certain NS5A inhibitor RASs were detected, SVR occurred in 18 of 30 (60%). Importantly, NS5B inhibitor RASs (eg, S282T) known to confer

decreased activity of sofosbuvir were observed in 3 of 12 (25%) patients for whom the retreatment regimen was not successful. The additional finding of the Q80K substitution has implications for the retreatment regimen selected for these patients (see Retreatment of Persons in Whom Prior Therapy Has Failed).

Second, for those treatment-naïve or PEGIFN/ribavirin-experienced persons with genotype 1a HCV who are being treated with elbasvir/grazoprevir, the presence of baseline NS5A RASs significantly reduces rates of SVR 12 using a 12-week elbasvir/grazoprevir regimen (Zeuzem, 2017). NS5A RASs were identified at baseline in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study of which 58% (11/19) achieved SVR12 compared to an SVR12 rate of 99% (133/135) in patients without these RASs receiving 12 weeks of elbasvir/grazoprevir (Zeuzem, 2017). Among treatment-naïve patients, the presence of baseline NS5A RASs with a larger than 5-fold shift to elbasvir was associated with the most significant reductions in SVR 12 with only 22% (2/9) of genotype 1a patients with these high fold-change RASs achieving SVR12. The recommendation to extend duration of treatment to 16 weeks with inclusion of ribavirin for treatment-naïve genotype 1a patients with baseline NS5A RASs is based on extrapolation of data from the C-EDGE TE trial (Kwo, 2015). Based on known inferior response in patients with presence of baseline high fold-change NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for therapy with elbasvir/grazoprevir. If baseline high fold-change RASs are present, ie, substitutions at amino acid positions 28, 30, 31, or 93, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) is recommended to decrease relapse (see Initial Treatment of HCV Infection or Retreatment of Persons in Whom Prior Therapy Has Failed sections).

Third, for treatment-naïve patients or those experienced with PEG-IFN/ribavirin who have HCV genotype 1a infection and cirrhosis, testing for the Q80K NS3 RAS is recommended when simeprevir and sofosbuvir are being considered as treatment. In the OPTIMIST-2 study, in which patients with cirrhosis were treated with simeprevir and sofosbuvir, the presence of NS3 RASs, specifically the Q80K substitution, was associated with a decreased SVR rate. SVR occurred in 25 of 34 (74%) patients with HCV genotype 1a infection and the Q80K RAS and in 35 of 38 (92%) patients with HCV genotype 1a infection without the Q80K RAS (see Initial Treatment of HCV Infection or Retreatment of Persons in Whom Prior Therapy Has Failed sections).

NS5A RAS testing is also recommended in persons with genotype 3 HCV who are considering treatment with sofosbuvir/velpatasvir or daclatasvir/sofosbuvir-based regimens. Baseline NS5A substitutions in genotype 3 impact DAA treatment response, with the Y93H substitution being most problematic. In the ALLY-3 study the Y93H was detected in 13 (9%) of patients with an SVR12 of 54% (7/13); including a 67% SVR12 in patients without cirrhosis. In the ASTRAL-3 study the Y93H was detected in 25 (9%) of patients with an SVR12 rate of 84% (21/25). Treatment-experienced cirrhotic patients are already recommended to have ribavirin added with or without extension of therapy depending on the specific regimen, thus baseline testing for NS5A RASs in genotype 3 is only recommended for treatment approaches for treatment-naïve patients with cirrhosis or treatment-experienced patients without cirrhosis. Pending further data on optimal therapy in the setting of baseline Y93H substitution in these particular patient populations, the addition of ribavirin for patients with cirrhosis is recommended.

If there remains uncertainty regarding the applicability of RAS testing, consultation with an expert in the treatment of HCV infection may be useful.

Recommended Follow-up for Patients Who Achieve a Sustained Virologic Response (SVR).

- For patients who do not have advanced fibrosis (ie, those with Metavir stage F0-F2), recommended follow-up is the same as if they were never infected with HCV.
  Rating: Class I, Level B

- Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV RNA assay rather than an anti-HCV serology test is recommended to test for HCV recurrence or reinfection.
  Rating: Class I, Level A

- Surveillance for hepatocellular carcinoma with twice-yearly ultrasound examination is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4) who achieve an SVR.
  Rating: Class I, Level C

- A baseline endoscopy is recommended to screen for varices if cirrhosis[‡] is present. Patients in whom varices are found should be treated and followed up as indicated.
  Rating: Class I, Level C

- Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving an SVR.
  Rating: Class I, Level C

[‡] For decompensated cirrhosis, please refer to the appropriate section.

With the advent of highly effective HCV antiviral regimens, the likelihood of achieving an SVR among adherent, immunologically competent, treatment-naïve patients with compensated liver disease generally exceeds 90%. Of patients who achieved an SVR with PEG-IFN/ribavirin treatment, more than 99% have remained free of HCV infection when followed up for 5 years after completing treatment (Manns, 2013). Thus, achieving an SVR is considered a virologic cure of HCV infection.

SVR typically aborts progression of liver injury with regression of liver fibrosis in most but not all treated patients (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Because of lack of progression, patients without advanced liver fibrosis (ie, Metavir stage F0-F2) who achieve an SVR should receive standard medical care that is recommended for patients who were never infected with HCV.

Among patients with advanced liver fibrosis (ie, Metavir stage F3 or F4) who achieve an SVR, decompensated liver disease (with the exception of hepatocellular carcinoma) rarely develops during follow-up, and overall survival is prolonged (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Patients who have advanced fibrosis or cirrhosis continue to be at risk for development of hepatocellular carcinoma after achieving an SVR, although the risk in these patients is lower than the risk in persistently viremic patients (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Patients with cirrhosis who achieve SVR experience increased survival

(compared with patients with cirrhosis who are untreated or in whom treatment fails), but still may be at some risk for hepatocellular carcinoma; thus, they should continue to undergo regular surveillance for hepatocellular carcinoma despite the lowered risk that results after viral eradication (Bruix, 2011). The risk of hepatocellular carcinoma among patients with advanced fibrosis prior to treatment but who have regression to minimal fibrosis after treatment is not known. In the absence of data to the contrary, such patients remain at some risk for hepatocellular carcinoma and should be monitored at regular intervals for hepatocellular carcinoma. Alpha-fetoprotein (AFP) is considered an inadequate screening test for HCC (Bruix, 2011).

Liver fibrosis and liver function test results improve in most patients who achieve an SVR (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Bleeding from esophageal varices is rare after an SVR (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Patients with cirrhosis should receive routine surveillance endoscopy for detection of esophageal varices if not previously done and these should be treated or followed up as indicated (Garcia-Tsao, 2007).

Patients in whom an SVR is achieved but who have another potential cause of liver disease (eg, excessive alcohol use, metabolic syndrome with or without proven fatty liver disease, or iron overload) remain at risk for progression of fibrosis. It is recommended that such patients be educated about the risk of liver disease and monitored for liver disease progression with periodic physical examinations, blood tests, and potentially, tests of liver fibrosis by a liver disease specialist.

Periodically testing patients with ongoing risk for HCV infection (eg, illicit drug use, high-risk sexual exposure) for HCV reinfection is recommended. Flares in liver enzyme test results should prompt evaluation of possible de novo reinfection with HCV through a new exposure (see Management of Acute HCV Infection). Antibody to HCV (anti-HCV) remains positive in most patients following an SVR. Thus, testing for reinfection with HCV is recommended and should be performed with an assay that detects HCV RNA (eg, a quantitative HCV RNA test).

Monitoring for HCV During Chemotherapy and Immunosuppression

- Prospective monitoring for HCV recurrence among patients who achieved a sustained virologic response and who are receiving immunosuppressive treatment (eg, systemic corticosteroids, antimetabolites, chemotherapy, etc) is NOT routinely recommended.
  Rating: Class III, Level C

Acute liver injury is common among patients receiving chemotherapy or immunosuppressive agents; thus, testing for hepatitis viruses should be included in the laboratory assessment of the cause of liver injury. However, while individuals with inactive (no detectable virus) or past hepatitis B virus infection may experience reactivation and clinically apparent hepatitis during immunosuppressive treatment or chemotherapy, this does not occur with hepatitis C infection. Although some patients with active HCV infection, primarily those with hematologic malignancy, may have a flare in their liver enzymes during chemotherapy, this is unusual (Mahale, 2012). Furthermore, reactivation of past HCV infection, such as after SVR or spontaneous clearance, is not anticipated since there is no residual reservoir for the virus. Thus, in this latter group, routine testing of HCV RNA during immunosuppressive treatment or prophylactic administration of antivirals during immunosuppressive treatment is not recommended.

> Click Here to Review Regimens Not Recommended in HCV Treatment <

Changes made April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Summary of the Recommendations for Monitoring Patients Who Are Starting HCV Treatment, Are on Treatment, or Have Completed Therapy

Recommended Assessments Prior to Starting Antiviral Therapy

- **Staging of hepatic fibrosis is essential prior to HCV treatment (see Testing and Linkage to Care and see When and in Whom to Treat).**

- **Assessment of potential drug-drug interactions with concomitant medications is recommended prior to starting antiviral therapy.**
  - **Patients should also be educated on the proper administration of medications (eg, dose, frequency of medicines, food effect, missed doses, adverse effects, etc), the crucial importance of adherence, and the necessity for close supervision and blood tests during and after treatment.**

The following laboratory tests are recommended within 12 weeks prior to starting antiviral therapy:

- **Complete blood count (CBC); international normalized ratio (INR)**
- **Hepatic function panel (albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels)**
- **Calculated glomerular filtration rate (GFR)**
- **Thyroid-stimulating hormone (TSH) if IFN is used**

The following laboratory testing is recommended at any time prior to starting antiviral therapy:

- **HCV genotype and subtype**
- **Quantitative HCV RNA (HCV viral load)**

Rating for all statements above: Class I, Level C

- **Patients scheduled to receive an HCV NS3 protease inhibitor (paritaprevir, simeprevir, grazoprevir) should be assessed for a history of decompensated liver disease and for severity of liver disease using CTP score. Patients with current or prior history of decompensated liver disease or with a current CTP score of 7 or greater should NOT receive treatment with regimens that contain NS3 protease inhibitors due to increased area under the curve (AUC) and/or lack of safety data. Similarly, patients with a CTP score of 5 or 6, who cannot be closely monitored for laboratory or clinical symptoms during treatment, should not receive treatment with a regimen that contains paritaprevir/ritonavir.**
  Rating: Class I, Level A

- **All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc.**
  Rating: Class IIa, Level B

- **Testing for the presence of resistance-associated substitutions (RASs) prior to starting treatment should be performed as recommended in the Initial Treatment and the Retreatment Sections.**
  Rating: Class IIb, Level B

Recommended Monitoring During Antiviral Therapy

- **Clinic visits or telephone contact are recommended as clinically indicated during treatment to ensure medication adherence and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications.**

- **Complete blood count (CBC), creatinine level, calculated glomerular filtration rate (GFR), and hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated. Thyroid-stimulating hormone (TSH) is recommended every 12 weeks for patients receiving IFN. More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving ribavirin) is recommended as clinically indicated. Patients receiving elbasvir/grazoprevir should be monitored with hepatic function panel at 8 weeks (and again at 12 weeks if receiving 16 weeks of treatment).**

- **A 10-fold increase in alanine aminotransferase (ALT) activity at week 4 should prompt discontinuation of therapy. Any increase in ALT of less than 10-fold at week 4 and accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase, or international normalized ratio, should also prompt discontinuation of therapy. Asymptomatic increases in ALT of less than 10-fold elevated at week 4 should be closely monitored and repeated at week 6 and week 8. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.**

Rating: Class I, Level B

- **Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy. Antiviral drug therapy should NOT be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.**

- **Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy.**

Rating: Class I, Level B

- **Patients with compensated cirrhosis[‡] who are receiving paritaprevir/ritonavir-based regimens should be assessed for clinical signs of decompensated liver disease (eg, ascites, encephalopathy) and for biochemical evidence of liver injury with a hepatic function panel at week 2 and week 4 of treatment, and as needed during the remainder of treatment. Paritaprevir/ritonavir-based regimens should be discontinued if patients develop ascites or encephalopathy or a significant increase in direct bilirubin or ALT or AST.**
  Rating: Class I, Level A

- **For HBsAg+ patients who are not already on HBV suppressive therapy, monitoring of HBV DNA levels during and immediately after DAA therapy for HCV is recommended and antiviral treatment for HBV should be given if treatment criteria for HBV are met.**
  Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.

Recommendations for Discontinuation of Treatment Because of Lack of Efficacy

- **If HCV RNA is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment week 6). If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended.**

- **The significance of a positive HCV RNA test result at week 4 that remains positive, but lower, at week 6 or week 8 is unknown. No recommendation to stop therapy or extend therapy can be provided at this time.**

Rating: Class III, Level C

Recommended Monitoring for Pregnancy-related Issues Prior to and During Antiviral Therapy that Includes Ribavirin

- **Women of childbearing age should be counseled not to become pregnant while receiving ribavirin-containing antiviral regimens, and for up to 6 months after stopping.**

- **Male partners of women of childbearing age should be cautioned to prevent pregnancy while they are receiving ribavirin-containing antiviral regimens, and for up to 6 months after stopping.**

Rating: Class I, Level C

- **Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes ribavirin.**

- **Since the safety of DAA regimens that do not include ribavirin has not been established**

during pregnancy, counseling and serum pregnancy testing should be offered to women of childbearing age before beginning HCV treatment.
Rating: Class I, Level C

- **Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for 6 months after) ribavirin treatment for women of childbearing potential, and for female partners of men who receive ribavirin treatment.**
  Rating: Class I, Level C

Recommended Monitoring for Patients in Whom Treatment Failed to Achieve a Sustained Virologic Response

- **Disease progression assessment every 6 months to 12 months with a hepatic function panel, complete blood count (CBC), and international normalized ratio (INR) is recommended.**
  Rating: Class I, Level C

- **Screening for hepatocellular carcinoma with ultrasound examination every 6 months is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4).**
  Rating: Class I, Level C

- **Endoscopic screening for esophageal varices is recommended if cirrhosis[‡] is present.**
  Rating: Class I, Level A

- **Evaluation for retreatment is recommended as effective alternative treatments become available.**
  Rating: Class I, Level C

[‡] For decompensated cirrhosis, please refer to the appropriate section.

Recommended Follow-up for Patients Who Achieve a Sustained Virologic Response (SVR).

- **For patients who do not have advanced fibrosis (ie, those with Metavir stage F0-F2), recommended follow-up is the same as if they were never infected with HCV.**
  Rating: Class I, Level B

- **Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV RNA assay rather than an anti-HCV serology test is recommended to test for HCV recurrence or reinfection.**
  Rating: Class I, Level A

- **Surveillance for hepatocellular carcinoma with twice-yearly ultrasound examination is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4) who achieve an SVR.**
  Rating: Class I, Level C

- **A baseline endoscopy is recommended to screen for varices if cirrhosis[‡] is present. Patients**

in whom varices are found should be treated and followed up as indicated.
Rating: Class I, Level C

- **Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving an SVR.**
  Rating: Class I, Level C

[†] For decompensated cirrhosis, please refer to the appropriate section.
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The following monitoring is Not Recommended during or after therapy.

- **Monitoring for HCV drug resistance-associated substituions during or after therapy is Not Recommended.**
  Rating: Class IIb, Level C

Monitoring for HCV During Chemotherapy and Immunosuppression

- **Prospective monitoring for HCV recurrence among patients who achieved a sustained virologic response and who are receiving immunosuppressive treatment (eg, systemic corticosteroids, antimetabolites, chemotherapy, etc) is NOT routinely recommended.**
  Rating: Class III, Level C

> Click Here to Review Regimens Not Recommended in HCV Treatment <

Changes made April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

UNIQUE PATIENT POPULATIONS: PATIENTS WITH HIV/HCV COINFECTION

(Expansions and notes for abbreviations used in this section can be found in Methods Table 3. The summary of recommendations for HIV-coinfected patients is in the box.)

This section provides guidance on the treatment of chronic HCV infection in HIV/HCV-coinfected patients. For individuals with acute HCV infection, please refer to the Acute HCV section. HIV/HCV-coinfected patients suffer from more liver-related morbidity and mortality, nonhepatic organ dysfunction, and overall mortality than HCV-monoinfected patients (Lo Re, 2014); (Chen, 2009). Even in the potent HIV antiretroviral therapy era, HIV infection remains independently associated with advanced liver fibrosis and cirrhosis in patients with HCV coinfection (Thein, 2008a); (de Ledinghen, 2008); (Fierer, 2013); (Kirk, 2013).

Similar to HCV-monoinfected patients, HIV/HCV-coinfected patients cured with PEG-IFN/ribavirin have lower rates of hepatic decompensation, hepatocellular carcinoma (HCC), and liver-related mortality (Berenguer, 2009); (Limketkai, 2012); (Mira, 2013). Uptake of HCV therapy was lower in the HIV/HCV-coinfected population, owing to historically lower response rates, patient comorbidities, patient and practitioner perceptions, and adverse events associated with IFN-based therapy (Mehta, 2006a); (Thomas, 2008). With the availability of HCV direct-acting antivirals (DAAs), these barriers should diminish; however, treatment of HIV/HCV-coinfected patients requires continued awareness and attention to the complex drug interactions that can occur between DAAs and antiretroviral medications. Drug interactions with DAAs and antiretroviral agents are summarized below as well as in the Department of Health and Human Services treatment guidelines, www.aidsinfo.nih.gov. Another resource for screening for drug interactions with DAAs is the University of Liverpool website, www.hep-druginteractions.org.

Recommendations Related to HCV Medication Interactions with HIV Antiretroviral Medications

Listed in order of level of evidence, then within group alphabetically.

- Antiretroviral drug switches, when needed, should be done in collaboration with the HIV

practitioner. For HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended.
Rating: Class I, Level A

- Daclatasvir when used in combination with other antivirals:
- Daclatasvir requires dose adjustment with ritonavir-boosted atazanavir (a decrease to 30 mg daily) and efavirenz or etravirine (an increase to 90 mg daily).
Rating: Class IIa, Level B

- Daily fixed-dose combination of elbasvir/grazoprevir:
- Elbasvir/grazoprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir.
Rating: Class IIa, Level B

- Simeprevir when used in combination with other antivirals:
- Simeprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir, (and probably dolutegravir), rilpivirine, and tenofovir.
Rating: Class IIa, Level B

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg):
- Sofosbuvir/velpatasvir can be used with most antiretrovirals, but not efavirenz or etravirine. Because velpatasvir increases tenofovir levels, when given as tenofovir disoproxil fumarate (TDF), concomitant use mandates consideration of renal function and should be avoided in those with eGFR below 60 mL/min. In patients with eGFR > 60 mL/min concomitant dosing of velpatasvir and TDF with ritonavir-boosted or cobicistat-boosted regimens did not result in renal toxicity in 56 subjects. Renal monitoring is recommended during the dosing period. Tenofovir alafenamide (TAF) may be an alternative to TDF during sofosbuvir/velpatasvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.
Rating: Class IIa, Level B

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg):
- Ledipasvir/sofosbuvir can be used with most antiretrovirals. Because ledipasvir increases tenofovir levels, when given as tenofovir disoproxil fumarate (TDF), concomitant use mandates consideration of estimated glomerular filtration rate (eGFR) and should be avoided in those with eGFR below 60 mL/min. Because potentiation of this effect occurs when TDF is used with ritonavir-boosted or cobicistat-boosted regimens, ledipasvir should be avoided with this combination (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high. Tenofovir alafenamide (TAF) may be an alternative to TDF during ledipasvir/sofosbuvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.
Rating: Class IIa, Level C

- For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended.
Rating: Class IIa, Level C

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (paritaprevir/ritonavir/ombitasvir plus dasabuvir or PrOD):
- Paritaprevir/ritonavir/ombitasvir plus dasabuvir should be used with antiretroviral drugs with which they do not have substantial interactions: atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir.

- The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with paritaprevir/ritonavir/ombitasvir plus dasabuvir and then restored when HCV treatment is completed. The HIV protease inhibitor should be administered at the same time as the fixed-dose HCV combination.

Rating: Class IIa, Level C

Regimens Not Recommended for Patients with HIV/HCV Coinfection

- Antiretroviral treatment interruption to allow HCV therapy is Not Recommended.
  Rating: Class III, Level A
- Elbasvir/grazoprevir should NOT be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.
  Rating: Class III, Level B
- Sofosbuvir/velpatasvir should NOT be used with efavirenz, etravirine, or nevirapine.
  Rating: Class III, Level B

- Sofosbuvir-based regimens should NOT be used with tipranavir.
  Rating: Class III, Level B
- Paritaprevir/ritonavir/ombitasvir plus dasabuvir should NOT be used with darunavir, efavirenz, ritonavir-boosted lopinavir, ritonavir-boosted tipranavir, etravirine, nevirapine, cobicistat, or rilpivirine.
  Rating: Class III, Level B
- Paritaprevir/ritonavir/ombitasvir with or without dasabuvir should NOT be used in HIV/HCV-coinfected individuals who are not taking antiretroviral therapy.
  Rating: Class III, Level B

- Ribavirin should NOT be used with didanosine, stavudine, or zidovudine.
  Rating: Class III, Level B

- Simeprevir should NOT be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.
  Rating: Class III, Level B

Pharmacokinetics and Drug Interactions

Extensive recommendations for antiretroviral therapy use, including for persons anticipating HCV

treatment, are found at jama.jamanetwork.com and aidsinfo.nih.gov.

Antiretroviral drug switches may be performed to allow compatibility of DAAs, with the goal of maintaining HIV suppression without compromising future options. Considerations include prior treatment history, responses to antiretroviral therapy, resistance profiles, and drug tolerance (Gunthard, 2014); (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2014; aidsinfo.nih.gov). Treatment interruption in HIV/HCV-coinfected individuals is not recommended, as it is associated with increased cardiovascular events (Strategies for Management of Antiretroviral Therapy (SMART) Study Group, 2006) and increased rates of fibrosis progression and liver-related events (Tedaldi, 2008); (Thorpe, 2011). If HCV treatment is nonurgent and antiretroviral compatibility and safety with DAAs is unclear, expert consultation should be sought or postponing HCV treatment should be considered until additional data are available.

Daclatasvir

Daclatasvir is approved by the US Food and Drug Administration (FDA) for use in combination with sofosbuvir for persons with HCV genotype 3 infection. Daclatasvir is a substrate and a very weak inducer of CYP3A4 and a substrate and inhibitor of P-gp. Daclatasvir also inhibits OATP1B1, BCRP, and organic cation transporter 1. Given that daclatasvir is a CYP3A4 substrate, it is susceptible to drug interactions with potent inducers and inhibitors of this enzyme. An increased dose of daclatasvir (120 mg vs 60 mg) was studied in combination with efavirenz, a potent CYP3A4 inducer, in uninfected volunteers. The results suggested that doubling the daclatasvir dose was excessive, and based on modeling and simulation, a 90 mg dose of daclatasvir is recommended with efavirenz (Bifano, 2013). A reduced dose of daclatasvir (20 mg vs 60 mg) was studied in combination with ritonavir-boosted atazanavir, a potent CYP3A4 inhibitor, in uninfected volunteers. The results suggested that dose reduction of daclatasvir to 20 mg was excessive, and based on modeling and simulation, a 30 mg dose of daclatasvir is recommended with ritonavir-boosted atazanavir. Based on the results of this study, a similar interaction was expected with ritonavir-boosted darunavir or lopinavir, and individuals received a reduced dose of daclatasvir 30 mg in the ALLY-2 trial (described below). Subsequent studies suggested that individuals should receive full doses of daclatasvir 60 mg with ritonavir-boosted darunavir or lopinavir. The pharmacokinetics of darunavir and lopinavir are not substantially affected by daclatasvir (Gandhi, 2015). Daclatasvir does not have clinically significant interactions with tenofovir (Bifano, 2013) or dolutegravir (Song, 2015). Daclatasvir has not been studied with emtricitabine, abacavir, rilpivirine, raltegravir, cobicistat-boosted elvitegravir, or maraviroc, but substantial interactions are not expected based on the pharmacology of these agents. There is potential for a decrease in daclatasvir levels with etravirine, and an increased dose (90 mg) of daclatasvir is recommended when used with etravirine, as with efavirenz. Antiretroviral agents allowed in the ALLY-2 trial, which determined the safety and efficacy of daclatasvir and sofosbuvir in HIV/HCV-coinfected individuals, were ritonavir-boosted atazanavir, darunavir, or lopinavir, efavirenz, nevirapine, rilpivirine, raltegravir, and dolutegravir (Wyles, 2015).

Elbasvir/grazoprevir

Elbasvir is a substrate for CYP3A4 and P-gp. Elbasvir is an inhibitor of the drug transporters BCRP and P-gp. Grazoprevir is a substrate for CYP3A4, P-gp and OATP1B1. Moderate and strong CYP3A and P-gp inducers (including efavirenz) are not recommended for coadministration with EBR/GZR. OATP1B1 inhibitors are also not recommended with grazoprevir. In terms of its ability to act as a perpetrator in interactions, grazoprevir is an inhibitor of CYP3A4 (weak), UGT1A1 (weak), and BCRP. Elbasvir 50 mg and grazoprevir 100 mg are only available in a fixed-dose combination (hereafter, elbasvir/grazoprevir).

Elbasvir/grazoprevir is incompatible with all ritonavir-boosted HIV protease inhibitors and efavirenz. While this DAA combination has not been studied with etravirine or cobicistat-boosted elvitegravir, drug interactions are expected and these combinations should be avoided. Elbasvir/grazoprevir is compatible with raltegravir, dolutegravir, rilpivirine, and the HIV nucleos(t)ide analogs.

Sofosbuvir

Sofosbuvir is not metabolized nor does it induce or inhibit any cytochrome P450 (CYP) enzymes. Sofosbuvir is a substrate (but not an inhibitor) of the drug transporters, p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Drug interaction studies with antiretroviral drugs (ie, efavirenz, tenofovir, emtricitabine, rilpivirine, ritonavir-boosted darunavir, and raltegravir) in uninfected persons identified no clinically significant interactions (Kirby, 2012). Sofosbuvir is not recommended for use with tipranavir because of the potential of this antiretroviral drug to induce P-gp (see sofosbuvir prescribing information).

Ledipasvir/sofosbuvir

Ledipasvir is available only in a fixed-dose combination tablet with sofosbuvir (hereafter ledipasvir/sofosbuvir). Ledipasvir undergoes minimal metabolism and does not inhibit or induce CYP enzymes. Ledipasvir is a substrate of P-gp and an inhibitor of P-gp and BCRP. Drug interaction studies of ledipasvir (with or without sofosbuvir) with antiretroviral drugs in uninfected persons did not identify clinically significant interactions with abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, or rilpivirine (German, 2014); (Garrison, 2015). Interactions with maraviroc and enfuvirtide are not expected based on their pharmacologic profiles. Ledipasvir area under the curve (AUC) is decreased by 34% when coadministered with efavirenz-containing regimens and increased by 96% when coadministered with ritonavir-boosted atazanavir (German, 2014). No dose adjustments of ledipasvir are recommended to account for these interactions.

Ledipasvir increases tenofovir levels, which may increase the risk of tenofovir-associated renal toxicity. The magnitude of the increase in tenofovir levels is dependent on the tenofovir formulation used (ie, tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) and other concomitant antiretroviral drugs. With the addition of ledipasvir/sofosbuvir, tenofovir levels (when given as TDF) are increased with efavirenz, rilpivirine, (German, 2014) dolutegravir, ritonavir-boosted atazanavir, and ritonavir-boosted darunavir (German, 2015). The absolute tenofovir levels are highest when TDF is administered with ritonavir-boosted protease inhibitors. When ledipasvir/sofosbuvir is administered to individuals taking TDF and ritonavir-boosted HIV protease inhibitors, the tenofovir levels exceed those deemed renally safe. Thus, to date, individuals receiving ritonavir-boosted HIV protease inhibitors have been excluded from clinical studies of ledipasvir/sofosbuvir. Individuals receiving elvitegravir and cobicistat have also been excluded from clinical studies of ledipasvir/sofosbuvir because cobicistat trough levels are increased 4-fold (see ledipasvir and sofosbuvir prescribing information) by ledipasvir.

In the ERADICATE study, ledipasvir/sofosbuvir was administered to 37 HIV/HCV-coinfected patients taking combination antiretroviral therapy, including 16 taking regimens containing tenofovir disoproxil fumarate, emtricitabine, and efavirenz, and all with baseline eGFR of 60 mL/min or higher (Osinusi, 2014). Changes in creatinine level or glomerular filtration rate (GFR) in these 37 patients were similar to patients not taking antiretroviral therapy. Further safety data from the phase III ION-4 study are described below regarding interactions between ledipasvir/sofosbuvir and raltegravir, rilpivirine, or efavirenz, each in combination with fixed-dose tenofovir disoproxil fumarate and emtricitabine.

Renal parameters should therefore be checked at baseline and regularly thereafter while on therapy when ledipasvir/sofosbuvir is administered with tenofovir disoproxil fumarate-containing regimens. Baseline parameters should include measuring creatinine level, electrolytes (including phosphorus), and urinary protein and glucose measurements, according to recent guidelines for management of chronic kidney disease in those with HIV that include indications for nephrology consultation (Lucas, 2014). Changing antiretroviral therapy or delaying HCV treatment if nonurgent may be considered for those at high risk for renal toxicity (especially those with an eGFR between 30 mL/min and 60 mL/min or who have preexisting evidence of Fanconi syndrome) and particularly those taking tenofovir disoproxil fumarate and a ritonavir-boosted HIV protease inhibitor, as there are currently few efficacy or safety data for these combinations (see ledipasvir/sofosbuvir prescribing information). If the urgency of HCV treatment and the risk of switching antiretroviral regimens are both high and there is no safer alternative to ledipasvir/sofosbuvir, then frequent monitoring (every 2-4 weeks) of urine parameters is recommended for concomitant use with tenofovir disoproxil fumarate and a ritonavir-boosted HIV protease inhibitor. Tenofovir disoproxil fumarate should also be properly dosed and adjusted for eGFR at baseline and while on therapy (Lucas, 2014).

Though there is an absence of data at this time on the renal safety of tenofovir when given as TAF with ledipasvir/sofosbuvir, a study of tenofovir pharmacokinetics in healthy volunteers receiving the combination of TAF, emtricitabine, and cobicistat-boosted elvitegravir with ledipasvir/sofosbuvir found that tenofovir levels were only 20% of the typical tenofovir exposures seen with TDF (Garrison, 2015). Based on these pharmacokinetic data in healthy volunteers, TAF may be an alternative to TDF during ledipasvir/sofosbuvir treatment for patients who take elvitegravir/cobicistat or ritonavir-boosted HIV protease inhibitors as part of their antiretroviral therapy; however, there are no safety data for this combination in coinfected patients.

Based on data in healthy volunteers, tenofovir pharmacokinetics are lower with tenofovir alafenamide (TAF) relative to TDF, thus TAF may be an alternative to TDF during ledipasvir/sofosbuvir treatment for patients who take elvitegravir/cobicistat or ritonavir-boosted HIV protease inhibitors as part of their antiretroviral therapy, however there are no safety data for this combination in coinfected patients.

Paritaprevir/ritonavir/ombitasvir + dasabuvir

Paritaprevir is an inhibitor of the organic anion-transporting polypeptide 1B1 (OATP1B1). Ritonavir is coformulated with paritaprevir and ombitasvir and used to improve the pharmacokinetics of paritaprevir. As ritonavir has anti-HIV activity, HIV/HCV-coinfected patients should have achieved HIV RNA suppression prior to initiation of this regimen; those not taking antiretroviral therapy should avoid use of this fixed-dose combination due to the potential for low-dose ritonavir to select for HIV protease-inhibitor resistance.

Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir are metabolized by, and inhibitors of CYP enzymes (3A4 and 2C8), P-gp, BCRP and the hepatic uptake transporter OATP1B1. Studies of uninfected volunteers did not reveal notable pharmacologic interactions with paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus dasabuvir (250 mg) (hereafter PrOD) or tenofovir disoproxil fumarate and emtricitabine (when tested separately from other fixed-dose combinations), raltegravir, (Khatri, 2015b) abacavir, lamivudine, or dolutegravir (Khatri, 2015). In uninfected volunteers, when PrOD was combined with efavirenz, emtricitabine, and tenofovir disoproxil fumarate, clinically significant gastrointestinal and neurologic adverse events occurred, coincident with elevations of alanine aminotransferase levels. When PrOD was combined with rilpivirine, exposures to rilpivirine were

substantially increased. Therefore, rilpivirine and efavirenz should not be used with PrOD.

Because ritonavir is a component of the fixed-dose combination of paritaprevir and ombitasvir, the total daily dose of ritonavir must be carefully considered when using PrOD with ritonavir-boosted HIV protease inhibitors. Coadministration with ritonavir-boosted lopinavir would result in a 300 mg daily dose of ritonavir, a dose associated with substantial gastrointestinal adverse effects; this combination is not recommended. Once- and twice-daily doses of darunavir have been studied with PrOD in uninfected individuals. Darunavir trough levels are lowered 48% and 43% with once- and twice-daily doses of darunavir, respectively. The average absolute darunavir trough levels in these studies were 30% to 50% of typical values. Paritaprevir AUC is increased 30% with once-daily darunavir and decreased 41% with twice-daily darunavir. The mechanism and clinical significance of the discrepant effect on paritaprevir is unclear. Thus, PrOD should not be used with ritonavir-boosted darunavir pending further data. PrOD can be given with atazanavir, but the separate ritonavir boosting tablet should be held during PrOD therapy and atazanavir should be administered at the same time as the fixed-dose combination of ritonavir-boosted paritaprevir and ombitasvir. Paritaprevir levels are increased 1.5- to 3-fold with atazanavir, but no dose adjustment of paritaprevir is recommended (Khatri, 2016). Inhibition of OATP1B1 by PrOD increases indirect bilirubin concentrations, and this effect may be attenuated in individuals taking atazanavir (Eron, 2014).

Twenty-eight HIV/HCV-coinfected subjects already taking ritonavir-boosted atazanavir (with ritonavir coming from the HCV regimen during the time of coadministration) were treated with a regimen of PrOD and ribavirin as part of the TURQUOISE-1 study (Sulkowski, 2015).

Simeprevir

Simeprevir is metabolized primarily by CYP3A4 and is therefore susceptible to drug interactions with inhibitors and inducers of this enzyme. Simeprevir is also an inhibitor of OATP1B1 and P-gp. Drug interaction studies with antiretroviral drugs in HIV-uninfected volunteers suggested no substantial interactions with tenofovir, rilpivirine, or raltegravir; however, simeprevir concentrations were substantially decreased when dosed with efavirenz and substantially increased when dosed with ritonavir-boosted darunavir. Use with efavirenz, etravirine, cobicistat, or boosted HIV protease inhibitors is not recommended (Kiser, 2013).

Sofosbuvir/velpatasvir

Velpatasvir is available only in a fixed-dose combination tablet with sofosbuvir (hereafter sofosbuvir/velpatasvir). Velpatasvir is metabolized by CYP3A4, CYP2C8, and CYP2B6. It does not appear to inhibit or induce any CYP enzymes. Velpatasvir is a substrate for P-gp and BCRP, and inhibits P-gp, BCRP, and OATP1B1/1B3, but does not induce any transporters. Velpatasvir absorption is pH-dependent. Refer to product labeling for guidance on temporal separation and dosing of gastric acid modifying agents.

Drug interaction studies with sofosbuvir/velpatasvir have been performed in HIV and HCV seronegative volunteers. As with ledipasvir/sofosbuvir, tenofovir exposures are increased, which may be problematic for individuals with eGFR values of less than 60 mL/min or in those receiving ritonavir or cobicistat-containing antiretroviral therapy with tenofovir disoproxil fumarate (TDF). Fifty-six HIV/HCV coinfected individuals receiving the combination of TDF with ritonavir or cobicistat-containing antiretroviral therapy were treated with sofosbuvir/velpatasvir in the ASTRAL-5 study with no difference in median creatinine

clearance before and after sofosbuvir/velpatasvir treatment, but poor renal function was an exclusion for this study. Consider the use of tenofovir alafenamide (TAF) in place of TDF in those requiring ritonavir or cobicistat-containing antiretroviral therapy. If the combination of TDF with a ritonavir- or cobicistat-containing antiretroviral therapy is required, renal parameters should be checked at baseline and regularly thereafter while on sofosbuvir/velpatasvir. Velpatasvir exposures are significantly reduced with efavirenz and this combination is not recommended. Etravirine has not been studied with sofosbuvir/velpatasvir but is also not recommended. Indirect bilirubin level increases have been reported when sofosbuvir/velpatasvir was used in patients on atazanavir/ritonavir. These changes are not considered clinically significant.

Based on data in healthy volunteers, tenofovir pharmacokinetics are lower with tenofovir alafenamide (TAF) relative to TDF, thus TAF may be an alternative to TDF during sofosbuvir/velpatasvir treatment for patients who take elvitegravir/cobicistat or ritonavir-boosted HIV protease inhibitors as part of their antiretroviral therapy, however there are no safety data for this combination in coinfected patients.

Table. Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs

	Sofosbuvir	Ledipasvir	Velpatasvir	Simeprevir	Daclatasvir	Elbasvir/ grazoprevir	Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)	Paritaprevir, ritonavir, ombitasvir (PrO)
Ritonavir-boosted atazanavir	No data	Ledipasvir ↑; atazanavir ↑[a]	Velpatasvir ↑; atazanavir ↑[a]	No data	Daclatasvir ↑[b]	Elbasvir ↑; grazoprevir ↑; atazanavir ↑	Paritaprevir ↑; atazanavir ↑	Paritaprevir ↑; atazanavir ↔
Ritonavir- boosted darunavir	Sofosbuvir ↑; darunavir ↔	Ledipasvir ↑; darunavir ↔[a]	Velpatasvir ↔; darunavir ↔[a]	Simeprevir ↑; darunavir ↔	Daclatasvir ↑; darunavir ↔	Elbasvir ↑; grazoprevir ↑; darunavir ↔	Paritaprevir ↓/↑; darunavir ↓	Paritaprevir ↑; darunavir ↔
Ritonavir-boosted lopinavir	No data	No data[a]	Velpatasvir ↔; lopinavir ↔[a]	No data	Daclatasvir ↑; lopinavir ↔	Elbasvir ↑; grazoprevir ↑; lopinavir ↔	Paritaprevir ↑; lopinavir ↔	Paritaprevir ↑; lopinavir ↔
Ritonavir-boosted tipranavir	No data	No data	No data	No data	No data	No data	No data	No data
Efavirenz	Sofosbuvir ↔; efavirenz ↔	Ledipasvir ↓; efavirenz ↓[a]	Velpatasvir ↓; efavirenz ↓	Simeprevir ↓; efavirenz ↔	Daclatasvir ↓[b]	Elbasvir ↓; grazoprevir ↓; efavirenz ↓	No pharmacokinetic data[c]	No data
Rilpivirine	Sofosbuvir ↔; rilpivirine ↔	Ledipasvir ↔; rilpivirine ↔	Velpatasvir ↔; rilpivirine ↔	Simeprevir ↔; rilpivirine ↔	No data	elbasvir ↔; grazoprevir ↔; rilpivirine ↔	Paritaprevir ↑; rilpivirine ↑	No data
Etravirine	No data	No data	No data	No data	Daclatasvir ↓[b]	No data	No data	No data

Raltegravir	Sofosbuvir ↔; raltegravir ↔	Ledipasvir ↔; raltegravir ↔	Velpatasvir ↔; raltegravir ↔	Simeprevir ↔; raltegravir ↔	No data	Elbasvir ↔; grazoprevir ↔; raltegravir ↑	PrOD ↔; ↑ raltegravir	PrO ↔; raltegravir ↑
Cobicistat-boosted elvitegravir	Sofosbuvir ↑[a]; cobicistat ↑	Ledipasvir ↑; cobicistat ↑[a]	Velpatasvir ↑; cobicistat ↑[a]	No data	Daclatasvir ↑ [b]	Elbasvir ↑; grazoprevir ↑; cobicistat ↑	No data	No data
Dolutegravir	No data	Ledipasvir ↔; dolutegravir ↔	Velpatasvir ↔; dolutegravir ↔	No data	Daclatasvir ↔; dolutegravir ↑	Elbasvir ↔; grazoprevir ↔; dolutegravir ↑	Paritaprevir ↓; dolutegravir ↑	No data
Maraviroc	No data	No data	No data	No data	No data	No data	No data	No data
Tenofovir disoproxil fumarate	Sofosbuvir ↔; tenofovir ↔	Ledipasvir ↔; tenofovir ↑	Velpatasvir ↔; tenofovir ↑	Simeprevir ↔; tenofovir ↔	Daclatasvir ↔; tenofovir ↔	Elbasvir ↔; grazoprevir ↔; tenofovir ↑	PrOD ↔; tenofovir ↔	Pro ↔; tenofovir ↔
Tenofovir alafenamide	Sofosbuvir ↑; tenofovir ↑[d]	Ledipasvir ↔; tenofovir ↑[d]	Velpatasvir ↔; tenofovir ↑[d]	No data	No data	No data	No data	No data

[a] Only problematic when administered with tenofovir disoproxil fumarate; tenofovir levels are increased.

[b] Decrease daclatasvir dose to 30 mg once daily with atazanavir; increase daclatasvir dose to 90 mg once daily with efavirenz or etravirine.

[c] PrOD administered with efavirenz led to premature study discontinuation owing to toxic effects.

[d] Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

Ribavirin

Ribavirin has the potential for dangerous drug interactions with didanosine resulting in mitochondrial toxicity with hepatomegaly and steatosis, pancreatitis, and lactic acidosis; thus, concomitant administration of these 2 drugs is contraindicated (Fleischer, 2004). The combined use of ribavirin and zidovudine has been reported to increase the rates of anemia and the need for ribavirin dose reduction; thus, zidovudine is not recommended for use with ribavirin (Alvarez, 2006).

Recommended Regimens for HIV/HCV-Coinfected Individuals

Listed in order of level of evidence, then within group alphabetically.

- HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed).

Rating: Class I, Level B

- Daily daclatasvir (refer above for dose) plus sofosbuvir (400 mg), with or without ribavirin (refer to Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections for duration) is a Recommended regimen when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals.
  Rating: Class I, Level B

Regimens Not Recommended for Patients with HIV/HCV Coinfection

- Treatment courses shorter than 12 weeks, such as the use of 8 weeks of ledipasvir/sofosbuvir.
  Rating: Class IIb, Level C

Although fewer HIV/HCV-coinfected patients than HCV-monoinfected patients have been treated in trials of DAAs, efficacy rates thus far have been remarkably similar between the groups (Sulkowski, 2013); (Sulkowski, 2014); (Dieterich, 2014b); (Rodriguez-Torres, 2015); (Osinusi, 2015); (Sulkowski, 2015); (Dieterich, 2015); (Naggie, 2015); (Wyles, 2015). Thus, results from HCV monoinfection studies largely justify the recommendations for HIV/HCV coinfection (discussed in the Initial Treatment and Retreatment sections). Discussion specific to studies of HIV/HCV coinfection is included here.

Daclatasvir + sofosbuvir

ALLY-2 is a phase III clinical trial that evaluated the 12-week regimen of daclatasvir with sofosbuvir in patients with HIV/HCV coinfection and HCV genotypes 1 to 4 (Wyles, 2015). This open-label clinical trial enrolled both treatment-naïve (n= 151) and -experienced (n= 52) HIV/HCV-coinfected patients. Treatment-naïve patients were randomly assigned (2:1), with stratification by cirrhosis status and HCV genotype, to receive 12 weeks or 8 weeks of once-daily daclatasvir 60 mg (dose adjusted based on antiretroviral regimen) and sofosbuvir 400 mg; treatment-experienced patients received daclatasvir and sofosbuvir for 12 weeks. Genotype distribution was 83%, 9%, 6%, and 2% of patients, respectively, for genotypes 1, 2, 3, and 4 HCV infection, and 14% of all participants had cirrhosis. Antiretroviral drugs allowed were ritonavir-boosted darunavir, atazanavir, or lopinavir, efavirenz, nevirapine, rilpivirine, raltegravir, and dolutegravir. The combination of daclatasvir and sofosbuvir once daily for 12 weeks achieved an SVR12 in 97% of HIV/HCV-coinfected patients with HCV genotype 1, 2, 3, or 4, and was safe and well tolerated. Ninety-seven percent of treatment-naïve patients and 98% of -experienced patients achieved an SVR. However, among patients who received 8 weeks of combination therapy, only 76% of patients achieved an SVR. Factors associated with relapse in this patient group included high baseline HCV RNA level (> 2 million IU/mL; 69%), concomitant use of a boosted darunavir-based antiretroviral regimen with 30 mg of daclatasvir (67%), and the presence of cirrhosis (60%). More data are needed in certain subgroups (eg, patients with HCV genotype 3 and cirrhosis who had lower response rates to this regimen and patients without HIV infection) (Nelson, 2015).

Many HIV/HCV-coinfected patients are on antiretroviral regimens with drug interactions that absolutely preclude otherwise recommended DAA regimens. Switching an optimized antiretroviral regimen carries risks, including adverse effects and HIV viral breakthrough (Eron, 2010). HIV viral breakthrough is a

particular concern for those with substantial antiretroviral experience or known resistance to antiretroviral drugs. For these situations, given the compatibility of daclatasvir and sofosbuvir with nearly all antiretroviral regimens (see pharmacologic considerations above), daclatasvir and sofosbuvir is recommended in order to avoid unnecessary switching of effective HIV antiretroviral regimens. When the optimal combination of DAAs and antiretroviral drugs is unclear, expert consultation is recommended.

Elbasvir/grazoprevir

The safety, tolerability, and efficacy of a novel second-generation NS3/4A serine protease inhibitor grazoprevir (MK-5172) plus NS5A inhibitor, elbasvir (MK-8742) was assessed in patients with HCV and HIV coinfection in this study. C-EDGE was a phase III, non-randomized, open-label, single-arm study in which treatment-naïve patients with chronic HCV genotype 1, 4, or 6 infection and HIV coinfection, with or without cirrhosis, were enrolled in Europe, the USA, and Australia (Rockstroh, 2015). All patients were either naïve to treatment with any antiretroviral therapy (ART) with a CD4+ T cell count more than 500 cells/mm^3 (N= 211) or stable on current ART for at least 8 weeks with a CD4+ T cell count more than 200 cells/mm^3 (N= 7) and undetectable HIV RNA levels. All 218 enrolled patients received elbasvir (50 mg) plus grazoprevir (100 mg) in a single-pill combination (elbasvir/grazoprevir) once daily for 12 weeks. All 218 patients completed follow-up at week 12. Median baseline CD4+ T cell counts were 568 (424-626) cells/mm^3. Limited ARVs were allowed: specifically a nucleoside/nucleotide backbone of abacavir (21.6%) versus tenofovir (75.2%), in combination with raltegravir (52%), dolutegravir (27%), or rilpivirine (17%). SVR12 was achieved by 210 (96%) of 218 patients (95% CI 92.9–98.4). One patient did not achieve SVR12 because of a non-virological reason, and seven patients without cirrhosis relapsed (two subsequently confirmed as reinfections, highlighting the requirement of continued harm-reduction strategies post SVR). Thirty-five patients with cirrhosis achieved SVR12. The most common adverse events were fatigue (29; 13%), headache (27; 12%), and nausea (20; 9%). No patient discontinued treatment because of an adverse event. Three out of six patients who relapsed before SVR12 had NS3 and/or NS5A RASs, while the others had wild type at the time of relapse. Two patients receiving ART had transient HIV viremia, but subsequently retuned to undetectable levels without change in ART. No significant changes were observed with CD4+ T cell counts or new opportunistic infections. Elbasvir/grazoprevir *without ribavirin* seems to be effective and well tolerated for patients coinfected with HIV with or without cirrhosis. These data are consistent with previous trials of this regimen in the monoinfected population (Zeuzem, 2017).

Ledipasvir/sofosbuvir

The safety and efficacy of 12 weeks of ledipasvir/sofosbuvir was evaluated in the phase II ERADICATE study, which treated 50 HIV/HCV-coinfected, HCV genotype 1-infected, treatment-naïve patients without cirrhosis from an urban population in a single-center, open-label clinical trial (Osinusi, 2015). Thirteen patients were not receiving antiretroviral therapy and 37 patients were on protocol-allowed medications (tenofovir, emtricitabine, rilpivirine, raltegravir, and efavirenz). Although the inclusion criteria for patients receiving antiretroviral therapy allowed CD4+ T cell counts of greater than 100/μL, the median CD4+ T cell count was 576/μL. Overall, 98% achieved sustained virologic response at 12 weeks (SVR12; 13/13 in treatment-naïve arm and 36/37 in treatment-experienced arm). There were no deaths, discontinuations, or clinically significant serious adverse events. Renal function was monitored frequently during this trial and after administration of study drugs using a battery of tests (serum creatinine, eGFR, urinary beta-2 microglobulin, proteinuria, and glycosuria). No clinically significant changes in these parameters or renal toxicity were observed. A larger study, ION-4, reported similar outcomes with ledipasvir/sofosbuvir (Naggie, 2015). A total of 335 HCV treatment-naïve and -experienced HIV/HCV-coinfected patients were

enrolled in the study and received ledipasvir/sofosbuvir once daily for 12 weeks. Patients received tenofovir disoproxil fumarate and emtricitabine with raltegravir (44%), efavirenz (48%), or rilpivirine (9%). HCV genotypes included were 1a (75%), 1b (23%), and 4 (2%); 20% of patients had cirrhosis, 34% were black, and 55% had not responded to prior HCV treatment. Overall, the SVR12 rate was 96% (321/335); 2 patients had on-treatment virologic failure judged to be a result of nonadherence, 10 had virologic relapse after discontinuing treatment, 1 died from endocarditis associated with injection drug use, and 1 was lost to follow-up. SVR12 rate was 94% (63/67) among patients with cirrhosis and 97% (179/185) among treatment-experienced patients. No patients discontinued the study drug because of an adverse event. Although all patients had GFRs above 60 mL/min at study entry, drug interaction studies suggested that some patients would have elevated levels of tenofovir disoproxil fumarate. There were 4 patients in whom serum creatinine level rose to 0.4 mg/dL or higher: 2 remained on tenofovir, 1 had the tenofovir dose reduced, and the other stopped taking tenofovir. Neither study reported clinically significant changes in CD4+ T cell counts or HIV RNA levels in the study subjects. Thus, these data suggest that 12 weeks of ledipasvir/sofosbuvir is a safe and effective regimen for HIV/HCV-coinfected patients with HCV genotype 1 taking select antiretroviral therapy (Osinusi, 2015); (Naggie, 2015). There are limited data regarding an 8-week duration of ledipasvir/sofosbuvir in HIV/HCV-coinfected patients (Ingiliz, 2016). Therefore, a shortened treatment course for HIV-infected persons cannot be recommended at this time.

Paritaprevir/ritonavir/ombitasvir + dasabuvir

PrOD was FDA-approved for use in HCV genotypes 1a and 1b because of its efficacy and safety in treatment-naïve patients and PEG-IFN/ribavirin treatment-experienced patients with and without cirrhosis. Available information about response rates with this regimen in HIV/HCV-coinfected patients comes from the first part of the phase II TURQUOISE-1 study. In this study, treatment-naïve (n= 42) and -experienced (n= 21) patients were randomly assigned to receive either 12 weeks or 24 weeks of PrOD and weight-based ribavirin (100 mg [< 75 kg] to 1200 mg [≥ 75 kg]). Of the 63 study subjects, 12 had cirrhosis, 56 had HCV genotype 1a, and 7 had HCV genotype 1b. Two study-permitted antiretroviral regimens were chosen based on pharmacokinetic data from uninfected volunteers: 35 patients entered taking tenofovir disoproxil fumarate and emtricitabine with raltegravir and 28 patients entered taking tenofovir disoproxil fumarate and emtricitabine with ritonavir-boosted atazanavir (with the ritonavir coming from the HCV regimen during the time of coadministration). Of the 31 patients who received 12 weeks of PrOD and ribavirin, 29 (93.5%) achieved an SVR12, 1 relapsed, and 1 withdrew consent from study participation. Similarly, of the 32 subjects in the 24-week arm, 29 (90.6%) achieved an SVR12, 1 experienced viral breakthrough, and 2 had apparent HCV reinfection. No treatment-related serious adverse events occurred and no subjects discontinued treatment because of medication intolerance (Sulkowski, 2015).

Simeprevir + sofosbuvir

The combination of simeprevir plus sofosbuvir with or without ribavirin has been studied in the phase II COSMOS trial in patients with HCV monoinfection (Lawitz, 2014b). This study is the main basis for the recommendation supporting the use of this all-oral combination for HCV genotype 1a or 1b monoinfection. Simeprevir plus sofosbuvir has been used anecdotally in patients with HIV/HCV coinfection, with a recent report of achieving an SVR in 11 (92%) of 12 patients (Del Bello, 2016). Despite the dearth of study data, this regimen may be considered for the treatment of HCV genotype 1 infection in patients with HIV infection who are receiving antiretroviral therapy that may be coadministered with simeprevir and sofosbuvir.

Similarly, few data exist for the combination of sofosbuvir plus simeprevir for the retreatment of HCV infection in HIV/HCV-coinfected patients. However, preliminary results obtained for HCV-monoinfected patients, including those with prior treatment failure and advanced fibrosis, support the expectation that this regimen will be highly effective in HIV/HCV-coinfected patients receiving compatible antiretroviral therapy as described above (see Retreatment of HCV-monoinfected patients); (Lawitz, 2014b).

Sofosbuvir/velpatasvir

The safety and efficacy of 12 weeks of sofosbuvir/velpatasvir was evaluated in a phase 3 study of 106 antiretroviral controlled HIV/HCV coinfected subjects (Wyles, 2016). HCV genotypes 1-4 were included and 18% (n= 19) had compensated cirrhosis. HIV was controlled on ART including non-nucleoside reverse-transcriptase inhibitor (NNRTI- rilpivirine), integrase inhibitor (raltegravir or elvitegravir/cobicistat), or ritonavir-boosted protease inhibitor (PI- atazanavir, lopinavir, or darunavir) based regimens with either tenofovir/emtricitabine or abacavir/lamivudine. Fifty-three percent (n= 56) of subjects were on tenofovir with a pharmacologic boosting agent (either ritonavir or cobicistat). Neither efavirenz nor etravirine were allowed in this study as concomitant dosing with sofosbuvir/velpatasvir in healthy volunteers resulted in clinically significant decreases in velpatasvir exposures. SVR12 was 95% with 2 relapses, both occurring in genotype 1a-infected patients. Similar results were noted within genotypes, in subjects with cirrhosis and in those with baseline NS5A RASs (n= 12 at 15% threshold, SVR12= 100%). There was no clinically significant change in serum creatinine or GFR and no subject required a change in their antiretroviral therapy during the study period.

In general, few HIV/HCV-coinfected patients with cirrhosis have been included in clinical trials of DAAs, and no data are available regarding HIV/HCV-coinfected patients with renal insufficiency or who have undergone solid organ transplantation. Despite a lack of data, it is highly likely that response rates are similar to those of HCV-monoinfected patients, as no study thus far in the DAA era has showed a lower efficacy for HIV/HCV-coinfected patients. Therefore, the respective guidance from these sections should be followed if treatment is otherwise warranted, with consideration of drug interactions.

No data currently exist to guide recommendations for the retreatment of HIV/HCV-coinfected patients or for the retreatment of simeprevir- or sofosbuvir-experienced individuals. When treatment is necessary, guidelines for HCV-monoinfected individuals are recommended.

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

> Click Here to Review Regimens Not Recommended in HCV Treatment <

Changes made April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Summary of Recommendations for HIV/HCV-Coinfected Patients Who Are Being Treated for HCV

Recommendations Related to HCV Medication Interactions with HIV Antiretroviral Medications

Listed in order of level of evidence, then within group alphabetically.

- **Antiretroviral drug switches, when needed, should be done in collaboration with the HIV practitioner. For HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended.**
  Rating: Class I, Level A

- **Daclatasvir when used in combination with other antivirals:**
- **Daclatasvir requires dose adjustment with ritonavir-boosted atazanavir (a decrease to 30 mg daily) and efavirenz or etravirine (an increase to 90 mg daily).**
  Rating: Class IIa, Level B

- **Daily fixed-dose combination of elbasvir/grazoprevir:**
- **Elbasvir/grazoprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir.**
  Rating: Class IIa, Level B

- **Simeprevir when used in combination with other antivirals:**
- **Simeprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir, (and probably dolutegravir), rilpivirine, and tenofovir.**
  Rating: Class IIa, Level B

- **Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg):**

- **Sofosbuvir/velpatasvir can be used with most antiretrovirals, but not efavirenz or etravirine. Because velpatasvir increases tenofovir levels, when given as tenofovir disoproxil fumarate (TDF), concomitant use mandates consideration of renal function and should be avoided in those with eGFR below 60 mL/min. In patients with eGFR > 60 mL/min concomitant dosing of velpatasvir and TDF with ritonavir-boosted or cobicistat-boosted regimens did not result in renal toxicity in 56 subjects. Renal monitoring is recommended during the dosing period. Tenofovir alafenamide (TAF) may be an alternative to TDF during sofosbuvir/velpatasvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.**
  Rating: Class IIa, Level B

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg):**
- **Ledipasvir/sofosbuvir can be used with most antiretrovirals. Because ledipasvir increases tenofovir levels, when given as tenofovir disoproxil fumarate (TDF), concomitant use mandates consideration of estimated glomerular filtration rate (eGFR) and should be avoided in those with eGFR below 60 mL/min. Because potentiation of this effect occurs when TDF is used with ritonavir-boosted or cobicistat-boosted regimens, ledipasvir should be avoided with this combination (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high. Tenofovir alafenamide (TAF) may be an alternative to TDF during ledipasvir/sofosbuvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.**
  Rating: Class IIa, Level C

- **For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended.**
  Rating: Class IIa, Level C

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (paritaprevir/ritonavir/ombitasvir plus dasabuvir or PrOD):**
- **Paritaprevir/ritonavir/ombitasvir plus dasabuvir should be used with antiretroviral drugs with which they do not have substantial interactions: atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir.**

- **The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with paritaprevir/ritonavir/ombitasvir plus dasabuvir and then restored when HCV treatment is completed. The HIV protease inhibitor should be administered at the same time as the fixed-dose HCV combination.**

Rating: Class IIa, Level C

Recommended Regimens for HIV/HCV-Coinfected Individuals

Listed in order of level of evidence, then within group alphabetically.

- **HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications**

(see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed).
Rating: Class I, Level B

- **Daily daclatasvir (refer above for dose) plus sofosbuvir (400 mg), with or without ribavirin (refer to Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections for duration) is a Recommended regimen when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals.**
  Rating: Class I, Level B

Not Recommended

Regimens Not Recommended for Patients with HIV/HCV Coinfection

- **Antiretroviral treatment interruption to allow HCV therapy is Not Recommended.**
  Rating: Class III, Level A
- **Elbasvir/grazoprevir should NOT be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.**
  Rating: Class III, Level B
- **Sofosbuvir/velpatasvir should NOT be used with efavirenz, etravirine, or nevirapine.**
  Rating: Class III, Level B
- **Sofosbuvir-based regimens should NOT be used with tipranavir.**
  Rating: Class III, Level B
- **Paritaprevir/ritonavir/ombitasvir plus dasabuvir should NOT be used with darunavir, efavirenz, ritonavir-boosted lopinavir, ritonavir-boosted tipranavir, etravirine, nevirapine, cobicistat, or rilpivirine.**
  Rating: Class III, Level B
- **Paritaprevir/ritonavir/ombitasvir with or without dasabuvir should NOT be used in HIV/HCV-coinfected individuals who are not taking antiretroviral therapy.**
  Rating: Class III, Level B

- **Ribavirin should NOT be used with didanosine, stavudine, or zidovudine.**
  Rating: Class III, Level B

- **Simeprevir should NOT be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.**
  Rating: Class III, Level B

Regimens Not Recommended for Patients with HIV/HCV Coinfection

- **Treatment courses shorter than 12 weeks, such as the use of 8 weeks of ledipasvir/sofosbuvir.**
  Rating: Class IIb, Level C

> Click Here to Review Regimens Not Recommended in HCV Treatment <

Changes made April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

UNIQUE PATIENT POPULATIONS: PATIENTS WITH DECOMPENSATED CIRRHOSIS

(Expansions and notes for abbreviations used in this section can be found in Methods Table 3. The summary of recommendations for patients with decompensated cirrhosis is in the box. Recommendations for patients with decompensated cirrhosis who have HCV reinfection in the allograft post-liver transplantation are presented here.)

Recommended for All Patients with HCV Infection Who Have Decompensated Cirrhosis

- Patients with HCV infection who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).
  Rating: Class I, Level C

In the decompensated population, most subjects receiving DAA therapy experienced improvement in clinical and biochemical indicators of liver disease between baseline and post-treatment week 12 including patients with CTP class C cirrhosis (Fontana, 2015a). However, death and the need for liver transplantation were observed in treatment studies in the decompensated population, highlighting that not everyone benefits from therapy. Most deaths were related to the severity of underlying liver disease. The predictors of improvement or decline have not been clearly identified.

Decompensated Cirrhosis: HCV Genotype 1, 4, 5, or 6 Infection

Recommended Regimens for Patients with HCV Genotype 1, 4, 5, or 6 Infection Who Have Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment;

CTP Class B or C) Who May or May Not Be Candidates for Liver Transplantation, Including Those with Hepatocellular Carcinoma

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis.
  Rating: Class I, Level A•
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin‖ for 12 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis.
  Rating: Class I, Level A♦
- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 or 4 infection who have decompensated cirrhosis.
  Rating: Class I, Level B

‖ Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small number of patients with compensated cirrhosis.

Recommended Regimens for Patients with HCV Genotype 1, 4, 5, or 6 Infection Who Have Decompensated Cirrhosis and Are Ribavirin Ineligible

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis and are ribavirin ineligible.
  Rating: Class I, Level A♦
- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1 or 4 infection who have decompensated cirrhosis and are ribavirin ineligible.
  Rating: Class II, Level C
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis and are ribavirin ineligible.

Rating: Class II, Level C•

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small number of patients with compensated cirrhosis.

Recommended Regimens for Patients with HCV Genotype 1, 4, 5, or 6 Infection Who Have Decompensated Cirrhosis and in Whom Prior Sofosbuvir-based or NS5A-based Treatment Has Failed

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 24 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis and in whom prior sofosbuvir-based treatment has failed.

  Rating: Class II, Level C•

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin‖ for 24 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis and in whom prior sofosbuvir-based or NS5A-based treatment has failed.

  Rating: Class II, Level C♦

‖ Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small number of patients with compensated cirrhosis.

Ledipasvir/sofosbuvir

The SOLAR-1 study was a multicenter, randomized controlled trial of 108 patients with HCV genotype 1 and 4 who had decompensated cirrhosis, of whom 59 were classified as CTP class B (score 7 to 9) and 49 classified as CTP class C (score 10 to 12) cirrhosis. Subjects were randomly assigned to receive daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and ribavirin (initial dose of 600 mg, increased as tolerated) for 12 or 24 weeks (Charlton, 2015b). After excluding the 7 subjects who underwent transplantation during the study, the SVR rate was 87% in CTP class B patients who received 12 weeks of treatment and 89% in subjects who received 24 weeks of treatment. Post-therapy virologic relapse occurred in 8% and 5% of the 12- and 24-week groups, respectively. Similarly, the rates of SVR were 86% and 87%, respectively, with 12 and 24 weeks of antiviral therapy in the CTP class C subjects. In

the majority of subjects with CTP class B and C disease, the Model for End-Stage Liver Disease (MELD) and CTP scores decreased between baseline and post-treatment week 4. Of the 7 transplanted patients, 6 achieved a posttransplant virologic response and 1 died of multiorgan failure at posttransplant week 2. During the study, only 1 patient with CTP class C cirrhosis died. As expected, the frequency of serious adverse events increased with treatment duration in the CTP class B group (34% vs 10% in week 24 vs 12) as well as the CTP class C group (42% vs 26% in week 24 vs 12). Most serious adverse events were related to ribavirin. The mean daily dose of ribavirin in the decompensated patients was 600 mg/day and therapy was discontinued in 7% of the CTP class B patients and 8% of the CTP class C patients treated with 24 weeks.

The SOLAR-2 study was a multicenter randomized controlled trial of 108 patients with HCV genotypes 1 and 4 who had decompensated cirrhosis. Study participants who were treatment-naïve or -experienced, with CTP class B cirrhosis or CTP class C cirrhosis, were randomly assigned to receive daily fixed-dose combination ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) and ribavirin (initial dose of 600 mg, increased as tolerated) for 12 weeks or 24 weeks. All participants had a hemoglobin level greater than 10 g/dL and an estimated glomerular filtration rate (eGFR) greater than 40 mL/min (Manns, 2016).

Excluding 6 patients who had received a transplant, sustained virologic response (SVR) was achieved in 87% of those given the 12-week treatment course and 89% of those given the 24-week treatment course. Post-therapy virologic relapse occurred in 8% and 4% of the 12- and 24-week groups, respectively. Total bilirubin and serum albumin levels improved substantially at week 4 post-therapy compared with baseline in both treatment groups. Baseline CTP and MELD scores improved in more than 50% of the treated patients, but some patients did have worsening hepatic function. During the course of the study, 5 (5%) patients died from various causes but none of the deaths were attributed to antiviral therapy. Grade 3 or 4 adverse events were more common in the 24-week arm (34%) than in the 12-week arm (15%). These results indicate that a 12-week course of ledipasvir/sofosbuvir and ribavirin (initial dose of 600 mg, increased as tolerated) is an appropriate regimen for patients with decompensated cirrhosis who are infected with HCV genotype 1 or 4. Such therapy may lead to objective improvements in hepatic function and reduce the likelihood of recurrent HCV infection after subsequent transplantation. Most patients who started ribavirin at 600 mg per day did not receive higher doses.

A pilot study of 14 patients with compensated cirrhosis and HCV genotype 1 infection in whom prior sofosbuvir-based therapy had failed demonstrated that ledipasvir/sofosbuvir for 12 weeks was associated with a 100% SVR rate (Osinusi, 2014). In addition, results of a study of 51 HCV genotype 1-infected patients in whom prior sofosbuvir-based therapy had failed demonstrated that a 12-week course of ledipasvir/sofosbuvir and weight-based ribavirin (1000 to 1200 mg per day) led to a 98% rate of SVR at 12 weeks and the SVR rate in the 14 patients with compensated cirrhosis was 100% (SVR12) (Wyles, 2015b).

A multicenter, double-blind study from France reported on the use of daily ledipasvir/sofosbuvir for 24 weeks compared with daily ledipasvir/sofosbuvir and ribavirin for 12 weeks, with a 12-week placebo phase, in 154 patients with compensated cirrhosis and HCV genotype 1 infection in whom prior PEG-IFN/ribavirin treatment had failed (for most, treatment with PEG-IFN, ribavirin, and a protease inhibitor had also failed) (Bourliere, 2015). The mean MELD score was 7 (range, 6 to 16), 26% of patients had varices, and 13% had low serum albumin levels. The SVR12 rates were 96% with the 12-week regimen and 97% with the 24-week regimen. The most common adverse events were asthenia, headache, and pruritus, but the frequency of severe adverse events and the need for early drug discontinuation were

low in both treatment groups. In light of these results, it is reasonable to consider daily ledipasvir/sofosbuvir and ribavirin for 12 weeks in patients with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed.

Ledipasvir/sofosbuvir for 24 weeks also appears to be effective for patients with a 71% SVR in 41 HCV genotype 1-infected patients with compensated liver disease who failed a prior course of sofosbuvir-based therapy for 8 or 12 weeks (Lawitz, 2015b). As of February 2017, there are no data of this regimen given for 24 weeks in decompensated cirrhosis. However, a pilot study of 20 patients with CTP class B cirrhosis treated with ledipasvir/sofosbuvir for 12 weeks demonstrated an SVR of 65% (Gane, 2014a).

Data on the use of ledipasvir/sofosbuvir in patients with HCV genotypes 5 and 6 are very limited. Gane et al reported an SVR12 of 96% in 25 patients with HCV genotype 6 treated with ledipasvir/sofosbuvir in phase II clinical trials (Gane, 2015). Wong et al also reported an SVR12 of 95.3% with ledipasvir/sofosbuvir for 8 to 24 weeks without ribavirin in 65 adult Asian Americans with compensated cirrhosis and genotype 6 infection. The overall SVR was 92.3% in patients with cirrhosis and 97.4% in patients without cirrhosis (Wong, 2017). In an open-label study in France, ledipasvir/sofosbuvir was administered for 12 weeks to 41 treatment-naïve or previously-treated subjects with genotype 5 HCV infection, with or without cirrhosis. The overall SVR12 was 93% (38/41) (Abergel, 2016).

Sofosbuvir/velpatasvir

The ASTRAL-4 study was a multicenter, randomized, controlled trial of 267 patients with multiple HCV genotypes and decompensated cirrhosis who were treatment-naïve (45%) or -experienced (55%) with CTP class A (10%), B, or C cirrhosis. Patients were randomly assigned to receive daily fixed-dose combination sofosbuvir (400 mg) and velpatasvir (100 mg) (hereafter sofosbuvir/velpatasvir) with or without weight-based ribavirin (initial dose of 1000 mg/day if weight < 75 kg and 1200 mg/day if weight ≥ 75 kg) for 12 weeks or sofosbuvir/velpatasvir for 24 weeks in a 1:1:1 ratio. All participants had a hemoglobin level > than 10 g/dL and an eGFR greater than 40 mL/min and randomization was stratified by HCV genotype (Curry, 2015b). Overall, 60% of patients had HCV genotype 1a, 18% genotype 1b, 4% genotype 2, 15% genotype 3, 3% genotype 4, and < 1% genotype 6. 95% of the patients had a baseline MELD < 15.

SVR was achieved in 83% in those who received sofosbuvir/velpatasvir for 12 weeks, 94% in those who received sofosbuvir/velpatasvir with ribavirin for 12 weeks, and 86% in those who received sofosbuvir/velpatasvir for 24 weeks. Among patients with genotype 1, the SVR was 88%, 96%, and 92%, respectively. A total of 22 patients had virological failure including 20 patients with a post-therapy relapse and 2 patients with HCV genotype 3 who had an on-treatment virological breakthrough. The presence of baseline NS5A resistant substitutions was not associated with virological relapse. At post-treatment week 12, 47% had an improvement in CTP score while 42% had no change and 11% had worsening CTP scores. During the course of the study, 9 (3%) patients died from various causes, none of which were felt to be related to antiviral therapy. Serious adverse events were reported in 16% to 19% of the treated patients. Anemia defined as a hemoglobin < 10 g/dL was reported in 23% of the group receiving ribavirin and 8% and 9% in those who received 12 and 24 weeks of therapy without ribavirin, respectively.

Sofosbuvir/velpatasvir with weight-based ribavirin for 24 weeks was also given to 65 patients with compensated cirrhosis who had failed a prior NS5A-containing regimen (Gane, 2016). The overall SVR

was 95% and was 97% in subjects with HCV genotype 1a and 1b, 91% in genotype 2, and 76% in HCV genotype 3. As of May 2016, there are no data for this regimen given for 24 weeks in patients with decompensated cirrhosis.

In ASTRAL-1, sofosbuvir/velpatasvir without ribavirin was given for 12 weeks to 35 patients with compensated cirrhosis and genotype 5, and 41 patients with compensated cirrhosis and genotype 6 (Feld, 2015). The overall SVR12 was 97% in the genotype 5 patients and 100% in the genotype 6 patients. Of note, a 100% SVR was achieved in the small number of genotype 5 patients (n= 5) and genotype 6 patients (n= 6) with compensated cirrhosis enrolled in ASTRAL-1.

Daclatasvir + sofosbuvir

In the phase III ALLY-1 study (Poordad, 2016) daily daclatasvir (60 mg) was administered in combination with daily sofosbuvir (400 mg) and low initial dose of ribavirin (600 mg) for 12 weeks to treatment-naïve and -experienced patients who predominantly had HCV genotype 1 infection, in 2 specific populations: those with advanced cirrhosis (CTP class B and C; n= 60) and those with recurrent HCV infection posttransplant (n= 53). The SVR12 rate was 83% among those with advanced cirrhosis and 94% among those with recurrent HCV infection posttransplant. In the population with advanced cirrhosis, SVR12 rate was 76% among patients with HCV genotype 1a and 100% among patients with HCV genotype 1b. Response rates differed based on severity of disease among those with advanced cirrhosis, SVR12 rate was 94% among patients with CTP class B cirrhosis but only 56% among patients with CTP class C cirrhosis. Among subjects with HCV genotype 3, SVR12 rates were 83% and 91%, respectively, in those with advanced cirrhosis and recurrent HCV infection posttransplant.

Real-world studies

Observational cohort studies have evaluated other combinations of DAA agents in patients with decompensated cirrhosis. Foster and colleagues reported on the use of ledipasvir (90 mg)/sofosbuvir (400 mg) or daclatasvir (60 mg) plus sofosbuvir (400 mg) with or without ribavirin for 12 weeks in 235 genotype-1 patients from the United Kingdom (Foster, 2016). The SVR rates were similar in the 235 genotype-1 subjects receiving ledipasvir/sofosbuvir plus ribavirin or ledipasvir/sofosbuvir (86% to 81%, respectively) and those receiving daclatasvir plus sofosbuvir with ribavirin or daclatasvir plus sofosbuvir therapy (82% to 60%). In this real-world study, 91% of the patients received ribavirin and only 6% discontinued ribavirin while 20% required a ribavirin dose reduction. MELD scores improved in 42% of treated patients and worsened in 11%. In addition, there were 14 deaths and 26% of the patients had an SAE but none were treatment related.

A multicenter study from Spain also described the safety and efficacy of sofosbuvir-based therapy in 739 HCV patients with decompensated cirrhosis (Fernandez-Carillo, 2016). In this study, the majority of patients had HCV genotype 1a or 1b infection, 76% had CTP class A, and 24% had CTP class B/C cirrhosis. Patients were treated with a variety of regimens including simeprevir plus sofosbuvir (45%), daclatasvir plus sofosbuvir (22%), and ledipasvir/sofosbuvir (16%). Overall SVR was 94% in CTP class A patients compared to 78% in CTP class B/C patients and rates of virological relapse were 4% and 14%, respectively. Sixteen patients died. Both deaths and SAEs were significantly more common in those with CTP class B/C. These data highlight the lower efficacy and increased safety concerns when treating patients with more advanced liver failure.

Protease-inhibitor containing regimens

To date, the fixed-dose combination of elbasvir (50 mg) and grazoprevir (100 mg) (hereafter, elbasvir/grazoprevir) has not been studied in decompensated cirrhosis. A phase II, non-randomized, open-label study of elbasvir (50 mg) and grazoprevir (50 mg) for 12 weeks was completed in 30 HCV genotype 1 patients with CTP class B cirrhosis (Jacobson, 2015). The SVR12 rate was 90% and 1 patient died of liver failure at post-treatment week 4. MELD scores improved in 15 treated patients, were unchanged in 9, and increased in 6. However, there are no safety or efficacy data regarding the approved FDC elbasvir/grazoprevir doses in patients with decompensated cirrhosis. Therefore, until further data are available, treatment of patients with decompensated cirrhosis with elbasvir/grazoprevir is not recommended.

Recent data reported by the US FDA have demonstrated that some patients with compensated cirrhosis and HCV genotype 1 treated with paritaprevir, ombitasvir, and dasabuvir may develop rapid onset of direct hyperbilirubinemia within 1 to 4 weeks of starting treatment without ALT elevations that can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received PrOD and also developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died (Zuckerman, 2016). Therefore, this antiviral treatment regimen is CONTRAINDICATED in all patients with decompensated cirrhosis due to concerns of hepatotoxicity. In addition, all patients with cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks on therapy.

Decompensated Cirrhosis: Genotype 2 and 3 HCV Infection

Recommended Regimens for Patients with HCV Genotype 2 or 3 Infection Who Have Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; CTP Class B or C) and Who May or May Not Be Candidates for Liver Transplantation, Including Those with Hepatocellular Carcinoma

- Daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 2 or 3 infection who have decompensated cirrhosis and who may or may not be candidates for liver transplantation including those with hepatocellular carcinoma.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 2 or 3 infection who have decompensated cirrhosis and who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
  Rating: Class II, Level B

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.

Sofosbuvir/velpatasvir

In the ASTRAL-4 study, the SVR in 12 patients CTP class B cirrhosis with genotype 2 was 100% with sofosbuvir/velpatasvir for 12 weeks with and without ribavirin and 75% with sofosbuvir/velpatasvir for 24 weeks. Similarly, among 39 patients with CTP class B cirrhosis with HCV genotype 3, the SVR was 50% and 85% with sofosbuvir/velpatasvir for 12 weeks without and with ribavirin and 50% with sofosbuvir/velpatasvir without ribavirin for 24 weeks. Therefore, genotype 3 patients in particular appear to benefit from the addition of ribavirin to the regimen (Curry, 2015b). For decompensated HCV patients who are ribavirin ineligible, daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) for 24 weeks is currently recommended but further studies in larger numbers of patients are needed to define the optimal duration of therapy. Sofosbuvir/velpatasvir has not been studied in CTP class C patients.

Daclatasvir + sofosbuvir

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients without and with cirrhosis. Although daclatasvir with sofosbuvir was not approved for the treatment of HCV genotype 2 infection, daclatasvir maintains adequate activity against HCV genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir with sofosbuvir was associated with high rates of SVR in treatment-naïve patients with HCV genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014). It is unclear if there is a subgroup of HCV genotype 2-infected patients who would benefit from extending treatment to 24 weeks. For patients who require treatment but cannot tolerate ribavirin, an alternative regimen of daclatasvir with sofosbuvir for 12 weeks is recommended with consideration of extending treatment to 24 weeks for patients with poor baseline characteristics (ie, decompensated cirrhosis). Relevant data supporting daclatasvir, sofosbuvir, and ribavirin from the ALLY-1 trial are described here. In addition, use of daclatasvir plus sofosbuvir with or without ribavirin from an ongoing observational cohort study in 121 patients with decompensated cirrhosis and genotype 3 infection from the UK demonstrated an SVR of 70% and 71%, respectively (Foster, 2016). In comparison, the SVR in 68 patients with decompensated genotype 3 treated with ledipasvir/sofosbuvir with or without ribavirin were 43% and 59%, respectively.

A multicenter, compassionate use study of daclatasvir (60 mg), sofosbuvir (400 mg) ± ribavirin for 24 weeks in 101 genotype 3 European patients was reported (Welzel, 2015). 81% of the patients had CTP class B cirrhosis, the MELD score was > 15 in 16%, and 7% were LT recipients. To date, SVR 12 data has demonstrated an SVR of 85% to 100%. Twenty-two patients had an SAE and therapy was discontinued in 5, while 2 patients died.

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert

consultation should be sought.

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Changes made April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Summary of Recommendations for Patients with Decompensated Cirrhosis

Recommended for All Patients with HCV Infection Who Have Decompensated Cirrhosis

- Patients with HCV infection who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).
  Rating: Class I, Level C

Recommended Regimens for Patients with HCV Genotype 1, 4, 5, or 6 Infection Who Have Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; CTP Class B or C) Who May or May Not Be Candidates for Liver Transplantation, Including Those with Hepatocellular Carcinoma

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis.
  Rating: Class I, Level A•

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin‖ for 12 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis.
  Rating: Class I, Level A♦

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV

genotype 1 or 4 infection who have decompensated cirrhosis.
Rating: Class I, Level B

[||] Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small number of patients with compensated cirrhosis.

Recommended Regimens for Patients with HCV Genotype 1, 4, 5, or 6 Infection Who Have Decompensated Cirrhosis and Are Ribavirin Ineligible

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis and are ribavirin ineligible.
  Rating: Class I, Level A♦
- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1 or 4 infection who have decompensated cirrhosis and are ribavirin ineligible.
  Rating: Class II, Level C
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis and are ribavirin ineligible.
  Rating: Class II, Level C•

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small number of patients with compensated cirrhosis.

Recommended Regimens for Patients with HCV Genotype 1, 4, 5, or 6 Infection Who Have Decompensated Cirrhosis and in Whom Prior Sofosbuvir-based or NS5A-based Treatment Has Failed

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 24 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis and in whom prior sofosbuvir-based treatment has failed.

Rating: Class II, Level C•

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin‖ for 24 weeks is a Recommended regimen for patients with HCV genotype 1, 4, 5, or 6 infection who have decompensated cirrhosis and in whom prior sofosbuvir-based or NS5A-based treatment has failed.

  Rating: Class II, Level C♦

‖ Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small number of patients with compensated cirrhosis.

Recommended Regimens for Patients with HCV Genotype 2 or 3 Infection Who Have Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; CTP Class B or C) and Who May or May Not Be Candidates for Liver Transplantation, Including Those with Hepatocellular Carcinoma

- Daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 2 or 3 infection who have decompensated cirrhosis and who may or may not be candidates for liver transplantation including those with hepatocellular carcinoma.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 2 or 3 infection who have decompensated cirrhosis and who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
  Rating: Class II, Level B

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.

> Click Here to Review Regimens Not Recommended in HCV Treatment <

Changes made April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

UNIQUE PATIENT POPULATIONS: PATIENTS WHO DEVELOP RECURRENT HCV INFECTION POST-LIVER TRANSPLANTATION

(Expansions and notes for abbreviations used in this section can be found in Methods Table 3. The summary of recommendations for patients who develop recurrent HCV infection post-liver transplantation is in the box.)

Genotype 1 or 4

Recommended Regimens for Treatment-naïve and -Experienced Patients with HCV Genotype 1 or 4 Infection in the Allograft, Including Those with Compensated Cirrhosis

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 or 4 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class I, Level A

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 or 4 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class I, Level B

Recommended Regimens for Treatment-naïve Patients with HCV Genotype 1 or 4 Infection in the Allograft and with Compensated Liver Disease, Who Are Ribavirin Ineligible

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1 or 4 infection in the allograft and with compensated liver disease, who are ribavirin ineligible.
  Rating: Class I, Level B

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1 or 4 infection in the allograft and with compensated liver disease, who are ribavirin ineligible.
  Rating: Class II, Level C

Recommended Regimen for Treatment-naïve and -Experienced Liver Transplant Recipients with Decompensated Cirrhosis (Child Turcotte Pugh [CTP] Class B or C) Who Have HCV Genotype 1 or 4 Infection in the Allograft

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for liver-transplant recipients with decompensated cirrhosis (CTP class B or C) who have HCV genotype 1 or 4 infection in the allograft.
  Rating: Class I, Level B

Alternative Regimens for Patients with HCV Genotype 1 Infection in the Allograft, Including Those with Compensated Cirrhosis

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 12 weeks is an Alternative regimen for patients with HCV genotype 1 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class I, Level B

Alternative Regimens for Patients with HCV Genotype 1 Infection in the Allograft, Including Those with Early-stage Fibrosis (Metavir Stage F0-F2)

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1 infection in the allograft, who have early-stage fibrosis (Metavir stage F0-F2).
  Rating: Class I, Level B

Genotype 2

Recommended Regimens for Treatment-naïve and -Experienced Patients with HCV Genotype 2 Infection in the Allograft, Including Those with Compensated Cirrhosis

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg), with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class II, Level A

- Daily sofosbuvir (400 mg) and weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class II, Level C

Recommended Regimen for Treatment-naïve and -Experienced Patients with HCV Genotype 2 Infection in the Allograft, Including Those with Compensated Cirrhosis, Who Are Ribavirin Ineligible

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection in the allograft, including those with with compensated cirrhosis, who are ribavirin ineligible.
  Rating: Class II, Level C

Recommended Regimen for Treatment-naïve and -Experienced Liver-Transplant Recipients with Decompensated Cirrhosis (Child Turcotte Pugh [CTP] Class B or C) Who Have HCV Genotype 2 Infection in the Allograft

- Daily sofosbuvir (400 mg) and ribavirin (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose) for 24 weeks is a Recommended regimen for liver-transplant recipients with decompensated cirrhosis (CTP class B or C) who have HCV genotype 2 infection in the allograft.
  Rating: Class II, Level C

Genotype 3

Recommended Regimen for Treatment-naïve and -Experienced Patients with HCV

Genotype 3 Infection in the Allograft, Including Those with Compensated Cirrhosis

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class II, Level A

Recommended Regimen for Treatment-naïve and -Experienced Patients with HCV Genotype 3 Infection in the Allograft, Including Those with Compensated Cirrhosis, Who Are Ribavirin Ineligible

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 3 infection in the allograft, including those with compensated cirrhosis, who are ribavirin ineligible.
  Rating: Class II, Level C

Daclatasvir + sofosbuvir

In the phase III ALLY-1 study (Poordad, 2016), daclatasvir (60 mg daily) was administered in combination with daily sofosbuvir (400 mg) and ribavirin (initial dose, 600 mg) for 12 weeks to treatment-naïve and -experienced patients who predominantly had HCV genotype 1 infection, in two specific populations: those with advanced cirrhosis (Child Turcotte Pugh [CTP] class B or C; n= 60) and those with recurrent HCV infection posttransplant (n= 53). Rate of sustained virologic response of 12 weeks (SVR12) was 83% among those with advanced cirrhosis and 94% among those with recurrent HCV infection posttransplant. In the population with advanced cirrhosis, SVR12 rate was 76% among patients with HCV genotype 1a and 100% among patients with HCV genotype 1b. In the population with advanced cirrhosis, SVR12 rate was 94% among patients with CTP class B cirrhosis and 56% among patients with CTP class C cirrhosis. Among subjects with HCV genotype 3, SVR12 rates were 83% and 91%, respectively, in those with advanced cirrhosis and recurrent HCV infection posttransplant.

Fontana and colleagues (Fontana, 2016) reported on the use of daclatasvir-containing regimens with either sofosbuvir (n= 77) or simeprevir (n= 18) or both (n= 2) for 24 weeks in 97 liver-transplant recipients with severe recurrent HCV infection. 93% of the patients had HCV genotype 1, 31% had biopsy-proven cirrhosis, 37% had severe cholestatic HCV, and the proportion with CTP A/B/C was 51%/ 31%/12%. The mean MELD score was 13.0 + 6.0 and 35% of the cohort received ribavirin. The SVR12 rate was 87% overall, 91% in the group that received daclatasvir and sofosbuvir with or without ribavirin, and 72% in the group that received daclatasvir and simeprevir with or without ribavirin. Although 8 patients died during or after therapy from graft dysfunction, CTP and MELD scores were stable or improved in 87% and 83% of patients, respectively. There were 3 virologic breakthroughs and 2 relapses in patients treated with daclatasvir and simeprevir. These data along with those from others suggest that daclatasvir should preferentially be combined with sofosbuvir rather than simeprevir in liver-transplant recipients, particularly in those with advanced liver disease (EASL, 2015a). Herzer and colleagues (Herzer, 2015)

described 6 liver-transplant recipients with recurrent HCV infection, 4 (67%) of whom achieved SVR with a regimen of daclatasvir plus simeprevir with ribavirin. Overall, daclatasvir-containing regimens appear to be well tolerated, with anemia noted when ribavirin was used. Cyclosporine and tacrolimus increase daclatasvir area under the curve by 40% and 5%, respectively; these changes are not clinically significant. Daclatasvir does not cause clinically meaningful changes in calcineurin inhibitor, mammalian target of rapamycin (mTOR) inhibitor, steroid, or mycophenolate levels.

Ledipasvir/sofosbuvir

The SOLAR-1 study was a large, multicenter, randomized controlled trial that included liver-transplant recipients (n= 223) across a broad spectrum of histologic and clinical severity of recurrence (n= 111 with Metavir fibrosis stage F0-F3; n= 51 with HCV genotype 1 or 4 and compensated CTP class A cirrhosis; n= 61 with decompensated CTP class B or C cirrhosis). Study participants were randomly assigned to receive fixed-dose combination ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) and weight-based ribavirin (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for either 12 weeks or 24 weeks. On an intention-to-treat basis, SVR was achieved in 96% of patients with Metavir fibrosis stages F0 to F3 and in 96% of those with compensated cirrhosis, in both the 12- and 24-week arms; all patients received ribavirin. Ribavirin dose was weight based for patients with Metavir fibrosis stage F0 to F3 and CTP class A cirrhosis. For patients with CTP class B or C cirrhosis, ribavirin was initiated at 600 mg daily followed by dose escalation as tolerated (Reddy, 2014). Only 2% of patients discontinued treatment owing to adverse events. Efficacy was lower in patients with CTP class B cirrhosis (85% SVR12) or CTP class C cirrhosis (60% SVR12), with no increase in SVR observed in patients who received 24 weeks of treatment. Mortality rate was 10% during the study among patients with CTP class B or C cirrhosis. Very similar results were achieved using an identical study design in the SOLAR-2 study, which was conducted in Europe, Australia, and New Zealand. SOLAR-2 included 168 posttransplant patients without cirrhosis (fibrosis stage F0-F3) or with compensated cirrhosis (Child Turcotte Pugh [CTP] A) treated for 12 weeks (n= 86) or 24 weeks (n= 82). There were also 160 pre- and posttransplantation patients with decompensated cirrhosis (CTP B/C) treated for 12 weeks (n= 78) or 24 weeks (n= 82). SVR12 rates in posttransplant non-cirrhotic or compensated cirrhosis were 95% for 12 weeks of therapy and 98% for 24 weeks of therapy. Among patients with more severe disease, SVR12 rates were 85% for 12 weeks of therapy and 88% for 24 weeks of therapy.

As the importance of ribavirin cannot be ascertained from the SOLAR study, in which all patients received ribavirin, the safest presumption is that ribavirin may contribute to the high SVR12 rates observed. In a previous study of a similar patient population to that of the SOLAR study, 40 patients with recurrent HCV infection following liver transplantation were treated for 24 weeks with sofosbuvir plus ribavirin, with SVR12 achieved in 70% (Charlton, 2015b). Although the basis for attenuated SVR rate observed in patients with more advanced HCV infection post-liver transplant is not known, these results, together with those of the sofosbuvir compassionate-use program, (Forns, 2015) suggest that the optimal period to initiate therapy may be the first 6 months to 12 months posttransplant to minimize the likelihood of having to treat patients with more advanced liver disease.

No data on ledipasvir/sofusbuvir are available for patients with HCV genotype 3 infection in the posttransplant setting. Very limited phase II data are available from a single-center study (ELECTRON-II) that examined ledipasvir/sofosbuvir used with (n= 26) or without (n= 25) ribavirin for 12 weeks in treatment-naïve patients with HCV genotype 3 infection; 15% of patients had cirrhosis. All 26 (100%) patients in the ribavirin-containing arm achieved SVR12 compared with 16 of 25 (64%) of those in the ribavirin-free arm. Although these data raise the possibility that the addition of ledipasvir to sofosbuvir

and ribavirin may shorten the course of therapy for persons with HCV genotype 3 infection, the high effective concentration (EC_{50}) of ledipasvir for HCV genotype 3 (Wong, 2013); (Kohler, 2014) and the homogenous patient population studied limit the generalizability of this study. Until further data are available to confirm these findings, a recommendation for use of this regimen cannot be made at this time (Gane, 2013).

Paritaprevir/ritonavir/ombitasvir + dasabuvir

In a multicenter study of 34 liver-transplant recipients with mild recurrence (Metavir fibrosis stage F0-F2) of HCV genotype 1 infection, fixed-dose combination paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) and weight-based ribavirin was given for 24 weeks and achieved an SVR24 rate of 96% (Kwo, 2014). Because of the drug-drug interactions between ritonavir and calcineurin inhibitors, prospective dose adjustments were needed for cyclosporine and tacrolimus. Interactions between ritonavir and other medications commonly taken by liver-transplant recipients are also possible and will require detailed consideration when using this regimen. The efficacy and tolerability of this regimen in patients with more advanced HCV infection post-liver transplant are unknown.

Simeprevir + sofosbuvir

The GALAXY study prospectively assessed the use of simeprevir with sofosbuvir with or without weight-based ribavirin for 12 to 24 weeks in 46 non-cirrhotic patients with HCV genotype 1 (O'Leary, 2016). The SVR12 rate was 100% with simepevir and sofosbuvir for 12 weeks, 81.8% with simeprevir and sofosbuvir with ribavirin, and 91.7% with simeprevir and sofosbuvir with ribavirin for 24 weeks. A retrospective multicenter analysis of sofosbuvir (400 mg daily) plus simeprevir (150 mg daily) with or without ribavirin in 77 recipients reported an SVR4 rate of 92% (Pungpapong, 2015). Another recent multicenter retrospective study of 151 patients with recurrent HCV genotype 1 treated with simeprevir and sofosbuvir alone (n= 119) or with ribavirin (n= 32) was reported (Brown, 2016). The duration of therapy was 12 weeks for most patients but 15 did receive 24 weeks of therapy. Allograft cirrhosis had developed in 64.2% and 39.7% of patients had decompensated hepatic function. The overall SVR was 88% and 7% experienced virological relapse. Serious adverse events were reported in 11.9% and 3 deaths were not related to therapy. In healthy volunteers, the coadministration of single-dose cyclosporine with simeprevir resulted in a 19% increase in cyclosporine concentrations and simeprevir concentrations similar to historical data (see simeprevir prescribing information). However, in an interim analysis of an ongoing study in HCV-infected individuals (TMC435HPC3016), concomitant use of simeprevir (plus daclatasvir and ribavirin) with cyclosporine at steady state resulted in an approximately 6-fold increase in plasma concentrations of simeprevir compared with historical data of simeprevir in the absence of cyclosporine. This interaction may be caused by inhibition of organic ion-transporting polypeptide 1B1 (OATP1B1), p-glycoprotein (P-gp), and cytochrome P450 3A (CYP3A) by cyclosporine. Given these findings, simeprevir should not be coadministered with cyclosporine.

In healthy volunteers, the coadministration of single-dose tacrolimus with simeprevir did not result in a notable change of tacrolimus concentrations (see simeprevir prescribing information). In an ongoing study, concomitant use of simeprevir with tacrolimus resulted in a 2-fold increase in plasma concentrations of simeprevir compared with historical data (see simeprevir prescribing information). Based on phase I studies, a 2-fold increase in simeprevir concentrations is unlikely to be clinically significant.

Clinicians may consider the use of sofosbuvir plus simeprevir in patients receiving tacrolimus with therapeutic drug monitoring, particularly in those expected to have difficulty tolerating ribavirin (eg, patients with impaired renal function or anemia) or who are unable to forego proton pump inhibitor therapy (proton pump inhibitors attenuate ledipasvir absorption). A further option in patients who are ribavirin intolerant is 24 weeks of ledipasvir/sofosbuvir.

The interaction of direct-acting antiviral (DAA) agents and calcineurin inhibitors is complex and unpredictable without formal studies of drug-drug interactions. A summary of drug interactions between calcineurin inhibitors and direct-acting antiviral agents with recommended dosing is provided in the Table below. Based on the metabolism of grazoprevir and elbasvir, 15-fold increases in grazoprevir AUC and 2-fold increases in elbasvir AUC can be expected with coadministration with cyclosporine. Therefore, this combination should be avoided. Since a 40%-50% increase in tacrolimus levels is predicted during coadministration with grazoprevir, no dosing adjustments are anticipated, but TAC levels should be monitored.

Elbasvir/grazoprevir

Although fixed-dose combination elbasvir and grazoprevir (hereafter, elbasvir/grazoprevir) have been extensively studied in patients with HCV infection with genotypes 1 and 4 who have compensated liver disease, there are no reports of this combination in liver-transplant recipients. The actual impact of elbasvir or grazoprevir on immunosuppression pharmacokinetics is unknown. For this reason, elbasvir and grazoprevir are not recommended for the treatment of HCV infection in liver-transplant recipients. Data regarding the safety and efficacy of elbasvir and grazoprevir in patients with advanced liver disease are available only from a phase II open-label study of grazoprevir (50 mg)/elbasvir (50 mg), given for 12 weeks in 30 HCV genotype 1 patients with CTP class B cirrhosis (Jacobson, 2015). This grazoprevir dose used in this study is lower than the grazoprevir dose in the commercially available fixed-dose formulation (50 mg vs 100 mg). The great majority of patients had CTP scores of 7 or 8 (28/30). The SVR12 rate was 90%. One patient died of liver failure at posttreatment week 4. MELD scores improved in 15 treated patients, were unchanged in 9, and increased in 6. It is possible that patients receiving elbasvir/grazoprevir will undergo liver transplantation prior to completing therapy. Continuation of elbasvir/grazoprevir following liver transplantation is not recommended. Similarly, although elbasvir/grazoprevir is well tolerated and effective in patients with renal insufficiency, which is common in liver-transplant recipients, the likely drug-drug interactions with immunosuppression agents outweigh the benefits of low renal metabolism of grazoprevir and elbasvir.

Sofosbuvir/velpatasvir

There are no reports of the safety of efficacy of sofosbuvir/velpatasvir fixed-dose combination in liver-transplant recipients. In the non-transplant setting, discussed in detail in the initial and retreatment sections of this guidance, of 624 patients with HCV genotypes 1a (34%), 1b (19%), 2 (17%), 4 (19%), 5 (6%), and 6 (7%) who were randomly assigned to receive fixed-dose combination of sofosbuvir/velpatasvir or placebo for 12 weeks were reported in the ASTRAL-1 study (Feld, 2015). All patients with genotype 5 (n= 35) received active treatment. One third of patients were treatment experienced. Nineteen percent had CTP Class A cirrhosis. The 95% confidence interval for SVR12 was 98 to > 99%. The side-effect/adverse-event profile of sofosbuvir/velpatasvir was similar to placebo. In a separate study (ASTRAL-3) (Foster, 2015a), among patients with HCV genotype 3 (n= 552), the rate of sustained virologic response in the sofosbuvir/velpatasvir group was 95% (95% CI, 92 to 98), which was superior to the rate of 80% (95% CI, 75 to 85) for patients receiving sofosbuvir plus ribavirin for 12

weeks. In a third study (ASTRAL-4) (Curry, 2015b), 267 patients with HCV genotypes 1, 2, 3, 4, and 6 in patients with decompensated cirrhosis (90% CTP Class B or C) in which 55% of patients were treatment experienced, SVR12 was achieved in 83% in those who received sofosbuvir/velpatasvir for 12 weeks, 94% in those who received sofosbuvir/velpatasvir with ribavirin for 12 weeks, and 86% in those who received sofosbuvir/velpatasvir for 24 weeks. Among patients with genotype 1, the SVR was 88% and 96% with sofosbuvir/velpatasvir for 12 weeks without and with ribavirin respectively, and 92% with sofosbuvir/velpatasvir for 24 weeks. Posttreatment virologic relapse occurred in 12% and 9% in the groups that did not receive ribavirin vs 2% of the 12-week group of sofosbuvir/velpatasvir with ribavirin. Although the ASTRAL-4 study was not powered to generate statistical significance, the results suggest that sofosbuvir/velpatasvir with ribavirin for 12 weeks is the optimal choice for patients with genotypes 1 or 3 who have decompensated cirrhosis. The participant numbers were too small for genotypes 2, 4, and 6 to differentiate the comparative efficacy of the treatment arms.

Velpatasvir is a substrate for CYP3A4, CYP2C8, and CYP2B6 and a weak (P-gp, OATP) to moderate (breast cancer resistance protein, BCRP) transport inhibitor and is moderately affected by potent inhibitors and to a greater extent, potent inducers of enzyme/drug transporter systems (Mogalian, 2016). Based on this profile, which is similar to ledipasvir, clinically significant drug-drug interactions would not be expected for coadministration of sofosbuvir/velpatasvir with common immunosuppressive agents (eg, tacrolimus, cyclosporine, corticosteroids, mycophenolate mofetil, or everolimus). However, based on the lack of real-world experience of the pharmacokinetics of sofosbuvir/velpatasvir in liver-transplant recipients and because alternatives with similar projected efficacy are available for which interactions with immunosuppression agents have been reported, we do not recommend the use of velpatasvir in transplant recipients at this time.

Table. DAA Interactions with Calcineurin Inhibitors

	Cyclosporine	Tacrolimus
Sofosbuvir	4.5-fold ↑ in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Ledipasvir	No data; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No data; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Daclatasvir	No interaction observed; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Simeprevir	5.81-fold ↑ in SIM AUC; combination is not recommended	85% ↑ in SIM AUC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed

PrOD	5.8-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed	57-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed
PrO	4.3-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrO treatment, monitor CSA levels and titrate CSA dose as needed	86-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrO treatment, monitor TAC levels and titrate TAC dose as needed
Elbasvir/Grazoprevir	15-fold ↑ in GZR AUC and 2-fold ↑ in EBR AUC; combination is not recommended	43% ↑ in TAC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Velpatasvir	No interaction observed; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No data; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

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Changes made April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Summary of Recommendations for Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation

Recommended Regimens for Treatment-naïve and -Experienced Patients with HCV Genotype 1 or 4 Infection in the Allograft, Including Those with Compensated Cirrhosis

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 or 4 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class I, Level A
- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 or 4 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class I, Level B

Recommended Regimens for Treatment-naïve Patients with HCV Genotype 1 or 4 Infection in the Allograft and with Compensated Liver Disease, Who Are Ribavirin Ineligible

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1 or 4 infection in the allograft and with compensated liver disease, who are ribavirin ineligible.
  Rating: Class I, Level B

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1 or 4 infection in the allograft and with compensated liver disease, who are ribavirin ineligible.
  Rating: Class II, Level C

Recommended Regimen for Treatment-naïve and -Experienced Liver Transplant Recipients with Decompensated Cirrhosis (Child Turcotte Pugh [CTP] Class B or C) Who Have HCV Genotype 1 or 4 Infection in the Allograft

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for liver-transplant recipients with decompensated cirrhosis (CTP class B or C) who have HCV genotype 1 or 4 infection in the allograft.
  Rating: Class I, Level B

Alternative Regimens for Patients with HCV Genotype 1 Infection in the Allograft, Including Those with Compensated Cirrhosis

- Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 12 weeks is an Alternative regimen for patients with HCV genotype 1 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class I, Level B

Alternative Regimens for Patients with HCV Genotype 1 Infection in the Allograft, Including Those with Early-stage Fibrosis (Metavir Stage F0-F2)

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin for 24 weeks is an Alternative regimen for patients with HCV genotype 1 infection in the allograft, who have early-stage fibrosis (Metavir stage F0-F2).
  Rating: Class I, Level B

Recommended Regimens for Treatment-naïve and -Experienced Patients with HCV Genotype 2 Infection in the Allograft, Including Those with Compensated Cirrhosis

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg), with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class II, Level A

- Daily sofosbuvir (400 mg) and weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class II, Level C

Recommended Regimen for Treatment-naïve and -Experienced Patients with HCV Genotype 2 Infection in the Allograft, Including Those with Compensated Cirrhosis, Who Are Ribavirin Ineligible

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection in the allograft, including those with with compensated cirrhosis, who are ribavirin ineligible.
  Rating: Class II, Level C

Recommended Regimen for Treatment-naïve and -Experienced Liver-Transplant Recipients with Decompensated Cirrhosis (Child Turcotte Pugh [CTP] Class B or C) Who Have HCV Genotype 2 Infection in the Allograft

- Daily sofosbuvir (400 mg) and ribavirin (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose) for 24 weeks is a Recommended regimen for liver-transplant recipients with decompensated cirrhosis (CTP class B or C) who have HCV genotype 2 infection in the allograft.
  Rating: Class II, Level C

Recommended Regimen for Treatment-naïve and -Experienced Patients with HCV Genotype 3 Infection in the Allograft, Including Those with Compensated Cirrhosis

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection in the allograft, including those with compensated cirrhosis.
  Rating: Class II, Level A

Recommended Regimen for Treatment-naïve and -Experienced Patients with HCV Genotype 3 Infection in the Allograft, Including Those with Compensated Cirrhosis, Who Are Ribavirin Ineligible

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 3 infection in the allograft, including those with compensated cirrhosis, who are ribavirin ineligible.
  Rating: Class II, Level C

> Click Here to Review Regimens Not Recommended in HCV Treatment <

Changes made July 6, 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

UNIQUE PATIENT POPULATIONS: PATIENTS WITH RENAL IMPAIRMENT

(Expansions and notes for abbreviations used in this section can be found in Methods Table 3. The summary of recommendations for patients with renal impairment, including severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min) or end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis is found in the box.)

HCV is independently associated with the development of chronic kidney disease (Rogal, 2016); (Fabrizi, 2015). A recent meta-analysis demonstrated that chronic HCV infection was associated with a 51% increase in the risk of proteinuria and a 43% increase in the incidence of chronic kidney disease (Fabrizi 2015). There is also a higher risk of progression to ESRD in persons with chronic HCV and chronic kidney disease and an increased risk of all-cause mortality in persons on dialysis (Lee, 2014); (Fabrizi, 2012).

Recommended Dosage Adjustments for Patients with Mild to Moderate Renal Impairment

- **For patients with mild to moderate renal impairment (eGFR 30 mL/min-80 mL/min), no dosage adjustment is required when using daclatasvir (60 mg*), fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with (or without for HCV genotype 4 infection) twice-daily dosed dasabuvir (250 mg), simeprevir (150 mg), or sofosbuvir (400 mg) to treat or retreat HCV infection in patients with appropriate genotypes.**
  Rating: Class I, Level A

Recommended Regimens for Patients with Severe Renal Impairment, Including Severe Renal Impairment (eGFR <30 mL/min) or End-Stage Renal Disease (ESRD)

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **For patients with genotype 1a, or 1b, or 4 infection and eGFR below 30 mL/min, for whom treatment has been elected, daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen.**
  Rating: Class Ia, Level B

- **For patients with genotype 1b infection and eGFR below 30 mL/min, for whom treatment has been elected, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen.**
  Rating: Class IIb, Level B

- **For patients with HCV genotype 2, 3, 5, or 6 infection and eGFR below 30 mL/min, for whom the urgency to treat is high, PEG-IFN and dose-adjusted ribavirin** (200 mg daily) is a Recommended regimen.**
  Rating: Class IIb, Level B

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
**Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

Alternative Regimen for Genotype 1a-infected Patients with eGFR Below 30 mL/min

- **For HCV genotype 1a infection, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and dose-adjusted ribavirin** (200 mg daily) for 12 weeks is an Alternative regimen.**
  Rating: Class IIb, Level B

**Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

A recent study (C-SURFER) evaluated the safety and efficacy of 12 weeks of a second-generation NS3/NS4A protease inhibitor, grazoprevir (100 mg once daily) and an NS5A inhibitor, elbasvir (50 mg once daily) versus placebo for HCV genotype 1 patients with CKD stages 4/5. The original study was designed to randomize eligible patients to either immediate or deferred treatment with elbasvir and grazoprevir. The delayed treatment arm received placebo and was treated with elbasvir and grazoprevir later. The data for the immediate treatment arm have been published (Roth, 2015). The study participants were HCV genotype 1, CKD stages 4/5 (eGFR < 30 mL/min), 75% on hemodialysis, 45% were

African Americans. Small numbers of patients with compensated cirrhosis were allowed. The study reported an ITT and modified ITT of 94% and 99% for SVR12. There were no changes in hemoglobin or other adverse events or erythropoietin use in the treatment groups compared to placebo, while most patients in the treatment group normalized ALT and AST values compared to placebo. None of the genotype 1a patients with baseline NS5A RASs experienced viral relapse; the only reported relapse occurred in a patient with genotype 1b. The basis for the lack of impact of NS5A RASs on SVR rates in this population is unclear, but may relate to moderately increased AUCs of grazoprevir or elbasvir observed in stage 4/5 CKD (Merck PI). Based on these data, the fixed-dose combination elbasvir (50 mg) and grazoprevir (100 mg) (hereafter, elbasvir/grazoprevir) is recommended for the treatment of HCV genotype 1 infection in patients with severely compromised renal function. No strong recommendation for NS5A RAS testing can be made in this population. While C-SURFER did not evaluate patients with genotype 4 infection, it is likely that the high efficacy of elbasvir/grazoprevir in genotype 1 and 4 infection in persons with normal renal function can be extrapolated to genotype 4-infected persons with CKD stage 4/5. Treatment with elbasvir/grazoprevir in persons with CKD has been shown to be cost effective in the United States (Elbasha, 2016).

Sofosbuvir and ribavirin are renally eliminated. Safe and effective doses of sofosbuvir in those with eGFR less than 30 mL/min have not been established. If urgency for treatment is high, there is accumulating evidence on use of sofosbuvir-based regimens in persons with eGFR < 30 mL/min (Desnover, 2016).

Though recommendations exist for reducing ribavirin dose and/or dosing frequency in those with renal impairment, this drug is poorly tolerated in this population. Daclatasvir, elbasvir/grazoprevir, ledipasvir, PrOD, and simeprevir are primarily hepatically metabolized and undergo minimal renal elimination. While exposures to many of these agents are higher in severe renal impairment presumably due to effects of uremic toxins, parathyroid hormone, and/or cytokines on hepatic metabolism, they do not require dose adjustments in renal impairment. Refer to the table on drug dosing in renal impairment.

The HCV-TARGET study is an ongoing prospective observational cohort study that evaluates the use of direct-acting antiviral (DAA) agents across clinical practices in North America and Europe. The study reported the safety and efficacy of sofosbuvir-containing regimens in patients with mild to severe renal dysfunction (eGFRs < 30, 31-45, 46-60, and > 60 mL/min) (Saxena, 2016). The patients received different regimens that included sofosbuvir (PEG-IFN, ribavirin, and sofosbuvir; simeprevir and sofosbuvir with or without ribavirin; or sofosbuvir and ribavirin). Overall, the regimens were well tolerated with no increased discontinuation among patients with low eGFRs. The rates of sustained virologic response at 12 weeks (SVR12) were similar across the groups regardless of renal function. Notably, there was progressive deterioration of renal function and renal symptoms in the patients with eGFRs below 30 mL/min, suggesting the need for close monitoring of these patients. In summary, patients with low baseline renal function have a higher frequency of anemia, worsening renal dysfunction, and more severe adverse events, but treatment responses remain high and comparable to those without renal impairment.

Data on patients treated with a regimen of simeprevir and low-dose sofosbuvir without ribavirin have been reported. In one study, 18 HCV-infected patients (11 requiring hemodialysis, 3 with a mean eGFR of 16 mL/min) underwent open-label treatment with simeprevir and sofosbuvir. All patients received full-dose simeprevir (150 mg) daily. Sofosbuvir dose was reduced to 200 mg daily in 15 patients and 400 mg every other day in 3 patients. The length of therapy was 12 weeks in 17 patients and 24 weeks in 1 patient with cirrhosis. One patient developed new onset hepatic encephalopathy and another developed uncontrolled diarrhea, both requiring hospitalizations during treatment. Minor adverse events were fatigue (28%), anemia (11%), rash or itching (11%), and nausea (5%), and were managed medically;

there were no treatment discontinuations. Of the 16 patients who completed treatment, only 9 patients reached relevant milestones. Per the current per-protocol analysis, SVR4 was seen in 91% and SVR12 in 89%. One patient with cirrhosis (who had a prior HCV protease inhibitor-containing treatment failure) relapsed within 4 weeks after completion of treatment. In summary, the regimen of simeprevir and reduced-dose sofosbuvir is safe and well tolerated. In another study, 12 patients with eGFRs below 30 mL/min received sofosbuvir (400 mg) and simeprevir (150 mg). The regimen was well tolerated and resulted in viral suppression in all patients (Nazario, 2016).

Twenty patients with HCV genotype 1 infection and stage 4 or 5 (eGFR < 30 mL/min) chronic kidney disease (CKD) without cirrhosis were treated with daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) with or without ribavirin in a multicenter, open-label phase IIb study (Pockros, 2016). Notably, 70% of patients were black and 65% had CKD requiring hemodialysis. Ribavirin (in those with HCV genotype 1a only) was dosed 4 hours before hemodialysis and monitored with weekly hemoglobin assessments. Ribavirin doses were suspended for a 2 g/dL or more drop in hemoglobin level and resumed when the hemoglobin level normalized. All patients (10/10) achieved SVR4 (Pockros, 2016). Interestingly, the use of ribavirin was associated with more of a drop in hemoglobin level, and 8 of 13 patients required interruption of ribavirin dosing. Four of 8 patients also required erythropoietin treatment during the first 7 weeks of therapy. Mean drug concentrations (C_{trough}) of all drugs were measured and levels were within the range that was observed with previous pharmacokinetic studies in healthy volunteers. In summary, most patients with HCV genotype 1 with or without cirrhosis who were treated with PrOD with or without ribavirin achieved viral suppression. However, ribavirin-induced anemia can occur frequently, and close monitoring of all patients and judicious dose reductions of ribavirin are required. As described in other sections, PrOD should be used with caution in patients with Child Turcotte Pugh A cirrhosis and avoided in patients with CTP B or C cirrhosis.

For patients infected with HCV genotypes 2, 3, 5, or 6 with eGFR ≤ 30 mL/min for whom the urgency to treat is high, and for whom treatment has been elected before kidney transplantation, standard treatment remains PEG-IFN plus dose-adjusted ribavirin (200 mg daily). However, caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL. Ribavirin should be discontinued if hemoglobin level declines by more than 2 g/dL despite the use of erythropoietin. Few data exist to guide treatment with current IFN-free regimens. Consideration may be given on an individualized basis to a sofosbuvir-based regimen, with careful attention paid to patient comorbidities and toxicities. However, additional pangenotypic options are anticipated in this population in mid-2017.

Unique Patient Populations Table: Dose Adjustments Needed for Patients with Renal Impairment

Renal Impairment	eGFR (mL/min)	PEG-IFN	Ribavirin	Sofosbuvir	Ledipasvir	Daclatasvir	Ombitasvir	Dasabuvir	Paritaprevir	Simeprevir	Velpatasvir	Elbasvir	Grazoprevir
Mild	50-80	PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1.5 µg/kg	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard

Moderate	30-50	PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1 µg/kg (25% reduction)	Alternating doses 200 mg and 400 mg every other day	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard
Severe	< 30	PEG-IFN (2a) 135 µg; PEG-IFN (2b) 1 µg/kg (50% reduction)	200 mg/d	Limited data available	Data not available	Limited data available	Limited data available	Limited data available	Limited data available	Standard	Data not available	Standard	Standard
ESRD with HD		PEG-IFN (2a) 135 µg/wk or PEG-IFN (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk	200 mg/d	Limited data available	Data not available	Limited data available	Limited data available	Limited data available	Limited data available	Limited data available	Data not available	Standard	Standard

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis.

DAA Therapy in Renal Transplant Patients

A recent clinical trial described the safety and efficacy of ledipasvir/sofosbuvir in renal transplant recipients (N= 114) who were more than 6 months posttransplant (Colombo, 2016). The patients were mainly infected with genotype 1 or 4, with or without cirrhosis, and with or without prior treatment experience. Patients were randomized to receive ledipasvir/sofosbuvir for 12 or 24 weeks. Prior to treatment, median eGFR was 50 mL/min for those who were treated for 12 weeks and 60 mL/min for those who were treated 24 weeks. 96% achieved SVR12. Adverse events were common (64%) and 11% had a serious adverse event, but fewer than 1% discontinued treatment due to adverse effects (Colombo, 2016). In 3 patients, eGFR increased to greater than 30 mL/min at the last visit recorded; one patient who had interrupted study treatment had a final value of 14.4 mL/min. All but 1 of the 6 patients with cirrhosis whose eGFR decreased to below 40 mL/min continued study treatment without interruption; none permanently discontinued study treatment.

Several additional reports have described successful outcomes with DAA combination therapy in renal-transplant patients (Sawinski, 2016); (Kamar, 2016). Sawinski et al treated 20 HCV-infected kidney transplant recipients (88% genotype 1, half with advanced fibrosis, and 60% treatment-experienced) with sofosbuvir-based regimens and reported resulted 100% SVR (Sawinski, 2016). Various sofosbuvir-based DAA combinations were used, including simeprevir plus sofosbuvir (n= 9), ledipasvir/sofosbuvir (n= 7), sofosbuvir plus ribavirin (n= 3), and daclatasvir plus sofosbuvir (n= 1). Two patients required dose reductions due to anemia (associated with ribavirin use), however no significant changes in serum creatinine, proteinuria, or graft rejection were seen before or after treatment. Forty-five percent of patients required dose reduction of immunosuppressive agents while on therapy (Sawinski, 2016).

A study of 25 kidney transplant recipients with chronic HCV infection that were treated with sofosbuvir-based regimens reported a 100% SVR (Kamar, 2016). Patients included were infected with genotype 1 (76%), had eGFR > 30 mL/min (100%), and had advanced fibrosis (44%). Treatment regimens included ledipasvir/sofosbuvir (n= 9), daclatasvir plus sofosbuvir (n= 4), sofosbuvir plus ribavirin (n= 3), ledipasvir/sofosbuvir plus ribavirin (n= 1), simeprevir plus sofosbuvir plus ribavirin (n= 1), simeprevir plus sofosbuvir (n= 6), and sofosbuvir plus pegylated IFN/ribavirin (n= 1). Treatment was well tolerated without any discontinuations, dose reductions, graft rejections, or changes in serum creatinine levels, and no

drug interactions with calcineurin inhibitors were observed (Kamar, 2016).

Another study that treated three HCV genotype 4 renal transplant patients with sofosbuvir (400 mg) plus ribavirin (1000 mg) for 24 weeks reported a 100% SVR (Hussein, 2016). Anemia was reported in two patients related to concomitant ribavirin use. No other adverse events were reported (Hussein, 2016).

Drug interactions are an important consideration with antiviral therapy in renal transplant recipients. Please see the section titled, "Unique Patient Populations: Patients Who Develop Recurrent HCV Infection Post Liver Transplantation" for a table of drug interactions with DAAs and calcineurin inhibitors.

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Changes made April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Summary of Recommendations for Patients with Renal Impairment, Including Severe Renal Impairment (eGFR <30 mL/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis

Recommended Dosage Adjustments for Patients with Mild to Moderate Renal Impairment

- **For patients with mild to moderate renal impairment (eGFR 30 mL/min-80 mL/min), no dosage adjustment is required when using daclatasvir (60 mg*), fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with (or without for HCV genotype 4 infection) twice-daily dosed dasabuvir (250 mg), simeprevir (150 mg), or sofosbuvir (400 mg) to treat or retreat HCV infection in patients with appropriate genotypes.**
  Rating: Class I, Level A

Recommended Regimens for Patients with Severe Renal Impairment, Including Severe Renal Impairment (eGFR <30 mL/min) or End-Stage Renal Disease (ESRD)

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **For patients with genotype 1a, or 1b, or 4 infection and eGFR below 30 mL/min, for whom treatment has been elected, daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen.**
  Rating: Class Ia, Level B

- **For patients with genotype 1b infection and eGFR below 30 mL/min, for whom treatment has been elected, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a**

Recommended regimen.
Rating: Class IIb, Level B

- **For patients with HCV genotype 2, 3, 5, or 6 infection and eGFR below 30 mL/min, for whom the urgency to treat is high, PEG-IFN and dose-adjusted ribavirin** (200 mg daily) is a Recommended regimen.**
  Rating: Class IIb, Level B

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
**Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

Alternative Regimen for Genotype 1a-infected Patients with eGFR Below 30 mL/min

- **For HCV genotype 1a infection, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and dose-adjusted ribavirin** (200 mg daily) for 12 weeks is an Alternative regimen.**
  Rating: Class IIb, Level B

**Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

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Changes made April 12, 2017.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

MANAGEMENT OF ACUTE HCV INFECTION

(Expansions and notes for abbreviations used in this section can be found in Methods Table 3. A summary of recommendations for Managing Acute HCV Infection is found in the box.)

This section provides guidance on the diagnosis and medical management of acute HCV infection, which is defined as presenting within 6 months of the exposure. During this time, there is a 20% to 50% chance of spontaneous resolution of infection (Kamal, 2008). In the past, cure rates of acute infection with IFN-based treatment were very high (Grebely, 2014). The present guidance reflects current trends transitioning toward safer, IFN-sparing treatments for chronic infection and the implications for the approach to acute HCV treatment.

Acute HCV infection may result from exposure to the virus through various routes. The highest risk is associated with repeated parenteral exposures from contaminated equipment in an injection drug use (IDU) setting. Lower rates of HCV transmission occur from needlestick injuries in which healthcare workers are exposed to the blood of an HCV-infected patient. Heterosexual exposure risk is very low. In comparison, transmission rates among HIV-infected men who have unprotected sex with men are much higher, particularly among those who engage in high-risk sexual practices that increase trauma to the mucosal membranes and exposure to blood (Boesecke, 2012).

Recommended Testing for Diagnosing Acute HCV Infection

- **HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels (see Figure).**
  Rating: Class I, Level C

Recommendations for HCV testing are also found in the **HCV Testing and Linkage to Care** section.

Diagnosis of acute infection permits estimation of annual incidence rates and transmission patterns, thereby facilitating implementation and assessment of prevention programs. At the individual level, a diagnosis of acute infection expedites linkage to care, counseling regarding high-risk behavior, and

timely interventions to reduce transmission of the virus and progression of liver disease (Bruneau, 2014). Indeed, some persons involved in high-risk behaviors practice serosorting, defined as using anti-HCV antibody serostatus to determine whether to engage in high-risk behaviors with certain individuals (Smith, 2013). Thus, undiagnosed acutely infected persons may be at greater risk of transmitting HCV to their presumably seronegative contacts than would be expected by chance.

The best laboratory evidence to support a diagnosis of acute HCV infection is (1) a positive HCV RNA test in the setting of a negative HCV antibody test (identification during the seronegative "window" period), (Cox, 2005) or (2) a positive HCV antibody test after prior negative HCV antibody test (termed seroconversion). There are rare instances in which these approaches may be misleading, such as in immunosuppressed individuals with impaired antibody production (Chamot, 1990).

Discrete Exposure

The above types of clear laboratory documentation of acute infection are easiest to achieve when there has been a discrete exposure (eg, after new onset or a change in drug injection practice, a percutaneous needlestick exposure to an HCV-infected individual, a potentially nonsterile tattoo, or sexual assault). In those instances, baseline HCV antibody and RNA testing should be done within 48 hours of the exposure to document whether there was antecedent HCV infection (see Figure). If baseline testing is negative, repeat testing is recommended. Frequency of testing can be tailored based on management objectives (eg, monthly testing to identify and treat acute infection). If baseline anti-HCV antibody testing is positive but RNA testing is negative, repeat HCV RNA and alanine aminotransferase (ALT) testing is recommended to identify an acute reinfection. When baseline HCV antibody and RNA testing are both positive, the person most likely already has chronic HCV infection from prior exposures. The frequency of repeat testing should reflect management goals. At a minimum, repeat testing should be done 4 months to 6 months later. When earlier identification of infection or reinfection is desired, HCV RNA and ALT testing every 4 weeks to 6 weeks for 6 months is recommended.

No Discrete Exposure

Often, individuals suspected of having acute HCV infection do not have a discrete exposure or have no prior baseline testing, making a diagnosis of acute infection more difficult (see Table below). Acute infection should be suspected if there is a new rise in the ALT level without an alternate cause (Blackard, 2008); (Kim, 2013). Acute infection should also be suspected when there are low (especially < 104 IU/mL) or fluctuating (> 1 log10 IU/mL) HCV RNA values, or spontaneous clearance, which do not commonly occur outside of the first 6 months after acute HCV infection (McGovern, 2009). A low signal-to-cutoff ratio of HCV antibody along with detectable HCV RNA may also be suggestive of the early weeks of acute primary infection, although this information may need to be specifically requested from the testing laboratory (Araujo, 2011). Patients suspected of having acute HCV infection should also have a laboratory evaluation to exclude other or coexisting causes of acute hepatitis (eg, hepatitis A virus, hepatitis B virus, HDV if chronically infected with hepatitis B (Kushner, 2015), or autoimmune hepatitis) and should be tested for HIV.

- **Preexposure or postexposure prophylaxis with antiviral therapy is Not Recommended.**
  Rating: Class III, Level C

Although new antiviral treatment regimens are highly efficacious and more tolerable than IFN-based therapy, there are no data on the efficacy or cost-effectiveness of antiviral therapy for preexposure or postexposure prophylaxis of HCV infection. Some studies have shown that postexposure treatment with IFN-based regimens does not prevent infection (Nakano, 1995); (Arai, 1996).

Table. Interpretation of Blood Testing During Diagnosis of Acute HCV Infection

Test	Interpretation for Diagnosis of Acute HCV Infection
HCV antibody	• May be negative in the first 6 weeks after exposure • May be delayed or absent when the individual is immunosuppressed • Presence alone does not distinguish between acute and chronic infection • Low signal-to-cutoff ratio may be present during acute HCV infection or represent a false-positive result
HCV RNA	• Viral fluctuations greater than 1 $\log_{10}$ IU/mL may indicate acute HCV infection • May be transiently negative during acute HCV infection • Alone does not distinguish between acute and chronic infection
Alanine aminotransferase (ALT)	• Fluctuating peaks during acute HCV infection suggest acute infection • May be normal during acute HCV infection • May be elevated due to other liver insults such as alcohol consumption

Recommendations for Medical Management and Monitoring in Acute HCV Infection

- **Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (eg, every 4 weeks to 8 weeks) for 6 months to 12 months is also recommended to determine spontaneous clearance of HCV infection versus persistence of infection.**
  Rating: Class I, Level B

- **Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (eg, acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others.**
  Rating: Class I, Level C

- **Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.**
  Rating: Class I, Level B

The patient with acute HCV infection should be counseled to reduce behaviors that could result in transmission, such as sharing of injection equipment or high-risk sexual practices. Because the risk of transmission of other infections is higher in the acute infection phase, some experts counsel patients with acute infection to consider using barrier precautions even in stable monogamous relationships (see **HCV Testing and Linkage to Care**). For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when appropriate (Litwin, 2009); (Strathdee, 2005).

Patients with acute HCV infection are often asymptomatic or have nonspecific symptoms (fatigue, anorexia, mild or moderate abdominal pain, low-grade fever, nausea, vomiting) that frequently are not recognized as being associated with acute HCV infection. A small proportion (< 25%) of patients with acute HCV infection will develop jaundice. Patients diagnosed with acute HCV infection should be initially monitored with hepatic panels (ALT, aspartate aminotransferase [AST], bilirubin, and international normalized ratio [INR] in the setting of increasing bilirubin level) at 2- to 4-week intervals (Blackard, 2008). Laboratory monitoring should continue until the ALT levels normalize and HCV RNA becomes repeatedly undetectable, suggesting spontaneous resolution. If this does not occur, frequency of laboratory monitoring for patients with persistently detectable HCV RNA and elevated ALT levels should follow recommendations for monitoring patients with chronic HCV infection (see **Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy**).

HCV infection will spontaneously clear in 20% to 50% of patients (Kamal, 2008). In at least two-thirds of patients, this will occur within 6 months of the estimated time of infection (median, 16.5 weeks); only 11% of those who remain viremic at 6 months will spontaneously clear infection at some later time (Grebely, 2014). Thus, detectable HCV RNA at 6 months after the time of infection will identify most persons who need HCV therapy (see **When and in Whom to Initiate HCV Therapy**). Those with spontaneous clearance should not be treated with antiviral therapy, but they should be counseled about the possibility of reinfection and tested routinely for reinfection if risk behaviors are ongoing (see **HCV Testing and Linkage to Care**). Of note, transient suppression of viremia can occur in those with acute HCV infection, even in those who progress to chronic infection. Thus, a single undetectable HCV RNA value is insufficient to declare spontaneous clearance (Villano, 1999); (Mosley, 2008) (see **HCV Testing and Linkage to Care**).

Predictors of spontaneous clearance include jaundice, elevated ALT level, hepatitis B virus surface antigen (HBsAg) positivity, female sex, younger age, HCV genotype 1, and host genetic polymorphisms, most notably those near the IL28B gene (Kamal, 2008); (Mosley, 2008).

There is no need to alter concomitant medications that are metabolized by hepatic enzymes unless there is concern for developing acute liver failure (eg, increasing bilirubin level and INR). Acetaminophen and alcohol consumption should be avoided during acute HCV infection (Proeschold-Bell, 2012); (Dieperink, 2010); (Whitlock, 2004). Hospitalization is rarely indicated unless nausea and vomiting are severe. Although acute liver failure is very rare (< 1%), it represents a serious and life-threatening complication of acute HCV infection. Patients with an INR above 1.5 or those who exhibit any signs of acute liver failure (eg, hepatic encephalopathy) should be referred to a liver transplant center immediately. The use of HCV antiviral regimens in acute liver failure should be managed by a clinician experienced in HCV treatment, ideally in consultation with a liver transplant specialist.

Recommended Treatment for Patients with Acute HCV Infection

- **If the practitioner and patient have decided that a delay in treatment initiation is acceptable, monitoring for spontaneous clearance is recommended for a minimum of 6 months. When the decision is made to initiate treatment after 6 months, treating as described for chronic hepatitis C is recommended (see Initial Treatment of HCV Infection).**
  Rating: Class IIa, Level C

- **If a decision has been made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 weeks to 16 weeks before starting treatment is recommended to allow for spontaneous clearance.**
  Rating: Class IIa, Level C

Recommended Regimens for Patients with Acute HCV Infection.

- **Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.**
  Rating: Class IIa, Level C

- **For patients in whom HCV infection spontaneously clears, treatment is Not Recommended.**
  Rating: Class III, Level B

In the interferon era, the efficacy of the treatment of acute HCV infection (particularly for genotype 1), including with abbreviated regimens, was superior to the treatment of chronic infection (See 2009 AASLD guidelines, [Ghany, 2009]). There are emerging data on the treatment of acute HCV infection with shortened courses of all-oral DAA regimens both in HCV monoinfection and HIV/HCV coinfection, but there are, as yet, not enough data to support a particular regimen or duration. Until more definitive data are available, monitoring for spontaneous clearance for a minimum of 6 months before initiating treatment is recommended. When the decision is made to initiate treatment after 6 months, treatment as described for chronic hepatitis C is recommended.

There are instances, however, where clinicians may decide that the benefits of early treatment outweigh waiting for HCV clearance. These include situations where importance is placed on the prevention of HCV transmission (eg, surgeon, IVDU, and or HIV+ MSM with sexual transmission), mitigation of clinical consequences (eg, patient with cirrhosis who is acutely superinfected with HCV), or reduction in likelihood of loss-to-follow-up in patients who may not be engaged in care in 3-to-6 months. Where relevant, referral to addiction specialists and harm reduction counseling should be provided. If for these reasons a decision has been made to initiate treatment during the acute infection period, the same regimens recommended for chronic HCV infection (see **Initial Treatment of HCV Infection** and **When and in Whom to Initiate HCV Therapy** sections) are recommended for acute infection given their high efficacy and safety in chronic HCV infection.

Changes made July 6, 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Summary of Recommendations for Management of Acute HCV Infection

Recommended Testing for Diagnosing Acute HCV Infection

- **HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels (see Figure).**
  Rating: Class I, Level C

Recommendations for Medical Management and Monitoring in Acute HCV Infection

- **Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (eg, every 4 weeks to 8 weeks) for 6 months to 12 months is also recommended to determine spontaneous clearance of HCV infection versus persistence of infection.**
  Rating: Class I, Level B

- **Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (eg, acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others.**
  Rating: Class I, Level C

- **Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.**
  Rating: Class I, Level B

Recommended Treatment for Patients with Acute HCV Infection

- **If the practitioner and patient have decided that a delay in treatment initiation is acceptable, monitoring for spontaneous clearance is recommended for a minimum of 6 months. When the decision is made to initiate treatment after 6 months, treating as**

described for chronic hepatitis C is recommended (see Initial Treatment of HCV Infection).
Rating: Class IIa, Level C

- **If a decision has been made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 weeks to 16 weeks before starting treatment is recommended to allow for spontaneous clearance.**
  Rating: Class IIa, Level C

Recommended Regimens for Patients with Acute HCV Infection.

- **Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.**
  Rating: Class IIa, Level C

Not Recommended

The following are Not Recommended in the Management of Acute HCV Infection.

- **Preexposure or postexposure prophylaxis with antiviral therapy is Not Recommended.**
  Rating: Class III, Level C

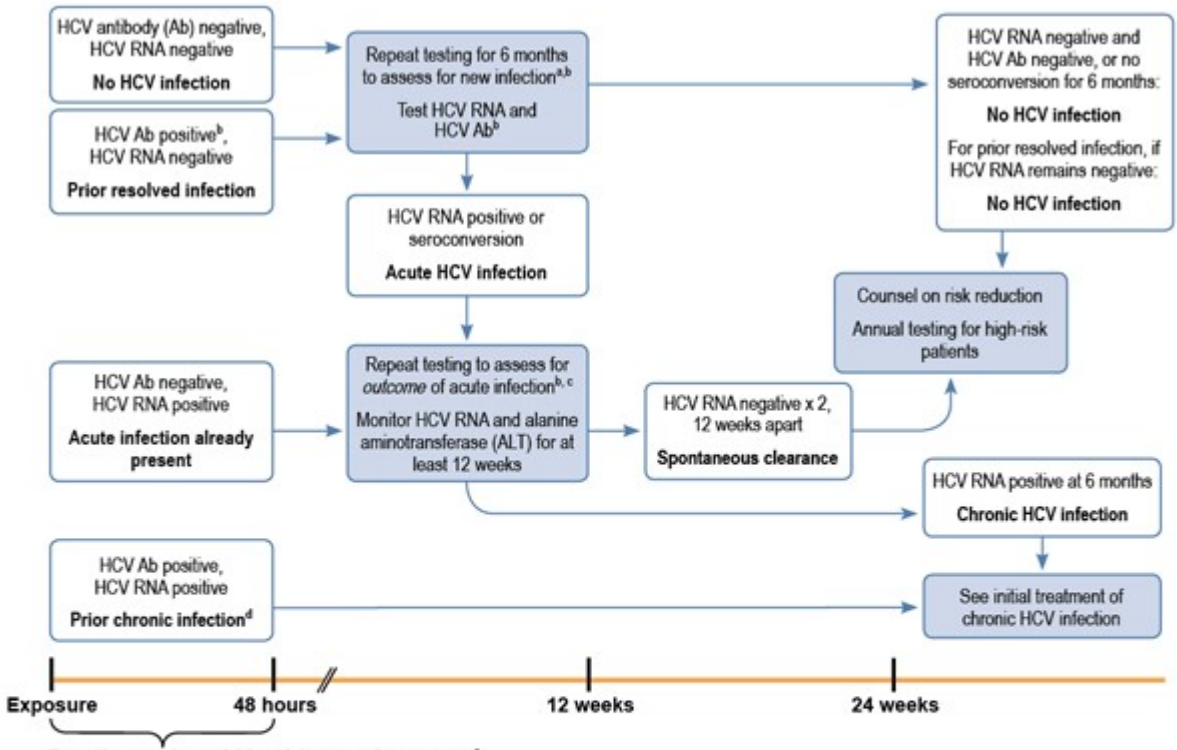
- **For patients in whom HCV infection spontaneously clears, treatment is Not Recommended.**
  Rating: Class III, Level B

Changes made on July 6, 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Acute Figure. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure

Figure. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure[a]



[a] Often there is no discrete exposure or the entry to health care occurs with jaundice or elevated liver enzymes. In those instances, baseline testing cannot be done and the diagnosis of acute infection is more challenging (see text).

[b] Repeat HCV Ab is not needed if it is positive at baseline. Frequency of testing can be tailored based on management objectives (eg, monthly testing to identify and treat acute infection).

[c] Some would treat after waiting 8 weeks to 12 weeks for spontaneous clearance (see text). Benefits of HCV antiviral therapy or IFN-based (alternative) within 12 weeks of acute infection are that this may decrease transmission risk to others (eg, among injection drug users or surgeons), prevent severe complications (eg, underlying cirrhosis superinfected with acute HCV infection), and minimize chance of being lost to follow-up.

[d] If there were additional exposures in the preceding 6 months, a patient with a new diagnosis who is HCV RNA and HCV Ab positive may still be in the acute infection phase. Symptoms, high ALT level, or viral fluctuations may help distinguish acute from chronic HCV.

[e] Baseline testing should be done within 48 hours of exposure to determine existing infection status: HCV RNA, HCV Ab, and ALT.

Reviewed June 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

NOT RECOMMENDED REGIMENS IN HCV TREATMENT

Skip to: Pregnancy | Decompensated Cirrhosis | Transplant | Summary

Regimens Not Recommended

- Daily sofosbuvir (400 mg) and weight-based ribavirin for 24 weeks.[f]
  Rating: Class IIb, Level A
- PEG-IFN/ribavirin with or without sofosbuvir, simeprevir, telaprevir, or boceprevir.
  Rating: Class IIb, Level A
- Monotherapy with PEG-IFN, ribavirin, or a direct-acting antiviral.
  Rating: Class III, Level A

[f]Due to fewer options in the posttransplant population, sofosbuvir and ribavirin for 24 weeks is recommended in patients with genotype 2 infection.

Although regimens of sofosbuvir and ribavirin or PEG-IFN/ribavirin plus sofosbuvir, simeprevir, telaprevir, or boceprevir are FDA-approved for particular genotypes, they are inferior to the current recommended regimens. The efficacy of sofosbuvir plus ribavirin for 24 weeks is well demonstrated to be inferior to combination DAA therapy for genotype 1 and 3. For genotype 4, it has not been compared head-to-head with DAA combination therapy, but shorter, well-tolerated DAA combination regimens are now available. The IFN-containing regimens are associated with higher rates of serious adverse events (eg, anemia and rash), longer treatment duration in some cases, high pill burden, numerous drug-drug interactions, more frequent dosing, and higher intensity of monitoring for safety or treatment response.

Regimens Not Recommended with Regard to Pregnancy-Related Issues

- Treatment with ribavirin is Not Recommended during pregnancy or for women who are unable or unwilling to adhere to use of adequate contraception, including those who are receiving ribavirin themselves or are sexual partners of male patients who are receiving ribavirin.

Rating: Class III, Level C

- Female patients who have received ribavirin and sexual partners of male patients who have received ribavirin should NOT become pregnant for at least 6 months after stopping ribavirin.
  Rating: Class III, Level B

Regimens Not Recommended for Patients with Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; Child Turcotte Pugh Class B or C)

- Simeprevir-based regimens.
  Rating: Class III, Level B
- Paritaprevir-based regimens.
  Rating: Class III, Level B
- Elbasvir/grazoprevir-based regimens.
  Rating: Class III, Level C

IFN should not be given to patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) because of the potential for worsening hepatic decompensation. Minimal data exist for the use of simeprevir in patients with decompensated cirrhosis (Modi, 2016). Until additional data become available, simeprevir should not be used in patients with decompensated cirrhosis. No data exist for the use of currently approved doses of elbasvir and grazoprevir for patients with decompensated cirrhosis, and this combination should not be used in this population until additional data become available.

Recent data reported by the US FDA have demonstrated that some patients with compensated HCV genotype 1 cirrhosis treated with paritaprevir, ombitasvir, and dasabuvir may develop rapid onset of direct hyperbilirubinemia within 1 to 4 weeks of starting treatment without ALT elevations that can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received PrOD and also developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died (Zuckerman, 2016). Therefore, this antiviral treatment regimen is CONTRAINDICATED in all patients with decompensated HCV cirrhosis due to concerns of hepatotoxicity. In addition, all patients with cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks on therapy.

Regimens Not Recommended for Patients with HCV Infection in the Allograft, Including Those with Compensated Cirrhosis

- Elbasvir/grazoprevir-based regimens.
  Rating: Class III, Level C

Regimens Not Recommended for Patients with Decompensated Cirrhosis Who Have HCV Infection in the Allograft

- Regimens containing simeprevir.
  Rating: Class III, Level B
- Fixed-dose combination of paritaprevir, ritonavir, and ombitasvir with or without dasabuvir or ribavirin.
  Rating: Class III, Level B

- Elbasvir/grazoprevir-based regimens.
  Rating: Class III, Level C

Changes made July 6, 2016.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

Summary of Not Recommended Regimens in HCV Treatment

Regimens Not Recommended

- Daily sofosbuvir (400 mg) and weight-based ribavirin for 24 weeks.[f]
  Rating: Class IIb, Level A
- PEG-IFN/ribavirin with or without sofosbuvir, simeprevir, telaprevir, or boceprevir.
  Rating: Class IIb, Level A
- Monotherapy with PEG-IFN, ribavirin, or a direct-acting antiviral.
  Rating: Class III, Level A

[f]Due to fewer options in the posttransplant population, sofosbuvir and ribavirin for 24 weeks is recommended in patients with genotype 2 infection.

Regimens Not Recommended with Regard to Pregnancy-Related Issues

- Treatment with ribavirin is Not Recommended during pregnancy or for women who are unable or unwilling to adhere to use of adequate contraception, including those who are receiving ribavirin themselves or are sexual partners of male patients who are receiving ribavirin.
  Rating: Class III, Level C
- Female patients who have received ribavirin and sexual partners of male patients who have received ribavirin should NOT become pregnant for at least 6 months after stopping ribavirin.
  Rating: Class III, Level B

Regimens Not Recommended for Patients with Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; Child Turcotte Pugh Class B or C)

- Simeprevir-based regimens.
  Rating: Class III, Level B

- Paritaprevir-based regimens.
  Rating: Class III, Level B

- Elbasvir/grazoprevir-based regimens.
  Rating: Class III, Level C

Regimens Not Recommended for Patients with HCV Infection in the Allograft, Including Those with Compensated Cirrhosis

- Elbasvir/grazoprevir-based regimens.
  Rating: Class III, Level C

Regimens Not Recommended for Patients with Decompensated Cirrhosis Who Have HCV Infection in the Allograft

- Regimens containing simeprevir.
  Rating: Class III, Level B
- Fixed-dose combination of paritaprevir, ritonavir, and ombitasvir with or without dasabuvir or ribavirin.
  Rating: Class III, Level B

- Elbasvir/grazoprevir-based regimens.
  Rating: Class III, Level C

Changes made July 6, 2016.

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Reviewed February 2016.